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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY DEVICES PANEL

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October 27, 2020
9:00 a.m.

Via Zoom

PANEL MEMBERS:

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Patient

ANNETTE CASCIANO
Wife of Patient

MARK SOBERANO
Patient

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Patient

DONNA SUMMERS
Wife of Patient

LAURIE VANDENBOSSCHE
Patient

DONALD SCOTT
Patient

TAMMY HOPKINS
Patient

CLYDE HART
Patient

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M E E T I N G

(9:00 a.m.)

DR. LANGE: Great, it's 9:00 a.m., October 27th. I'd like to call this meeting of the Circulatory Devices Panel to order. I'm Richard Lange, the chairperson of this Panel. I'm president of Texas Tech University Health Sciences Center in El Paso, where I'm also dean of the Paul L. Foster School of Medicine, and previously was an interventional cardiologist.

I want to thank everybody for participating on this Panel. These are obviously challenging times and extenuating circumstances. I want to express my appreciation to the FDA and our audiovisual personnel who have worked beforehand to try to make this go as seamlessly as possible.

I do want to comment, though. If you have any difficulties, we shared three e-mails with you, you can e-mail Aden, you can e-mail Jim, or you can e-mail me. Now, if you e-mail me for audiovisual help, I just want to remind you that, between the third and fifth grade, I did replace a bulb in the carousel and ran the 8 mm film. So I'll be your last resort.

Again, I want to thank everybody for participating and especially those on the West Coast, Pacific time, where it's 6:00 a.m. So thank you, everybody.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application, that is the PMA, for the Neovasc Reducer System sponsored by Neovasc, Inc.

Before we begin, I would like to ask our distinguished Committee members and FDA attending virtually to introduce themselves. Committee members, to do so, I'll remind you to please turn on your video monitors if you have not already done so, and you need to

unmute your phone before you speak. I will call your name. At that time if you'll please state your area of expertise, your position, and your affiliation.

And I'll start with Dr. George Vetrovec. Please unmute yourself.

DR. VETROVEC: -- after a long interventional career, beginning with the first stent in 1970 -- first PCI in 1977 -- committees at the University and do some teaching as well as writing and information for the ACC.org. I'm excited about today's meeting.

DR. LANGE: Thank you for joining us, George.

Dr. Randall Starling.

DR. STARLING: Good morning, my name is Randy Starling. I have, of course, an M.D. and master's in public health and epidemiology. My specialty in cardiology is heart failure and transplant. I've been at the Cleveland Clinic for 25 years. I'm Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University. I have served in an ad hoc basis on previous FDA panels and have recently become a member of this particular circulatory assist devices panel. So I'm looking forward to working with this esteemed group of colleagues.

DR. LANGE: Thank you, Dr. Starling.

Dr. Jason Connor.

DR. CONNOR: Hi, I'm Jason Connor, founder and biostatistician at ConfluenceStat and Assistant Professor of Medical Education at the University of Central Florida College of Medicine.

DR. LANGE: Thank you, Jason.

Dr. Ralph Brindis.

DR. BRINDIS: Good morning. Ralph Brindis. I'm a Clinical Professor of Medicine at UCSF at the Philip R. Lee Institute of Health Policy Studies. I'm a cardiologist by training, experience in cardiovascular outcomes research, and also served as the chief medical

officer/external affairs at the National Cardiovascular Data Registry.

DR. LANGE: Thank you, Ralph.

DR. BRINDIS: And I have no new conflicts to disclose.

DR. LANGE: Great, thank you.

Dr. Janet Wittes.

DR. WITTES: Hi, I'm Janet Wittes. I'm a statistician and president of Statistics Collaborative, and I was a member of this Panel about 15 years ago, so it's good to be back and I'm looking forward to today.

DR. LANGE: Thank you, Janet, for joining us.

Dr. Pramod Bonde.

DR. BONDE: Hi, I'm Pramod Bonde. I'm Associate Professor of Surgery at Yale University. I specialize in adult cardiac surgery with a subspecialty in mechanical circulatory support.

DR. LANGE: Thank you, Pramod.

Dr. Richard Page.

DR. PAGE: Good morning, my name is Rick Page. I'm Professor of Medicine and dean of the Larner College of Medicine at the University of Vermont. I am a practicing cardiac electrophysiologist, although I'm noninvasive these days, and I'm the past chair of this Panel.

DR. LANGE: Thank you, Rick, good to have you on board again.

Dr. David Yuh.

DR. YUH: Good morning. David Yuh. I'm the Chairman of Surgery at Stamford Hospital in Connecticut, with an academic appointment at Columbia. I'm a clinically active adult cardiac surgeon primarily in coronary bypass surgery and minimally invasive valve repair.

DR. LANGE: Thank you, David, for joining us.

DR. YUH: You're welcome.

DR. LANGE: Dr. Robert Yeh.

DR. YEH: Hi, everyone. Robert Yeh. I'm an Associate Professor of Medicine at Harvard Medical School. I direct our complex coronary intervention program here at Beth Israel Deaconess Medical Center, and I direct the Smith Center for Outcomes Research in Cardiology also at the Beth Israel.

DR. LANGE: Thank you, Robert.

Dr. Keith Allen.

DR. ALLEN: Hi there, good morning. Keith Allen. I am at the Mid America Heart Institute in Kansas City, Missouri. I am a cardiac as well as vascular surgeon, director of surgical research, and the surgical director of our structural heart program.

DR. LANGE: Great. Thank you, Keith, for joining us.

Dr. Wayne Batchelor.

(No response.)

DR. LANGE: All right.

Dr. Magnus Ohman.

DR. OHMAN: Good morning, everybody. My name is Magnus Ohman, I'm a Professor of Medicine at Duke University in North Carolina, and I am an interventional cardiologist. I'm also the director of the Duke program for advanced coronary disease, so I'm very familiar with these types of patients. I'm looking forward to our discussion today.

DR. LANGE: Magnus, thanks for joining us.

Dr. Joaquin Cigarroa.

DR. CIGARROA: Good morning, I'm Joaquin Cigarroa and I'm Professor of Medicine at OHSU, clinical chief of the Knight Cardiovascular Institute, and division head of

cardiology. I'm a general cardiologist with added training in capabilities in interventional cardiology.

DR. LANGE: Great. Thank you, Joaquin.

Dr. John Hirshfeld. John, I'll ask you to unmute yourself.

DR. HIRSHFELD: Good morning, I'm John Hirshfeld. I'm a Professor of Medicine at the University of Pennsylvania School of Medicine. I've been a member of this Panel for a number of years and chaired it. I'm an interventional cardiologist who practiced interventional cardiology for 45 years and stopped actually doing procedures 2 years ago.

DR. LANGE: Great. John, thanks for joining us.

Dr. Verghese Mathew.

DR. MATHEW: Good morning, my name is Verghese Mathew and I'm the director of the Worldwide Network for Innovation in Clinical Education Research, or WNICER, which is a cardiovascular think tank and research collaborative; also continuing to be a practicing interventional cardiologist in a regional healthcare system in northeast Wisconsin now, and spent the last 22 years in academic cardiology including most recently as chair of cardiology at Loyola University in Illinois, as well as the Mayo Clinic in Minnesota. Thank you.

DR. LANGE: Thanks, Verghese.

Dr. Bernie Gersh. Bernie, you have to unmute. There you go.

DR. GERSH: Good morning, I'm Bernard Gersh. I'm a cardiologist with a wide range of interests at the Mayo Clinic. I'm Professor of Medicine at the Mayo Clinic College of Medicine, and this is my first meeting of this group, I'm looking forward to it very much.

DR. LANGE: Great. Thank you, Bernie, for joining us.

Dr. John Somberg.

DR. SOMBERG: Good morning, I'm John Somberg. I'm a Professor Emeritus of Cardiology, Pharmacology, and Medicine at Rush University. I'm also the editor of

Cardiology Research and practice cardiology in Lake Bluff, Illinois at the moment, and I have been on this Panel for over 35 years. So that's a long time and I'm looking forward to our discussions today.

DR. LANGE: Thanks for serving again.

Jeff Borer. Jeff, I don't see your picture up here, are you on?

(No response.)

DR. LANGE: All right, we'll have to see if we can get you back on.

Our Consumer Representative, Jacqueline Alikhaani. And, Jacqueline, you'll need to unmute.

MS. ALIKHAANI: Good morning, I'm Jacqueline Alikhaani and I am a heart survivor and volunteer patient advocate for the American Heart Association here in Los Angeles and for across the country, and I'm also an ambassador for the Patient-Centered Outcomes Research Institute, and I also volunteer with a number of other community healthcare stakeholder organizations like AARP and others.

DR. LANGE: Jacqueline, thank you for serving today.

Patient Representative Debra Dunn. Debra, are you on?

MS. ASEFA: Debra just e-mailed me and she's actually on her way to her office, so she should pop in soon, hopefully.

DR. LANGE: Thank you very much, Aden.

Is Gary Jarvis on?

MS. ASEFA: Gary Jarvis is also experiencing some IT issues, so he will not be able to be on until maybe 11:00 a.m. this morning.

DR. LANGE: Okay. Thank you, Aden.

From the FDA, Dr. Bram Zuckerman.

DR. ZUCKERMAN: Good morning, my name is Bram Zuckerman. I'm the director,

FDA Office of Cardiovascular Devices and a cardiologist by background. Thank you.

DR. LANGE: Thank you, Bram.

And then, Aden, if you'll introduce yourself.

MS. ASEFA: Hi, I'm Aden. I'm the DFO for this Committee, so if you have any questions, please let me know. Thank you.

DR. LANGE: All right. Probably the last remark I need to make is -- and I'm sorry I'm not wearing my coat. Besides being the area most affected by COVID in the United States right now, we had an ice storm last night, so my suit coat is sitting in the kitchen and my ex-arcuric (ph.) coat is right here. I put on a hoodie, but I've just decided to go coatless, so my apologies. It's no disrespect to the FDA or to the Sponsor, either one.

So with that, Aden Asefa, the Designated Federal Officer for today's Circulatory Devices Panel, will make some introductory remarks. Take it away, Aden.

MS. ASEFA: Good Morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Circulatory Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal

employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket application (PMA) for Neovasc Reducer System, by Neovasc, Inc., indicated for patients suffering from refractory angina pectoris despite guideline-directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Mr. Gary Jarvis is serving as the Industry Representative, acting on behalf of all related industry. He is employed by Alpha Medical.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusions will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review and included as part of the official transcript. Thank you.

And now I will read the Appointment to Temporary Voting Status Statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Circulatory Devices Panel for the duration of this meeting on October 27th, 2020:

Wayne Batchelor, Pramod Bonde, Jeffrey Borer, M.D., Joaquin Cigarroa, Bernard Gersh, John Hirshfeld, Verghese Mathew, Erik Magnus Ohman, Richard Page, John Somberg, George Vetrovec, Janet Wittes, David Yuh, M.D.

For the record, these individuals are special Government employees or regular Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This was signed by Jeffrey Shuren, Director of Center for Devices and Radiological Health, on October 15th, 2020.

A copy of this statement will be available for review and will be included as part of the official transcript. Thank you.

FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue.

Before I turn the meeting back over to Dr. Lange, I would like to make a few general announcements.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Transcripts of today's meeting will be available from Free State Court Reporting, Inc.

The press contact for today's meeting is Lindsey O'Keefe.

And for the record, FDA has received one written comment. Thank you very much.

And Dr. Lange, please continue.

DR. LANGE: Thank you very much, Aden.

We will now proceed to the Sponsor's presentation. I would like to invite the Sponsor begin.

I will remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair, and that would be me.

The Sponsor will have 90 minutes to present. And please begin your presentation.

MS. BEBEAU: Good morning, Mr. Chairman, members of the Committee, and members of the Food and Drug Administration. My name is Vicki Bebeau, I'm the Vice President of Clinical and Regulatory Affairs at Neovasc. We're pleased to be here today to present data on our Reducer device for patients who, despite receiving optimal medical treatment, continue to suffer from refractory angina pectoris.

Results from clinical trials and real-world experience provide strong evidence that the Reducer is safe and effective in providing symptom relief and improving quality of life in these patients who have failed other therapies and continue to suffer from this disabling condition.

Refractory angina pectoris severely impacts patients' quality of life, leaving them with pain and disability. These are common symptoms experienced by patients with coronary artery disease. More than 1.8 million people in the United States suffer from refractory angina pectoris. About 26,000 to 52,000 have Class III or IV angina, resulting in severe limitation in their ability to perform activities of daily living.

Despite advances in new drug and device therapies for treating coronary artery disease, many patients with refractory angina remain severely disabled by this condition.

The population of patients suffering with angina is rapidly growing, as available improvements in cardiovascular care have continued to extend life expectancy without the ability to treat refractory angina symptoms.

The Reducer is a therapy aimed at attenuating the disabling symptoms of angina and subsequently improving quality of life. It was designed to replicate key aspects of a surgical procedure developed by Dr. Claude Beck in 1950 to narrow the coronary sinus. This procedure was done before coronary angioplasty and bypass surgery were even available to treat patients. Dr. Beck's work demonstrated that the success of this procedure was likely driven by elevated coronary sinus pressure, which triggered protective mechanisms that improved perfusion of ischemic territories.

Beck's studies have been duplicated by other surgeons with equally positive results. For example, in a comparative study of 45 patients at Uppsala, 75% of patients treated with Beck's procedure reported complete or significant relief of their symptoms. Additionally, the portion of patients fit for work almost tripled in the treatment arm from 20 to 58%. However, this open chest procedure is too high risk for patients who can't undergo for the revascularization.

We designed the Reducer to replicate Beck's narrowing of the coronary sinus, creating a slight increase in back pressure in the coronary sinus and the small blood vessels of the heart using a minimally invasive catheterization procedure that can be performed on this patient population. This back pressure improves oxygenated blood flow into ischemic areas of the heart.

The Reducer is a balloon-expandable stainless steel device. Inflation of the balloon expands the Reducer to a final profile determined by the inflation pressure of the balloon. The Reducer is an over-the-wire catheter with a unique hourglass shaped balloon. The proximal and distal portions of the balloon have differing diameters to conform to the taper

typically encountered in the coronary sinus. It is available in one single model designed to fit the range of anatomies encountered in most patients. It is compatible with coronary sinus dimensions from 9.5 to 13 mm in diameter at the proximal implant site.

The Reducer is implanted in the coronary sinus, the large vein that drains blood from the heart muscle. The Reducer is implanted 2 to 4 cm distal to the ostium.

The procedure is done under local anesthesia so the patient can be discharged the same day. This procedure is done using a catheter inserted through a small needle puncture in the internal jugular vein, then advanced into the right atrium, then into the coronary sinus.

The Reducer is intended to create a narrowing in the coronary sinus to increase back pressure and redistribute blood flow from non-ischemic myocardium to more ischemic territories of the myocardium 4 to 6 weeks after implant when all but the center portion of the metal mesh is covered with tissue in-growth. This has been shown to relieve symptoms in refractory angina patients and significantly improve their quality of life.

Based on the data we will present today, we are proposing the following indication for use. The Reducer system is intended for patients suffering from refractory angina pectoris despite guideline-directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention. This proposed indication met the criteria for Breakthrough Device Designation. As noted by the Agency at that time, the final indication for our device will depend on the review of the marketing application, and we look forward to receiving any feedback from the Panel today regarding any changes to this proposed indication.

We started approval for the COSIRA study in both the United States and Europe in 2010, which, considering the time, many companies were seeking study approvals outside the United States. We were able to gain approval very quickly in Europe, where we chose

to initiate the study. The Reducer achieved CE mark in 2011 based on first-in-man and initial COSIRA data.

Although approved, we chose not to launch the Reducer until the COSIRA was completed and we had further safety and effectiveness data. The COSIRA final report was completed in November 2014 and we began a limited launch of the Reducer in 2015 in eight countries. Today, the Reducer is distributed in 18 countries. We continue to control distribution due to resources and the challenges of obtaining reimbursement coverage for a new device in Europe.

As part of our postmarket surveillance, we initiated the REDUCER-I study, which is monitored and has an independent CEC adjudication committee and planned 5-year follow-up. In 2017 we received IDE approval for the COSIRA-II study, which is now the basis of our proposed postmarket study.

In October 2018, the Reducer also received right to designation by FDA. This prompted us to consider submitting the device for PMA approval last December based on the volume of the data we had, especially given the focus of the program to provide more timely access of innovative medical devices for patients with unmet needs.

The goal of the Breakthrough Devices Program is to provide patients and healthcare providers timely access to medical devices by speeding up their development, assessment, and review. The program provides sponsors with a high level of interaction with FDA, prioritized review of submissions, and opportunities for flexible clinical study design. Another important feature is the balance of pre- and postmarket data collection allowing for postmarket trials to reduce any uncertainty regarding the device's clinical benefit.

Neovasc has a considerable premarket dataset that consists of a sham-controlled, double-blind, randomized clinical trial that reached statistical significance for its pre-specified primary endpoint. We will also present data from our postmarket observational

study that confirms the effects seen in COSIRA with current follow-up up to 5 years. This is supported with follow-up of first-in-human patients out to 12 years.

Additionally, there is considerable published real-world experience from investigator-initiated studies that further confirm the results seen in COSIRA. We will be presenting data selected from these 50 publications based on reported sample sizes of 40 or more patients.

FDA designated Reducer as a breakthrough device because it has the potential to meet an unmet need in this "no option" patient population.

Consistent with this regulatory strategy to balance data collection for novel breakthrough devices, Neovasc has proposed a robust post-approval study to further confirm the safety and effectiveness of the Reducer. REDUCER-II is a multicenter, randomized, 1:1 ratio, double-blind, sham-controlled clinical trial with up to 500 patients at up to 25 investigational centers in North America; will be randomized and followed at baseline procedure, discharge, 30 days, 90 days, 6 months, 12 months, and annually through 5 years. This will include sites in jurisdictions where the product is not yet approved, as well as select U.S. sites. If requested, patients may be unblinded to their treatment assignment after completion of their 6-month follow-up visit. Patients randomized to the sham-control arm will be allowed, but not required, to cross over to the treatment arm at the 6-month follow-up time point after completion of the study visit, provided they continue to meet all of the inclusion/exclusion criteria and are reevaluated and approved by the central screening eligibility committee.

FDA has published multiple guidance documents addressing innovative breakthrough medical devices and the factors that should be considered to ensure timely access to safe and effective medical devices. This includes the factors to consider when assessing the benefit-risk profile for PMA approval for novel innovative devices.

Neovasc has a considerable premarket dataset that consists of a sham-controlled, double-blind, randomized clinical trial that reached statistical significance. We also have an observational study that confirms the effects seen in COSIRA with current follow-up to 5 years. That is further supported with follow-up of first-in-human patients out to 12 years. Additionally, there is considerable published real-world experience from investigator-initiated studies that further confirm the results seen in COSIRA.

In summary, we believe the Reducer has a favorable benefit-risk profile for the following reasons: We met our primary endpoint for effectiveness, established a safe use profile, and are intending to treat a "no option" patient population with a very poor quality of life with this designated breakthrough device.

In FDA's published guidance on the considerations of uncertainty in determining benefit-risk, they provide examples that are intended to assist in the interpretation in the context of the statutory standard. Example 1(a) discusses a breakthrough device intended to treat a treatment resistant condition. Like that example, Reducer is a breakthrough device that is also intended to treat a treatment resistant condition. In that example, they discuss three scenarios of uncertainty. The greater the level of uncertainty, the greater the reliance on postmarket data collection.

As mentioned previously, Neovasc has proposed a robust postmarket study, the REDUCER-II study. This is also consistent with the regulatory strategy published in 2015 by FDA in a separate guidance entitled "Balancing premarket and postmarket data collection for devices subjected to premarket approval."

We will spend the next 90 minutes presenting the clinical data to support our position that the Reducer has a reasonable assurance of safety and effectiveness, and the benefits clearly outweigh the risks in this "no option" patient population.

Here now is the agenda for the remainder of our presentation. We are very

fortunate today to have this esteemed group of physicians presenting. All external presenters have been compensated for their time. I will now ask Dr. Henry to present on the unmet need in this refractory angina population.

DR. HENRY: Good morning, everyone. I am delighted to be here today. My name is Tim Henry and I'm an interventional cardiologist and currently the director of the Lindner Research Center at The Christ Hospital in Cincinnati. Prior to this, I was director of research at the Minneapolis Heart Institute in Minneapolis, and then chief of cardiology at Cedars-Sinai Medical Center in Los Angeles for the 5 years before coming here.

My presentation today will focus on refractory angina, specifically to describe key aspects of the patient population and importantly, the unmet clinical need. I have personally spent more than 25 years taking care of refractory angina patients and, in fact, I've had a dedicated refractory angina clinic for a long time, almost 2 decades.

As we all know, angina is common in the United States. The American Heart Association, in fact, estimates that there are 8 to 12 million patients with angina. But I want to specifically emphasize that our focus today is on refractory angina, a very specific subset of angina that has a major effect on patients' quality of life and leads to increased healthcare utilization. In fact, frequently, these patients have been referred to as "no option" patients. We talked about patients who have persistent angina and ischemia despite optimal medical management or medical intolerance in patients who are unsuitable for further percutaneous or surgical revascularization.

The most commonly used definition in the literature comes from the European Society of Cardiology, which is quite dated, actually, but it defines refractory angina as at least 3 months of angina due to demonstrated coronary insufficiency that persists despite optimal medical therapy in patients who are no longer amendable to percutaneous or surgical revascularization.

We recently published a manuscript describing four specific phenotypes in refractory angina and I think it's worth reviewing these to just get an idea of the patients we're talking about.

The first patient population in the upper left-hand corner is not the focus of today's presentation. These patients have microvascular angina, so they have minimal coronary disease but still severe angina due to microvascular dysfunction. And certainly, those patients can have refractory angina, but that's not who we're talking about and the ESC definition defined it that you have coronary insufficiency, that these are patients with coronary disease.

So the three phenotypes that are the focus of today are, first, in the left lower quadrant, these are patients who have one or two specific territories at risk that are collateral dependent. So this is the classic CTO patient and many, but not all, may be amenable to revascularization with advanced CTO technology, but these procedures have some risk and 15 to 20% are unsuccessful.

The third patient population in the upper right-panel describes patients who have diffuse thread-like coronary atherosclerosis. This is typical Type 1 or Type 2 diabetics that have diffuse distal and side branch disease that frequently is suboptimal for revascularization or, even if part of the coronary anatomy is amenable, there are territories that because of the diffuse disease are not amenable to revascularization.

And then finally, a fourth phenotype describes patients who have end-stage or advanced coronary disease. These are patients that we all know that have had one or more bypass surgeries, multiple PCIs, often 10 or 12 PCIs, and these are truly end-stage coronary disease patients that no longer have revascularization options and typically, they have areas of ischemia and multiple distributions.

I think reviewing these phenotypes is helpful because it illustrates the heterogeneity

of the refractory angina population.

There are many ways to grade angina, but the most common is the Canadian Cardiovascular Society scale. Most of you are familiar with this, but it's worth reviewing just to focus our attention today.

Class I is angina only with strenuous or prolonged exertion at work or recreation.

Class II is a slight limitation of ordinary activity. These are patients who can walk more than two blocks or more than a flight of stairs and are asymptomatic, but with extensive exertion or maybe with an additional -- after a meal or in cold weather might have angina. But those are not who we're talking about.

Our focus today really starts with Class III patients and it's a very important distinction. These are patients that, despite medical therapy and despite revascularization, have marked limitation of ordinary activity, so walking one or two blocks on the level or walking one flight of stairs precipitates angina. This is a severe limitation in activity.

And finally, Class IV patients are unable to do almost any activity without discomfort and frequently have angina at rest.

I want to emphasize, our focus is on Class III and Class IV angina for the discussion today. And these are patients who frequently have 20, 30 or even more episodes of angina per week.

The prevalence of refractory angina is another important issue and it's very difficult to determine and that's because there are no specific codes and there's limited registry data. So this is actually a figure from a manuscript that we have in press in *Circulation: Cardiovascular Intervention* that should be out, I think, in December, using data from both cardiac catheterization as well as angina populations.

If you start with the overall population of angina in the United States, it's 8 to 10 million. If you start with the cardiac cath lab, roughly 6 to 14% of patients undergoing

cardiac catheterization have coronary disease that's not amenable to revascularization.

Now, if you only include Class III and Class IV angina, it's estimated that this patient population is about 600,000 to 1.3 million. But I will point out that of the Class III/Class IV, most of those patients have an acute coronary syndrome or are not amenable for revascularization.

So finally, when you get to this point where you have stable coronary disease, not candidates for revascularization, Class III and Class IV angina and then with the additional greater than seven episodes a week, which is frequently used in clinical trials for enrollment purposes, this is a very specific population that we estimate to be between 26,000 and 52,000 patients a year, which is basically an orphan population.

So it's important to reiterate, there's no specific codes for refractory angina and only a limited number of registries. Therefore, it is challenging to know the total number. But clearly this is one of the major challenges in caring for these patients, that it's really difficult to know the total number.

In regards to the natural history of the disease, I'll use data from our dedicated refractory angina clinic that we published in the *European Heart Journal*. It's now a prospective registry that includes more than 2,000 patients.

In contrast to the previous historical data, we published this data in the *European Heart Journal* that indicates the actual mortality for the population is about 3 to 4% per year. It's a little higher when you include only Class III and Class IV, but even for Class III and Class IV patients, it's only about 5 to 6% per year. So this contemporary natural history data is not much higher in patients with stable coronary disease or age-matched controls.

So the issue is not mortality so much as it is these patients are left with severe limitations in their quality of life and have a significant increase in healthcare utilization. So from my perspective, it's very important to practice a patient-centered health assessment

approach. Measuring success of the therapy needs to focus on relieving symptoms, improving quality of life and functional capacity.

This is more data from our dedicated refractory angina clinic to provide some insights into the baseline characteristics of refractory angina patients. Whereas many of these patients have been smokers in the past, the majority have stopped smoking and current smoking is only roughly 10 to 15%. These are typically patients who are extremely well treated with both secondary prevention medications and antianginal medications. And in fact, the group we're talking about, by definition, has to have failed standard medical therapy.

About 30 to 40% of the population is diabetic. This has been consistent in clinical trials and registries. About 30% will have a history of heart failure. About 75% have a history of a previous myocardial infarction.

And in terms of revascularization, 70 to 80% of patients will have previous CABG or previous PCI. And if you consider any revascularization, it's over 90%. Of course, this depends a little bit on whether you include microvascular angina phenotype in your registry, but even if you only include patients with coronary disease, there are a few patients, for example, severe diabetics that might have never had revascularizations. Clearly, for sure, more than 90% will have had previous revascularization and the majority will have multiple procedures.

If you look at mortality, and I think I alluded to it, but to really emphasize again, the mortality at 5 years was only 17% and two-thirds of those deaths were cardiovascular in nature, so that means one-third were non-cardiovascular. And again, as we noted before, this is only slightly higher than stable coronary disease. So clearly, while we've made progress in reducing mortality, the challenge is to manage the debilitating symptoms.

Standard therapy for angina in the United States includes antianginals, beta blockers

and calcium channel blockers, short-acting nitrates, and ranolazine. These are frequently used in a stepwise manner, but often they're not well tolerated either due to side effects or relative hypotension, and it's rare that someone actually tolerates all four. And the average in clinical trials is about two and a half or so.

Another key factor in the medical treatment is secondary prevention with antiplatelet therapy, lipid-lowering agents, and blood pressure control, and it's a very important aspect of treatment of these patients.

And then finally, we have revascularization, which includes both percutaneous and surgical revascularization, both of which have improved over time, including new aggressive approaches to chronic total occlusion and certainly that's helped our therapy.

So these are the standard therapies for angina, which actually work quite well, and we've clearly made progress overall in the treatment of angina.

So it's important to emphasize again, the patients we're talking about today have Class III and Class IV angina despite secondary prevention, despite optimal antianginal therapy, and despite revascularization. They are suboptimal or unsuitable for revascularization for a variety of reasons. These are truly "no option" patients.

So what is available for these patients in the United States? Really, only two treatments. EECP, most of you are familiar with EECP, these are leg cuffs that we put on that sequentially inflate during diastole and then deflate during systole. And this is physiology similar to an intra-aortic balloon pump, it was approved more than 20 years ago, and the only randomized trial was the MUST-EECP trial, which was -- did include a sham procedure, it enrolled 137 patients and, in fact, only 116 were in the per-protocol analysis.

The problem, of course, with EECP is availability. It requires thirty-five 1-hour sessions 5 days a week for 7 weeks, so it's a significant time commitment and frequently, in my experience, it's logistically difficult because people have difficulty driving every day to

get to where an EECP therapy is. So there's limited availability for many patients in the United States. In addition, most of the patients that we're talking about have already had one or more EECP courses of therapy.

The second approved therapy for refractory angina in the United States is transmyocardial laser revascularization, or TMR, so this is laser treatment to create small channels in the myocardium to promote blood supply from the LV cavity. So TMR is infrequently used currently because of concerns over morbidity and mortality in the patient population. And again, there's limited availability and very little TMR is actually being done in the United States, at least standalone TMR is being done at this time.

So both of these therapies have limitations and again, I'll emphasize it's been more than 20 years since there's been a therapy approved for the treatment of refractory angina.

So today Dr. Stone will present data on a one and two CCS class improvement. So I'd like to at least spend a moment on the clinical relevance of this level of improvement.

Certainly, a two-class improvement in angina, going from Class IV to Class II or from Class III to Class I, is a significant improvement in quality of life. Really, an improvement of two classes enables the patient to be able to go back to work, to care for themselves, to do their activities of daily living, spend time with their children, it's really a major improvement in the quality of life. And I think our goal, when you take care of refractory angina patients, is to actually ideally get back to Class I or Class II where they can have a near normal or active life and it's unlikely that we'll ever really make patients completely angina free, but our goal is to actually improve by at least one class and ideally, two classes. So I think this is a clinically meaningful definition in improvement.

In summary, patients who have refractory angina or "no option" patients are a very specific subset of angina with severe limitations in quality of life and high healthcare utilization. These patients, unfortunately, have very limited treatment options in the

United States at this time; they are severely disabled and are a very challenging patient population to care for.

Thank you very much for your time and next, Dr. Shmuel Banai will discuss the mechanism of action for the Reducer.

DR. BANAI: Good morning, my name is Shmuel Banai and I am the medical director for Neovasc. I'm also the director of the Division of Cardiology at the Tel Aviv Medical Center, Professor of Cardiology at the Tel Aviv University School of Medicine. Additionally, I am the head of the Center for Cardiac Research and Biomedical Engineering at the Tel Aviv University. Today I will share with you the Reducer mechanism of action.

This is a schematic illustration of the full thickness of the left ventricular wall. At the top is the epicardial coronary artery and the epicardium, and at the bottom, the endocardial layers of the myocardium and the adjacent left ventricular cavity. The arrows on the left indicate blood flow into the myocardium.

In the normal healthy heart, blood flow in the subendocardial layers of the myocardium is higher than in the subepicardial layers of the myocardium. During exercise and increased demand, the physiologic compensatory mechanism causes selective sympathetically mediated vessel constriction and increased resistance to flow in the subepicardial blood vessels, favoring subendocardial perfusion and allowing an appropriate augmented contractility. This increased demand and augmented blood flow is represented by the larger arrow on the left of the illustration. As a result, in the healthy heart the ratio of endocardial to epicardial blood flow is approximately 1.2:1 due to preferential dilation of the subendocardial arterioles, causing a larger diastolic flow through the subendocardium. In other words, in the normal heart, the subendocardium receives approximately 20% of blood flow.

In contrast, in the ischemic heart, as represented here with yellow obstructive

plaque in the epicardial coronary artery, the situation changes. The subendocardium is more vulnerable to ischemia than the subepicardium. The compensatory mechanism I told you about, which normally preserves preferential blood flow through the subendocardial myocardium, becomes dysfunctional and the transmyocardial perfusion is redistributed towards the subepicardial layers of the ventricle, represented here by the larger arrow directing into the subepicardium. Resistance to flow in the subendocardial layers of the myocardium is increased and the endocardial to epicardial blood flow ratio becomes abnormal and falls from 1.2 at baseline to 0.5.

As a result, the perfusion of the subendocardium during exercise becomes compromised, causing ischemia, impaired contractility, and elevated left ventricular end-diastolic pressure, which compresses further on the subendocardial blood vessels, thereby exacerbating ischemia. This creates a vicious cycle of ischemia. Exercise-induced ischemia leads to anginal symptoms. Reduced left ventricular contractility with increased left ventricular end-diastolic pressure results in shortness of breath.

The mechanism of action presented here is based on animal research using ischemic heart model with and without elevating coronary sinus pressure. When the Reducer is implanted in the coronary sinus of an ischemic heart and after the device is fully covered with tissue in-growth, it elevates backward venous pressure which results in redistribution of blood into the ischemic subendocardium, breaking this vicious cycle of ischemia. Elevating backward pressure results in a slight dilation of the diameter of arterioles and leads to a reduction of vascular resistance in the subendocardium with a subsequent normalization of the endocardial to epicardial blood flow ratio back to 1.2 that drives blood flow back into the ischemic subendocardium.

Consequently, blood flow in the ischemic subendocardial layers of the myocardium is enhanced, contractility improves, and left ventricular end-diastolic pressure decreases. This

breaks the vicious cycle of ischemia, improves left ventricular contractility with reduction of left ventricular end-diastolic pressure, and improves exercise-induced shortness of breath. Improvement of subendocardial blood flow leads to improvement of angina symptoms.

In summary, by increasing coronary sinus pressure, the Reducer restores the endocardial to epicardial blood flow ratio to normal, improves blood flow to the ischemic subendocardium, increases left ventricular contractility, and reduces left ventricular end-diastolic pressure.

Thank you. I will now turn the presentation over to Dr. Victoria Hampshire.

DR. HAMPSHIRE: Thank you, Dr. Banai. My name is Victoria Hampshire, I'm a veterinarian by training and I've spent the last 30 years in animal research support in the evaluation of medical devices. For the first 10 years of my career I was on the front lines of research support at the NIH for cardiovascular and other animal models coming through the research pipeline. I then transferred to the FDA and worked there for 15 years. Five years were spent at the Center for Veterinary Medicine as the chief safety officer overseeing post-marketed veterinary products, and the last 10 at the Center for Devices and Radiological Health in the Division of Cardiovascular Devices. In 2015 I left the federal government to start a preclinical consulting company, where I've been busy helping dozens of companies at all phases of animal study design, conduct, and reporting. I've been working with Neovasc for the past 5 years to help communicate the totality of their animal data to the FDA. I'm very happy to be here today to speak to the preclinical animal data for the Reducer.

From 2002 to 2009, Neovasc conducted three animal studies using pig models. Two were pilot animal studies that evaluated the Reducer in 39 pigs. The pivotal study evaluated the Reducer in 13 pigs. Four pigs were studied acutely and two pigs were studied at 24 hours. The remaining seven pigs were studied chronically between 57 days and as

late as 140 days. This subset of pigs had survived the index procedure of the Reducer implant and went on to their respective endpoint where terminal end-life assessments and pathology from their tissues was obtained for evaluation.

The evaluators of these studies included an internationally recognized cardiologist; two highly experienced interventionalists; and three board certified pathologists, one human and two veterinary. Each evaluator independently reported similar findings.

Although not strictly GLP, these studies were undertaken using protocols and standard operating procedures that included modern methods of humane animal experimentation. They were conducted at experienced and respected international animal facilities by trained support personnel, and they were consistent with the level of preclinical research typically conducted for first-in-man or breakthrough technology.

Importantly, formalin-fixed heart and histologic assessments critical to the questions raised by FDA were provided by independent examiners at GLP pathology laboratories in the United States.

The in-life and afterlife methods include sophisticated preoperative preparation, interventional procedures and monitoring, imaging, echocardiographic and angiographic assessment, performance and handling assessment, and gross and histological processing.

To begin summarizing, critical to some of the questions today is an understanding of some key anatomic differences of quadrupeds that are available for an implant the size of the Reducer, including pigs.

Here on the left is a human image showing the human right coronary artery circulation as compared to the latex-perfused circulation in the pig heart on the right. Viewers can see that the pig and also, by the way, other quadrupeds have impressive azygos vein contribution to the right heart circulation which is not present in humans. This vein drains the four legs.

Please remember today that any pressure reports for swine outcomes are useful but not necessarily translational to humans because of these anatomic differences. The 6-month outcome of the pressure gradient across the coronary sinus in the pig is not concerning and in point of fact, was a bit of a favorable finding considering this anatomic difference.

Now, turning to the data that FDA did receive, the FDA was provided with final study reports and a final pathology report. For the pivotal animal study, the FDA was also provided source records containing data and information from implants, Reducer delivery system performance, and a final pathology report. This report contained macroscopic and microscopic data from the chronic animal subset of seven pigs. The Reducers were sectioned at three levels, proximal, mid, and distal, and were evaluated by light microscopy and histomorphometry.

This slide shows a variety of imaging data provided in the animal study report to the FDA. Before I describe this slide, I would like to clarify that the animal pathologist calls the inflow proximal because it is deeper inside the heart. The clinician, however, calls the outflow of the heart that is towards the right atrium proximal because it is closer to the ostium of the coronary sinus. The wider end of the Reducer, which is closer to the ostium, is proximal.

Neovasc did submit a variety of other imaging information to the FDA from the final pivotal animal study and in the final study report, beginning with angiographic documentation in-life and implant showing the Reducer deployed within the midsection, prominently demonstrative of the luminal restriction, and then again by macroscopic means at the terminal endpoint shown here in the middle, also taken from the final study report. In turn, there were also faxitron images to show preservation of stent integrity, and below the explanted preserved imprint of the Reducer from the pathology report.

The summary of the findings concluded that there was acceptable regional tissue-contacting gross pathology and histology with absence of migration and perforation. There was a hundred percent 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 very 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. Notably, these findings do support the mechanism of action of the Reducer.

Implantation of the Reducer is performed with an intentionally approximate 10% over-sizing of both wide ends of the device. Over-sizing is important and helps to achieve two goals. First, to anchor the elastic vessel wall to help prevent migration and trigger a process of tissue proliferation which is observable at 57 to 140 days after implantation, and covers the gaps between the middle struts. This aligns the data from preclinical feasibility studies.

Second, since the narrow central part of the device is not in direct contact with the vessel wall, there is no trigger for significant tissue overgrowth at this point and therefore the vessel lumen at the center of the device remains patent. In fact, the proliferative process is less intense and sometimes absent in the midsection of the Reducer. Any neointimal coverage of the midsection is the result of encroachment from either end, proximal or distal. Thus, embedding both wide ends of the Reducer in tissue is sufficient to create a tube-shaped narrowing even when the center struts are not fully endothelialized. The tube-shaped narrowing also establishes a mechanism for a pressure gradient across the narrow center of the device, which is consistent with the mechanism of action reported in the feasibility studies and in the literature.

And the totality of the histologic data is consistent with the postulated mechanism of action. Overall, the preclinical studies demonstrate acceptable in vivo performance for introduction, location, target anatomy, deployment, angiographic visualization, and delivery system of the device. Additionally, the histology of the device is acceptable for all inflammation and injury criteria.

Thank you for your attention to this important preclinical data. I am now going to turn over a few minutes of time to Dr. Rousselle, the study pathologist, to go over with the Panel the details about endothelialization so that everyone who is not a pathologist will understand the information before them on that particular topic.

Dr. Rousselle.

DR. ROUSSELLE: Thank you, Dr. Hampshire. My name is Serge Rousselle and I'm a board certified veterinary pathologist and have done medical device safety assessment for the last 20 years. I was involved in evaluations in some of the studies that are discussed here today.

On this slide we're showing the Reducer midsection and the final pathologist's report makes a distinction between coronary sinus luminal coverage, which was 100% endothelialized, and Reducer midsection struts, which were no more than 60% endothelialized. In the image on the slide there are two profiles visible, one delineating the sinus profile in pale blue and the other delineating the Reducer profile. Both outlines have importance in this model and the scoring of these two features for endothelial coverage was intended to provide a higher level of data granularity. The data demonstrated that the sinus lumen tissue was fully endothelialized and the device was also endothelialized wherever it is in contact with the host tissue, as expected.

This slide represents two cases of the most advanced tissue integration of the device for Animal 1111 and the least advanced integration at the mid-level in Animal 1035. The

top example clearly demonstrates that as the device becomes fully integrated, there is growing neointimal formation, visually estimated at about 30% in this case, which reduces the lumen commensurately.

In the lower case, the sinus lumen remains open. Nonetheless, reduction of the lumen is evident for the combination of slight neointimal formation and frame of structure, visually estimated here at 5 to 10%.

The negative restenosis values that were presented in the pathology report resulted from an artifact of calculation, i.e., a reduction of device lumen relative to sinus lumen. The calculation of sinus lumen restenosis, so sinus lumen compared to original sinus profile, would deliver positive values at all mid-levels regardless of -- studies.

Thank you for your time. I'll now turn the presentation over to Dr. Stone.

DR. STONE: Well, hello, everybody. I'm Gregg Stone from the Mount Sinai Heart Health System, and it's a pleasure to be able to speak to you today. I'm going to go over the detailed study design for the Reducer studies that we completed to date, including the sham-controlled, randomized COSIRA data, and go over the principal safety and effectiveness outcomes. Specially, I'm going to focus primarily on three different datasets. First, a small first-in-human study, which was a prospective, open-label, multicenter feasibility study of 15 patients at three sites, and I'll use that mostly to look at the very long-term data. I'm going to spend most of the time emphasizing the results from the COSIRA trial. This was a prospective, randomized, double-blind, sham-controlled, multicenter trial in 104 patients at 11 sites. And as, of course, this Committee well knows, it's relatively unusual to have sham-controlled trials in interventional cardiology, so I'll be emphasizing all aspects of that important nature of the study. I'll also talk to you about the REDUCER-I study, this was a single-arm postmarket observational study, to date, in 241 patients at 20 sites with enrollment ongoing.

So let's really start with the COSIRA sham-controlled randomized trial. This was a study that began with 104 patients with refractory angina, and I'll describe the inclusion and exclusion criteria. At baseline, once patients passed screening, they had detailed assessments, of course, of angina status, their demographics, EKG, exercise tolerance was assessed, they had a Seattle Angina Questionnaire performed in addition to their assessment of the severity of angina by the Canadian Cardiovascular Society classification. They had a SPECT thallium performed, they had a dobutamine stress echo, and there were other imaging subset studies, as well.

Patients then underwent their final qualification during cardiac catheterization, at which time coronary sinus angiography was performed, and if the coronary sinus met the criteria for inclusion in the trial, which I will also describe, then they were randomized in a blinded manner 1:1 to either Reducer implantation or control. And I'll describe, again, the procedures that were put in place for the sham control.

Patients, after the procedure, were then followed up at 30 days, 3 months, and at 6 months. The study concluded at 6 months, at which time there was a comprehensive reevaluation done in addition to clinical outcomes, as well as repeat exercise testing. The study was assessed over time by independent blinded physicians who performed the pre- and post-procedure angina assessments both for the CCS scale and Seattle Angina Questionnaire, and I'll describe some of the blinding processes.

So patients were enrolled in COSIRA who were 18 years or greater age, who had symptomatic coronary disease with chronic refractory angina pectoris defined as Canadian Cardiovascular Class III or IV angina, despite attempted optimal medical therapy for at least 30 days prior to screening. These patients also had to have had limited treatment options for revascularization by either bypass surgery or PCI, as determined by the investigator, with evidence of reversible ischemia attributed to the left coronary artery system by

dobutamine echo.

The key exclusion criteria were unstable angina during the 30 days prior to the screening period, acute coronary syndrome within 3 months, a successful PCI or CABG within 6 months, decompensated heart failure or hospitalization for heart failure within 3 months, and arrhythmia that would require a defibrillator or a pacemaker or a defibrillator or a pacemaker electrode in their right atrium, right ventricle, or coronary sinus.

On the table, as I mentioned, coronary sinus venography was performed and patients were excluded if they had anomalous or an abnormal coronary sinus; for example, if the coronary sinus was excessively tortuous, had aberrant branches, if it was a left-sided SVC, etc., or more importantly, if the coronary sinus diameter at the site of the planned Reducer implantation was either less than 9.5 mm or greater than 13 mm in diameter.

Now, the primary effectiveness endpoint of COSIRA was the improvement in two or more CCS angina classes from baseline to the 6-month post-procedure evaluation. So let me go over the CCS angina class and explain a little bit why this was chosen as the primary endpoint.

So CCS angina Class IV is severe limitation, either angina at rest or basically angina with any activities at all. CCS III is marked limitation with symptoms of angina with everyday living activities, so most activities would cause angina, but not at rest. Class II would be slight limitation with angina during ordinary activities, so that might be, for example, during washing dishes or walking briskly. And Class I would be angina only during strenuous or prolonged physical activities, so almost no angina, but you could induce angina.

So there obviously can be some variability in the assessment of the determination of what is Class III or Class IV. So for the primary endpoint, this is a very clinically relevant classification system, the most widely used classification system still today for angina

assessment, and a two-class or greater reduction in angina was chosen because this is really a marked reduction in angina for which there really can't be that much question.

So for example, if the patient -- as you'll see, only patients with Class III and IV angina were allowed to be enrolled in the trial. So if the patient had Class IV angina where they were basically having rest angina or with any exertion at all, they had to reduce their angina to this fact where they are having almost no angina or only to the extent where they could still perform their daily activities. If the patients had Class III angina at baseline, they had to be reduced to almost no angina. So it's really a marked reduction in angina for the primary endpoint of this study.

There were multiple secondary effectiveness endpoints and these were not powered endpoints. The primary endpoint was powered, the secondary effectiveness endpoints were not. This was to look at improvement of one or more CCS angina class, exercise tolerance testing parameters changes, dobutamine echo wall motion score index, and Seattle Angina Questionnaire five-domain improvements. And again, the trial importantly was not powered to demonstrate improvement in any of these objective evidence of myocardial ischemia, it would've required greater than 200 patients for such a reduction. So really, you're just looking to see if there were trends present and these were really hypothesis-generating endpoints.

There were two major safety endpoints that were pre-specified, these were not powered endpoints, either, but periprocedural serious adverse events defined as the composite of death, myocardial infarction, cardiac tamponade, life-threatening ventricular arrhythmias, and respiratory failure through 30 days. This would also include a clinically driven re-dilation of a failed Reducer in the Reducer arm.

And then there were major adverse events, which someone called MACE, and that's the composite of cardiac death, major stroke or myocardial infarction through hospital

discharge and then at 30 days, 3 months, and at 6 months.

So in COSIRA, all patients were -- in addition to their maximally tolerated antianginal agents, all patients were pretreated with dual antiplatelet therapy, which was continued for 6 months. The Reducer patients, in addition, received either heparin or bivalirudin in the cath lab, where that was not administered to the placebo-treated -- or the sham-control treated patients.

So these were the measures that were put in place to ensure blinding. The physicians that were performing the implant or the sham procedure, of course, they were unblinded, but they were instructed before the procedure to behave in the exact same manner in both groups with a script that was discussed ahead of time.

The Sponsor was present for all these cases and ensured that the patients were either wearing headphones playing music or that the patients were heavily sedated, that is essentially unconscious, throughout the procedure.

The randomizations were opened -- the randomization envelopes were opened in the control room, not the catheterization laboratory, so if there was any discussion it was only in the control room.

The patients were aseptically draped and the way that the Reducer is put in required draping the patient's face and so the patients actually couldn't see the monitor throughout the entire procedure, again, even if the patient was at all awake.

The study personnel performing the follow-up Canadian Cardiovascular Society class and Seattle Angina Questionnaire assessments were blinded to randomization. The dobutamine echo and stress test core laboratories were blinded to randomization, and the CEC and the DSMB were blinded to randomization.

So let's talk about now the effectiveness results, and I'm going to talk about effectiveness of COSIRA and then other studies and then we'll transition over to safety.

So overall, 166 patients were consented. Of that, 107 met the clinical inclusion and exclusion criteria. Three patients did not meet the angiographic criteria and so 104 patients were ultimately randomized, 52 to the Reducer and 52 to no Reducer. Six-month follow-up was complete in essentially all patients, 104 patients. One patient in the control arm died, which is why it says 103 here, but it was essentially completed on all patients.

So this is what these patients with refractory angina looked like. Their mean age was about 68 years. Approximately 80% of the patients were male, about 85% of the patients were Caucasian, and they were mildly obese. Approximately 80% of the patients had Class III angina, where approximately 20% had Class IV angina. As would be expected, these patients had complex coronary artery disease, more than half of the patients had a prior myocardial infarction, and almost all the patients has prior PCIs, often multiple prior PCIs, and prior bypass surgery.

Diabetes was present in about 45% of the patients. About half the patients were smokers. Almost all had hypercholesteremia. Most had hypertension and a very high incidence of family history of cardiovascular disease.

Looking at the antianginal medications, you can see that there were high usage rates of beta blockers, calcium blockers, nitrates. Again, the goal was the patients were to be treated with as many antianginal medications that they could tolerate at maximal doses. There was also scattered use of nicroandil, ivabradine, and ranolazine. You can see the number of antianginal medications that patients were taking and approximately 70% of the patients were taking two or more antianginal medications.

So there were high rates of technical and procedural success achieved with the COSIRA implant, with the Reducer implant in COSIRA. Fifty of the 52 were successfully implanted, that's a 96.2% rate. In the two that could not be implanted, there was inadequate guide catheter support, so the patients were treated medically and no

complications occurred in those patients.

So the procedural successes were among those that had implants, that had no acute need for clinically driven intervention to address an adverse event or a serious adverse device-related event prior to discharge, and that was 100% or 50 of 50 implanted patients.

So this is the primary endpoint in COSIRA, which is an improvement in two or more CCS angina classes from baseline to 6 months, and we show you here on the left the intention-to-treat population, 52 versus 52 patients, and on the right the as-treated population, which is 50 Reducer implants versus 54 no Reducer implants.

You can see by intention to treat that 35% of the Reducer patients had a two or more CCS angina class improvement over 6 months compared to 15% of the sham-control group. That's a difference of approximately 19%. You can see that was a statistically significant difference. The number needed to treat to improve one patient by two or more CCS angina classes was about five. You can see the as-treated results were similar, if anything, slightly stronger.

Now, this is an important slide which shows the time course of the improvement in two or more CCS angina classes, and this not only speaks to the mechanism of the Reducer, but it also speaks to blinding and placebo effects. As you heard from Dr. Banai, we expect the Reducer to become active, if you will, in about 6 to 8 weeks as it endothelializes. At 30 days, there was no significant difference in the percentage of patients that had a two or greater CCS angina class improvement, 13.5% versus 11.8%. So I would most likely attribute this to a placebo effect that was present in both arms, with no significant difference. And again, we wouldn't expect there to be complete endothelialization at 30 days yet.

But at 3 months and at 6 months you can see that there are now differences that favor the Reducer arm, which becomes statistically significant by 6 months. You can also see that the control arm basically preserves the rate of improvement of two or more CCS

angina classes, whereas the Reducer arm continues to increase.

So to me, again, I think this is consistent with both the timing of the mechanism of action of the Reducer, that is when it endothelializes between 6 and 8 weeks. It's also consistent with the early modest placebo effect in both groups. It also shows that that placebo effect in the control group was likely continued over 6 months, suggesting that those patients were not unblinded, otherwise I would've expected that they would lose that placebo effect. So I think this important slide again points to both the mechanism and the timing of the effect, as well as the success in the sham-controlled randomized trial.

Now, the study was only 104 patients, so we don't have a lot of power to look at subgroups, but these were five pre-specified subgroups based on LVEF, CABG, diabetes, sex, and age, and if you just look basically over to the right you can see that there were no significant interactions between any of the subgroups and the primary endpoint effectiveness outcome.

Looking at now some of the hypothesis-generating secondary endpoints, improvement in one or more CCS angina class was also substantially better in the Reducer arm than in control. And here you can see approximately 71 to 72% of the Reducer patients improved by one or more CCS angina class compared to 42% of control patients. The number needed to treat therefore to incrementally benefit one treated patient with a reduction in angina was only about three and a half patients.

Here are all the different angina classes. You can see red is IV, yellow is III, blue is II, green is I, gray is no angina. All the patients had Class III or IV angina at baseline, and if you just look at kind of the blue and the green, you can see the improvement at 6-month follow-up.

So this slide shows, again, overall changes in angina class, and if you look to the right you can see we've got the Reducer treatment in the dark bars and the sham-control group

in the light bars. You can see the greater than or equal to two-class improvement, those are the data that I already showed you. The third set of bars are exactly one-class improvement and that favored the Reducer group. Looking at no change, that favored the Reducer group in a positive way. Fewer patients didn't change. And if you looked at one-class worsening, that's the set of bars over to the left, you could see that fewer patients had worsening angina that were treated with the Reducer compared to the sham control.

This slide shows the Seattle Angina Questionnaire and, as you know, there's five domains that were assessed here, quality of life, angina stability, angina frequency, physical limitations, and treatment satisfaction. And this slide is showing the change in each of those domains from baseline to 6 months.

Again, we were not powered to show differences in these domains, so these are hypothesized -- hypothesis-generating data. But you can see there actually was a statistically significant improvement in quality of life in the Reducer-treated patients compared to the sham-control treated patients, and there were directional improvements in angina stability and angina frequency, consistent with the primary endpoint results. Physical limitation, again, in the right direction, but the improvements were smaller. And treatment satisfactions were actually relatively high in both groups beforehand and there is no difference between the two groups at 6 months.

Now we go to some of the, again, hypothesis-generating underpowered exercise test data. You can see here -- and for time, I'm just going to show you some selected data, but here if you can look at the exercise testing, which was bicycle ergometry done by the ACIP protocol. You can see the Reducer from baseline to 6 months, those patients had on average a 65-second improvement in exercise time, whereas the control patients basically had absolutely no difference in exercise time from baseline to follow-up, and this trend did not quite reach statistical significance.

Here we look at the dobutamine stress wall motion score index, a negative number here is a better number. This is looking at the change from baseline to 6 months and you can see the Reducer treatment, in the dark bars, tended to have a greater change in wall motion score compared to the sham control. If you look at the right set of bars, that's probably the most relevant set because that is just in the left coronary artery distribution, which is really the major blood flow egress the Reducer would impact. Here you can see there tended to be a doubling of the improvement in the wall motion score, but again, these numbers aren't close to what was needed for statistical significance and so these values are NS but it is, again, suggestive.

So now let me go and look at the post-approval REDUCER-I study and look at the effectiveness outcomes here. There were actually three different cohorts of patients that were included in REDUCER-I. This whole experience would be up to 400 subjects, it's currently enrolling. Two hundred forty-one patients were enrolled as of March 12th for which we have the data on. The prospective arm, if you will, of REDUCER-I is called Arm 1 and these are new Reducer patients that were included in this formal study. These patients had similar inclusion and exclusion criteria as the COSIRA randomized trial, but it did also allow CCS Class II patients to be enrolled.

The Arm 2 patients, there were 11 patients where the patients in COSIRA were actually consented and were followed long term in this registry because this is a long-term registry.

And then there was Arm 3, which were patients implanted under CE mark before this formal REDUCER-I registry started. Those patients were also consented and added to the REDUCER-I observational study.

So overall, 241 patients; and these patients underwent assessment at baseline for the procedural outcomes, 30 days, 6 months, and then annual follow-up through 5 years.

And all their adverse events were adjudicated by a clinical events committee.

So if we compare the REDUCER-I patients in the middle set of data to the COSIRA Reducer arm patients, these 241 patients, you can actually see their demographics were very similar in terms of their age, their sex, about 20% women. Again, half prior MI. Almost all had prior revascularization procedures. You can see the biggest difference here is that we now have about 29% of the patients in REDUCER-I had Class II angina, whereas in COSIRA they all had Class III or IV angina. But again, diabetes, smoking, hypercholesteremia, hypertension, very similar.

Now, these are the outcomes data, this is just now the REDUCER-I study. These are patients that had at least one CCS class angina improvement, and these are paired data. Given the data that's available from baseline to 6 months, baseline to 12 months, and baseline to 2 years, you can see the number of patients. And if we just focus here on -- let's start with a one-class or more improvement in angina, you can see that it starts at 70% at 6 months and it slightly increases to 82% at 2 years. If you look at greater than or equal to two-class improvement, it's 24% at 6 months and it slightly increases to 31% at 2 years.

Now, if you look overall here at comparing these data to COSIRA, you can see we've got baseline and 6 months and the upper set is COSIRA and the lower set is the REDUCER-I. But for here we've just done the REDUCER-I and Class III or IV patients. And so if you focus on the dark set of bars, that might be the best way to go, now you're looking at Reducer to Reducer, you can see here that looking at the Class III/IV patients only for REDUCER-I at baseline, 93% of those were Class III, 7% were Class IV, and you can see that the Class I, II, III, IV at 6-month follow-up, 30% and 44% respectively were Class I and Class II, and these are really very similar to what we saw in the Reducer arm in the sham-controlled COSIRA trial. Slightly less Class IVs in Reducer compared to COSIRA. That might be because there were less Class IVs in REDUCER-I compared to COSIRA.

And again, these are all now the angina data on all angina classes in just REDUCER-I, all the way out through 5 years now. You can see, once we get to 3, 4, and 5 years, the number of patients start to get small, but these are all the data. And if you focus again on the -- I think the blue and the green segments of the bars, that's the Class I and Class II angina, you can see that the vast majority of the patients have Class I and Class II angina and you can get a sense that there seems to be a persistent effect all the way through 5-year follow-up.

This slide looks at, again, REDUCER-I but only the Class III or IV angina patients at baseline. This is the group, of course, that we're looking for labeling for, the ones who can really benefit the most from the Reducer. So if you look at these patients at baseline, of course, they all had Class III or IV angina and now you can see in Class I all the way out through 5 years approximately 10 to 20% of the patients had Class III or IV angina. So approximately 80% of these patients no longer have Class III or IV angina after Reducer implant. And of course, this is open label compared to COSIRA, that is its limitation, but nonetheless it looks quite effective.

Looking at the Seattle Angina Questionnaire assessments that were made in Reducer, this is the prospective arm only, they're the ones who got the Seattle Angina Questionnaire and you can see the improvements in -- now using the patient as their own control from baseline to 6 months, you can see substantial improvements in all five domains, quality of life, angina stability and angina frequency, with somewhat less improvements, but still highly statistically significant, in physical limitations and treatment satisfaction.

Going now just to the Class III or IV angina patients and thus comparing the COSIRA SAQ scores to the REDUCER-I SAQ scores, this is all Class III or IV in both groups, so it is apples to apples, you can see the data look actually very similar. You can see, remember in

COSIRA, there was a statistically significant improvement in quality of life. You can see a substantial improvement in quality of life in REDUCER-I from baseline to 6 months with the Reducer, as well, and you can see in all of the domains the outcomes tend to be greater in both studies with the Reducer. Perhaps the one exception is treatment satisfaction, which again tends to be high. So the patients were basically reasonably treated, that their doctors were doing a good job, as good as could be done at baseline; hard to improve that, but there was a little bit of improvement with Reducer treatment in both groups.

An interesting metric that was collected in the prospective arm of REDUCER-I is to look to see if there was a reduction in emergency department visits and you can see here, before the Reducer was implanted in these 113 patients, that they've now reached the 1-year post-Reducer implant, they were having an average of 0.7 emergency department visits per year and that was reduced to 0.2 within 1 year after the Reducer, a highly statistically significant number. So basically, it was 42% of the patients had visited the ER before the Reducer and now it's reduced to 13% after the Reducer, a total of 78 ED visits compared to 22 after the Reducer.

In addition to this data that I've shown you, there have been other investigator sponsored separate studies that have been reported and I show you now unselected data, all the studies that have been published with 39 or more patients in which they reported CCS angina class. If you look at the dark bars, the first set is COSIRA treatment with the Reducer, looking at a two or more greater CCS angina class at 6 months. Remember, that was 35%. In REDUCER-I, it was 24%. But again, probably a little less because there were Class II patients enrolled. If you look, though, at these other studies at 6 months, 14 months, 18 months, and 2 years respectively, you can see 36 to 50% improvements in two CCS angina classes.

This is the same data, same studies, now looking at one or more CCS angina class

improvement and you can see that's about 70% in both the COSIRA treatment group and the REDUCER-I implant group studies, and that Class I is about 76 to 85% in the four investigator separately reported studies. So again, consistent effectiveness.

And you see the same thing if you look at the Seattle Angina Questionnaire improvements. You can see the improvements in both the treatment arm of the COSIRA trial and the REDUCER-I study and similar or slightly greater improvements in the investigator reported studies.

So if I was going to summarize the results of effectiveness about the Reducer implant, most importantly, the sham-controlled COSIRA trial met its primary pre-specified powered endpoint. 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, statistically significant with a number needed to treat of about five patients, which is quite a low number, as you know.

The secondary non-powered endpoints were directionally supportive of the primary effectiveness results. The open-label REDUCER-I study demonstrated effectiveness with sustained response during long-term follow-up and the results were consistent in the COSIRA, REDUCER-I, and independent investigator-led studies.

So now let's look at the safety results. I remind you about the two pre-specified COSIRA safety endpoints, I won't read them again. These were not powered endpoints but were pre-specified.

So if we look to start at all serious adverse events within 6 months that were reported from the COSIRA study, in the Reducer group there were six patients or 12% that experienced one or more SAEs, a total of 10 SAEs. In the no Reducer group there were 11 patients or 20.4% of patients that experienced a total of 24 SAEs. So this trend towards fewer SAEs in the Reducer group was not statistically significant, but you could see it was

more than a 50% reduction in the number of SAEs with the Reducer compared to no Reducer.

If we look at the timing of the SAE reports, the first pre-specified safety endpoint was these SAEs within the first 30 days. You could see, prior to discharge, there were no SAEs in either group. In the discharge, the 30-day period, each group had two SAEs, so obviously very similar. Looking at 30-day to 3-month and 3-month to 6-month, this is when you see fewer SAEs after the Reducer compared to the sham-control group.

This lists all the different SAEs. You can see the 10 total SAEs in six patients in the Reducer group, the 24 total SAEs in 11 patients in the not Reducer group, and you can see the biggest differences here were less angina, chest pain, and unstable angina that were considered serious adverse events in the no Reducer group compared to the Reducer group -- maybe two versus zero acute coronary syndrome.

So this slide shows the second pre-specified safety endpoint from the COSIRA sham-controlled randomized trial, and that's the rate of major adverse events or also called major adverse cardiac events after 30 days and up to 6 months. And here you can see in the 50 Reducer-implanted patients there was only one MACE event or a 2% rate in the no Reducer patients, of which there were 54. There were four MACE events or 7.4%. And as I mentioned before, of the two Reducer patients that were initially assigned to the Reducer that did not have an implant, none of those patients had a MACE event. So the four MACE events were all in the 52 original patients assigned to the sham-control group. The one event in the Reducer group was a myocardial infarction between 30 days and 6 months. The four events in the patients who did not get a Reducer were cardiac death in one patient and three myocardial infarctions.

Now going to the REDUCER-I study where we can look at that same endpoint, MACE within 5 years, you can see now that there was a 15.7% rate of MACE within 5 years.

Looking at cardiac deaths, the cardiac death rate within 5 years was 5.2%, so about a 1% death rate per year in these 228 patients by Kaplan-Meier estimates and that's pretty remarkable given this extensive coronary artery disease and "no option" patients, 1% cardiac death rate per year. There were four total strokes and 16 patients had a myocardial infarction, approximately again a 2% or 2.4% per patient myocardial infarction rate per year. Only one of these events were considered as possibly being procedure related and it was a myocardial infarction that it was really adjudicated to be unknown whether or not it was related to the device or not.

Thus, looking at the timing of the MACE over time in the REDUCER-I, if you look, I think, most importantly in the periprocedural period, the first 30 days, there were no cardiac deaths, no strokes, and there were four myocardial infarctions out of the 241 patients. And then looking all the way out to 3 years you can see that a few patients are having events basically each year of each type, with myocardial infarction being the most common, but even these were very infrequent.

Now looking at the 6-month rates of MACE across all the Reducer studies, so this is 6 months looking at, to put it in perspective, COSIRA, the sham-control arm in the first data column; then after the vertical line, the COSIRA Reducer arm 6-month outcome; the first in human, 15 patients, 6-month outcome, of which there were no events; the REDUCER-I 6-month outcome excluding the 11 patients that were in the COSIRA group. So you have a total of 295 patients in yellow and at 6 months you can see there was no cardiac death, there was one stroke, there were eight MIs, and two procedure-related adverse events.

The independent studies also support Reducer safety and again, here I show you on the five lines here, all the safety data that have been reported with all the individual investigator sponsored and reported studies. You could see here, from Konigstein, Giannini, Gallone, D'Amico, and Ponticelli, that the rates of cardiac death, stroke, and myocardial

infarction have been quite low in these patients; in general, were consistent with what we saw in COSIRA and REDUCER-I.

As we mentioned, these truly are "no option" patients; they really have, despite having severe angina, no revascularization option, which of course would be the first way that we would want to treat them. You could see in COSIRA, looking at the Reducer arm, the no Reducer arm, not a single Reducer patient had a revascularization within 6 months. Two no Reducer patients did have an attempted revascularization procedure, a PCI, because of just severe refractory angina. In the REDUCER-I study, out to 5 years you could see that there's been about a 12% rate of attempted PCI or about 2% per year and no patient had a bypass surgery.

And then finally, looking at the coronary sinus related events, there is a learning curve, of course, to using the device. So we show you here the premarket outcomes in COSIRA in 52 attempted patients with the Reducer, the postmarket REDUCER-I study in 204 patients, and the postmarket commercial experience in 1840 patients. I will mention, the 1840 patients, this is a voluntary reporting system of these 1840 distributed devices, so it's up to the sites to report whether complications occurred. Although most of the complications on this slide are quite serious and related directly to the Reducer, so I would anticipate that most of them would've been reported, but we don't know for sure, there could be a component of underreporting here.

You could see here that the incidence of Reducer malposition, migration, or embolization with two patients in COSIRA, two patients in REDUCER-I, and there have been 10 patients or 0.5% incidence reported from the commercial experience.

Looking at coronary sinus dissections and perforations and fractures, dissections and perforations have been very rare. There have been only two cases of tamponade that have been reported. There have been no fractures reported, no coronary sinus thrombosis or

occlusion reported, and major bleeding events have been uncommon.

And then finally, we have the first-in-human follow-up safety data that goes all the way out to 12 years, that's the longest experience with the Reducer, and specifically repeat CTAs were performed in seven of these patients at 12 years in whom follow-up was completed, and all of these devices were patent, no thromboses were detected, no device fractures were observed, and no migrations were evident.

So in summary, while I could go down the litany of everything I just presented, I think I can basically conclude the totality of the evidence in more than 2,000 distributed Reducer devices has demonstrated that the Reducer implant is safe when used as indicated.

So if I were to try to summarize all of the data that I've shown you, the effectiveness and the safety, there's no doubt that it would be wonderful if we had a 500-patient sham-controlled trial with definitive evidence of reduced myocardial ischemia with more of a contemporary kind of clinical trial metrics that we're using in the last few years. But again, I do want to emphasize that what's important is to try to place these data in perspective in terms of, you know, have we demonstrated reasonable evidence of effectiveness and safety, in particular in the perspective of the unmet clinical need. And these really are patients who are desperate and would have been through multiple revascularization procedures, who are taking, in many cases, multiple medications and have just a miserable life with no therapeutic alternatives. And I believe that the totality of the data, in sum, has shown that we have a reasonable confidence that this is an effective device and it's quite safe for these patients with such an unmet clinical need.

So I'm going to turn it back over to Tim Henry now, who is going to give you his clinical perspectives.

DR. HENRY: Thanks, Gregg. And for the clinical perspective, I will keep my comments brief.

As noted before, I've spent more than 20 years taking care of patients with refractory angina, including the development of a specific refractory angina clinic, not only in Minneapolis and Los Angles, but now at The Christ Hospital in Cincinnati. This includes a prospective database with more than 2,000 people. I will tell you that this is a particularly challenging patient population and they really have extremely limited options. I think the comment of "no option" patients is really appropriate for them.

I've also had extensive clinical trial experience with refractory angina, including novel pharmaceutical agents, EECP, spinal cord stimulation, therapeutic angiogenesis with protein, gene and cell therapy, and then novel interventional techniques including CTO, shockwave therapy, as well as the Reducer. I've been a national PI or steering committee for nearly 20 different trials and I will tell you that doing these clinical trials is very challenging. It's challenging because when you carefully define refractory angina, as I tried to do earlier, it becomes a relatively small patient population and it's very difficult to find sites that are good at recruiting these patients.

For example, if you take Class III and Class IV patients who are not candidates for revascularization and who have more than seven episodes of angina per week, you're left with a very, very specific patient population that's very difficult to enroll. And this is reflected in the fact that it's been more than 20 years since a new therapy was approved for this challenging patient population.

So let me review the key points. Although angina is common, refractory angina defined as Class III or Class IV is not and potentially should be considered an orphan population.

By definition, "no option" patients have failed medical therapy and they have failed current revascularization techniques, both percutaneous and surgical.

We clearly have improved mortality. Realistically, it's 3 to 5% per year with

contemporary therapy. Slightly higher, maybe 5 to 6% percent per year if you have Class III and Class IV patients.

Importantly, these patients then are left with severe debilitating symptoms which interfere with their job, interfere with their family life, interfere with their ability to do activities of daily living, and as you will hear later today during the open mike, these patients are miserable and they're desperate.

Finally, for "no option" patients in the United States, the only therapeutic options currently available are EECP and most patients have either done that already or it's not logistically possible for them to do it, and TMR, which is seldom used in the United States for the reason we talked about before. So this really clearly leaves a majority of patients with absolutely no options at all. Again, truly "no option" patients.

So refractory angina patients in the United States are desperately in need of new options and I can tell you, I deal with this every week in clinic. It's important that these options are safe because we know the mortality rate is low and so you want to avoid risky therapies. Therapy also has to be effective in improving symptoms of refractory angina and it has to work. So from my perspective, the coronary sinus reducer meets those criteria. In particular, amazing, outstanding safety now in over 2,000 people that have been treated around the world and with selected but significant efficacy as you've seen from COSIRA-I. These results have been supported by ongoing registry data and in COSIRA-I, if you remember, there is clear significant improvement in angina and quality of life, and the subsequent extensive registry data and publications are very consistent in both safety and efficacy.

So I personally believe that the coronary sinus reducer is an option that should be available for "no option" patients in the United States who are truly, truly desperate. So I appreciate and I thank you for your time and attention.

DR. LANGE: Great. I believe that concludes the Sponsor's presentation and I would like to thank the Sponsor's representatives for their presentation.

And this is an opportunity for the Panel to ask any brief clarifying question. We have about 25 minutes dedicated to this before our break. I will look for hands to go up and I'll be multitasking. I see several. I see Bram, Dr. Somberg, Keith Allen, Rick Page, David Yuh. I'll try to do those in order and I'll just remind you to unmute.

So first, Bram, to you.

DR. ZUCKERMAN: Yes, thank you, Dr. Lange.

First of all, I want to thank the Sponsor for an excellent presentation, but I do want to note for the record that if this had been done in person instead of virtually, I would've stopped the presentation at several critical points. Specifically, our rules for sponsor presentations are such that it's standard practice that when data are being presented in a sponsor presentation that has not previously been reviewed by the FDA, the presenter notes that just to help the Panel properly interpret the strength of the data.

From my notes, I believe that, for the record, Slide 64, 76, 78, 79, 92, 94, and 96 contain data not previously reviewed by FDA. That's fine, but I would ask the Panel members, in their independent review, to properly consider this fact. Also, I would ask the Sponsor, in responding to subsequent Panel questions, to clearly demarcate whether or not the FDA has had a chance to independently review data being referred to. Finally, another standard practice that I would ask the Sponsor to adhere to is to indicate more clearly whether or not certain hypotheses were pre-specified and/or whether multiplicity adjustments were made. While this information is to be found on the slides, it's in very small type and many of us, including myself, have poor vision at our advanced age. Anything that the Sponsor can do to more clearly present the science would be greatly appreciated. Thank you.

DR. LANGE: Thank you very much, Bram.

And again, the Sponsor has an opportunity -- many of these questions, clarifying questions, we'll ask the Sponsor if there's additional data to acquire that over the lunch period or during the public portion, public presentation. But apropos to Dr. Zuckerman's comments, in the future, any slides referred to or any data, please specify whether the FDA has approved it and whether it was -- hypothesis was pre-specified and multiplicity examined.

Thank you, Bram.

Dr. Somberg, I think I saw your hand first. Go ahead, John, you're unmuted.

DR. SOMBERG: Okay, yes, John Somberg here.

I failed to mention that my area of expertise is cardiovascular pharmacology and I'd like to drill down upon that because it's repeatedly stated by the Sponsor that these are "no option" patients. So can they define how they went through over that 30-day period, a sequential test if pharmacologic therapy for angina was maximized? Or made maximum, I should say. Could they also address why a good third of the patients are on blood pressure-lowering therapies that are not antianginals such as ARBs, ACEs, and diuretics? Could they also mention why or if the medications were remaining constant throughout the study in COSIRA?

And I'm specifically talking about the randomized sham-controlled study. So can we drill down on why these are considered "no option" patients, pharmacologically? And also was there any review of the cardiac catheterization material by a central committee to say they had no interventional option? I'm trying to define this population, are they really drug resistant, are they really procedurally excluded? Thank you.

DR. LANGE: Great. Dr. Somberg, again, just for the Sponsor, when we come back from lunch, the things you mentioned, again, to discuss the 30-day sequential

pharmacologic maximization. Explain why a third of the patients weren't on antianginals or were on blood pressure medicine that were not antianginals, whether the medicines remain constant and whether the dose was maximized and finally, a review of cardiac catheterization data.

Thank you, Dr. Somberg.

Dr. Page, I saw your hand, as well.

DR. PAGE: Yes, thank you, Dr. Lange. Rick Page, for the record.

Two quick questions in terms of the -- I'm trying to get a handle on the mechanism of action here and the physiology that underpins a procedure that these patients with no hope are undergoing. As I read the information, I believe that that procedure, in addition to constricting the coronary sinus, involved pericardial irritation and wonder if there's any response to the fact that the response in patients was, for sure, related to the coronary sinus stenosis as opposed to the pericardial procedure.

The other thing is looking at Slide 45, and I believe Dr. Hampshire spoke about the intentional nature of making this hourglass stent, if you will, and I'm really struck by Animal 1111, which has a reverse hourglass in terms of the angio that I would imagine one would see in that it's more narrow at the area of the wide part of the hourglass stent and it's more open at the area where it would be narrower. So it's almost a reverse hourglass or a double hourglass effect, and wonder whether this stent is -- how they reconciled that with the shape of the stent, was this intentional or is this just observational and does this procedure require two stenoses? Are we interested in the pressure gradient at one -- at what we'll call the distal end and then at the drainage to the more proximal coronary sinus? I'm just interested if they can comment on the physiology behind what the stent is doing to pressure in the coronary sinus.

DR. LANGE: Great. So again, to summarize Dr. Page's two questions, the presenters

specified that the Beck surgery was due to coronary sinus occlusion or stenosis, but obviously there's pericardial irritation, how do they know that it is due -- the benefits are due to coronary sinus stenosis, and asking about Slide 45 and the reverse hourglass where there's some -- thank you very much.

Dr. Yuh, did you have your hand up, as well?

DR. YUH: Yes, thank you very much. David Yuh.

Two quick questions. I was struck in Dr. Henry's presentation that one specific group of anginal patients excluded intentionally were those suffering from microvascular disease and I was curious, because it seems like the putative mechanism behind this therapy might, in theory, benefit those patients the most and I wonder if that exclusion was at least partially responsible for the fact that so few women were enrolled in the study, you know, based on the preponderance of microvascular disease in that population.

And then secondly, in terms of the sham design, if I could get an approximate average time for deployment of the actual device, was it substantial enough that there was a significant time discrepancy, a total procedural time discrepancy between the sham and the study -- the treatment groups, whereby it might be discerned one way or the other what therapy or if the patient got or did not get the stent? Those are the two questions that I had.

DR. LANGE: Okay. So Dr. Yuh, again just to summarize, the discussion of exclusion of microvascular disease and whether that led to the low number of women in the study. And secondly, procedure time, sham versus treatment to see if there's a difference.

Okay, thank you very much.

Dr. Allen. And then I've got Dr. Cigarroa and then Dr. Wittes. Dr. Verghese, do you have your hand up? I'll get you next after that.

So, Dr. Allen, you're on mute right now. And then Magnus, okay. And then Ralph.

DR. ALLEN: Sorry about that. This is Keith Allen. Thank you all for letting me participate.

I've got several questions, they're relatively short. The first one is, were surgeons, coronary surgeons, involved in deeming these patients no option? I see an investigator who I assume is a cardiologist who can deem a patient not a candidate for PCI, but I don't ever see surgeons involved in deeming these patients no option.

Second question is to the effectiveness of blinding. While I applaud the team on doing a sham-controlled trial, I don't ever see any simple logistics confirming that patients actually stayed blinded. All you would need to do would be to look at a chest X-ray and you could see the device in the coronary sinus, so how is that done?

The third question relates to this and as to who was managing these patients' post-op medications. And it's important that medications didn't change in one group more significantly than the other, and I don't see that presented anywhere in the randomized trial. And it's also important that the person managing the medications was blinded. We only have to look back at, for example, CardioMEMS and the issues that had with being kind of overzealous and biased management of the treatment group that led to more favorable results.

And then the final question goes to pressures. I'm astounded by the fact that not once in the presentation do I actually ever see any validation that the hypothesis of how the Reducer works was documented, i.e., where are pressure measurements done in any animal that documents that? And I understand that they mention that quadrupeds have a problem doing that, but I also don't see any human data. And I would argue, as a vascular surgeon, that constriction of a vein, unlike an artery, leads to dilation of that vessel and the constriction of the coronary sinus will behave very differently and may not yield the results the Sponsor is actually looking at to validate their hypothesis of how this works.

DR. LANGE: Great. Okay, to summarize for the Sponsor, were surgeons involved in evaluation of revascularization? Talk about the confirmation of the effectiveness of blinding, please. Please discuss who managed the patient post-op and the number of medication changes made in the sham and control group or sham and treatment group. And then finally, provide pressure measurements in humans, please.

I've got right now Dr. Cigarroa, Dr. Wittes, Dr. Verghese, Dr. Ohman, and Dr. Brindis.

So Dr. Cigarroa. And then Dr. Borer.

DR. CIGARROA: Good morning from the West Coast, and thank you to the Sponsors for the presentations, and to our Chairman for providing me the opportunity for clarifying questions.

I have three. The first question is, were individuals who assessed the functional capacity, including angina, during the follow-up period blinded to medications, including whether or not an individual was on dual antiplatelet therapy or not, is my first question.

The second question goes to the point that, by my calculations, there were 34 of 52 in the active arm that did not have any change in angina versus 44 over 52. Were there any differences in diastolic filling period between those who responded and those who did not respond during this period?

And my final question is a follow-up to Dr. Allen's question with regards to pressure measurements and, as we know, change in pressure across a reduced cross-sectional area is influenced by flow and therefore understanding whether or not there is a pressure change across the Reducer at rest versus during increased heart rate would also be important to understand relative to this biologic plausibility of increasing CS pressure.

DR. LANGE: Okay. So to summarize, again, the three questions Dr. Cigarroa asked, and correct me if I misstate these. Are the people that assessed angina, were they blinded to medications and particularly to dual antiplatelet therapy? Was there any difference in

diastolic filling period between those treated and those who weren't, that had no change in their angina, no improvement? And then any measurements across the stent either at rest or with increased heart rate.

Did I summarize those, Dr. Cigarroa, adequately? Okay, great.

DR. CIGARROA: Yes, sir.

DR. LANGE: Great. Dr. Wittes.

DR. WITTES: Hi, this is Janet Wittes.

I have four questions, they're all pretty short, I think. The first is what countries were these, the 104 patients from? That's question one.

The second question is what percentage were current smokers? You showed 50%, more than 50% current or former smokers, but I would like to see what -- because this, the 50%, seems really high for current smokers in the U.S.

The other question is can you show Class IIIs had to move to Class I, the Class IVs had to go to II or I? Can you show the movement in both treatment and control, where the IIIs and IVs went?

And then finally, the more complicated question comes from Slide 75, 77, 78, and 81 and there may have been a few others, as well. You show a number of people at 1 year, some at 2 years, some at 5 years, and then you calculate the percentage of various things as a function of those denominators, but you didn't show how many people had reached 1 year, 2 years, 5 years. And so my question is did the number and the percentage that you're showing reflect the entire group of people that reached those landmark number of years or is it a selected group in some way and there's missing data?

DR. LANGE: Okay, thank you.

To summarize Dr. Wittes' comments, what countries enrolled a hundred and four patients in COSIRA, what percent are current smokers, please show the movement of Class

III and IV patients in the treatment and control groups. And then in the last Slides, 75, 77, 78, 81, do those patients represent the entire group at 6 months, 1 year, and 2 years?

Thank you, Dr. Wittes.

Okay, I've got Dr. Verghese, Ohman, Dr. Brindis, Dr. Borer, and then Dr. Connor and then Dr. Somberg, okay?

I think, Dr. Verghese, I'm going to turn it over to you.

DR. MATHEW: Dr. Lange, it's actually Dr. Mathew. Verghese is my first name.

DR. LANGE: I'm sorry, I'm sorry.

DR. MATHEW: That's all right, just for the record.

A couple of quick points, one to extend on Dr. Somberg's comment. Is there any information on -- there was a mention, not necessarily in this morning's presentation, but the advanced materials, that about 25% of patients were on zero or one antianginal therapy. That would be somewhat inconsistent with the refractory group, so if you can expand on that.

And then is there information on changes to or adherence to medication therapy over the course of follow-up in COSIRA at 6 months or the REDUCER trial out to 5 years, either increases or decreases in medical therapy in the respective groups of patients.

Second, I would echo sort of what three panelists have made comments on already in terms of mechanism. While mechanism may not be a requirement for approval in this process, I understand, I'm having difficulty drawing the lines between mechanism and the clinical benefit that's been attributed to that mechanism.

The third is the patient population with microvascular angina, which doesn't seem to have been included in this population. I would just make the statement that the IFU, while it includes patients who are not candidates for CABG or PCI, one might infer that it doesn't specifically exclude patients with microvascular angina. So the proposed IFU, I would just

say myocardial modification.

Then the last point, also in the advanced materials but not mentioned this morning, there was a categorization of technical mishandling of the device in eight out of the 50 COSIRA patients. If the Sponsor could expand upon on that and whether that should be of concern in extrapolating this procedure to a broader number of interventionalists and patients. Thank you.

DR. LANGE: Great. So again, 25% on zero or one medication don't appear to be refractory, please address that. Again, discuss the change in medications, adherence to medications in both groups in both COSIRA and REDUCER. Please address whether anybody with microvascular disease was enrolled, i.e., what did the angiography show? And then finally, please address the 8 over 50 individuals in which there were technical difficulties handling the device and whether it ought to be a concern.

Did that address -- summarize, Dr. Mathew?

DR. MATHEW: Indeed. Thank you, Dr. Lange.

DR. LANGE: Thank you very much, sir.

Dr. Ohman.

DR. OHMAN: Good morning, and this is Magnus Ohman for the record. I want to thank the Sponsor for an excellent presentation.

I have three fairly brief questions. In the original protocol of this device there were 124 patients, I believe, to have been randomized but only 104 actually did so. So the question I have, is this trial subject to early termination bias, i.e., that we're seeing more positive results because they were terminated early? It might be useful for the Sponsor to calculate a worst-case scenario, i.e., for the full sample size by applying the placebo rate or the control group rate to the remaining COSIRA patients, not the full sample size, just to get a feel for how sensitive this result is due to the smaller sample size than planned.

This is an extension, my second question is an extension of Dr. Somberg's question. I would like to see the COSIRA results with the 25% who were on minimal therapy excluded to see if there's any remaining treatment effect in this study.

And finally, my third question is in going to the Sponsor's Slide 90 and 91, I counted up two myocardial infarctions versus one. So here on 90 you see acute myocardial infarction on top and a little bit further down you see myocardial infarction again, and then on the next slide there's only actually one given, I believe, if I saw the slide correctly. So the question here, is that accurate? And of course, if we're talking about two out of 50 versus one out of 50, there's a fairly big difference in this small sample size for the confidence interval around such observations. Thank you.

DR. LANGE: Thank you, Dr. Ohman.

Again, to ask the Sponsor for the sensitivity analysis, considering the possibility of early termination on account of some of the effects. Exclude the 25% of COSIRA patients that were on zero or no medications to see if there was still an effect. And then to reconcile the number of MIs in Slides 90 and 91.

Okay, thank you, Dr. Ohman.

Dr. Brindis.

DR. BRINDIS: Thanks. And again, I want to thank the Sponsor for a terrific presentation.

Most of my questions have already been posed by my esteemed colleagues. My last one is focusing on safety. So the Sponsor's presentation stated that out of approximately 2,000 follow-ups there's been no coronary sinus thrombosis noted to date. In some of the materials sent to us there was a CT scan or MRI scan evidence of thrombus, not insignificant within the occluder device. So I was interested in more comments related to that and also the utilization of antiplatelet therapy long term, dual or -- appreciating, of course, that a lot

of these patients with underlying coronary disease would be on antiplatelet therapy.

DR. LANGE: Okay. So the two issues, Dr. Brindis, one is the presenter made a comment of 2,000 follow-ups, there was no CS thromboses, please explain how that was documented. And then address the issue of dual antiplatelet therapy and how long that was continued. Great.

DR. BRINDIS: Yes, and the issue of presence of thrombus within the device --

DR. LANGE: Great.

DR. BRINDIS: -- on scanning.

DR. LANGE: Okay. Now I'm going to take the last two or three questions and then we'll have more opportunity to do this. And I'll get to you, Dr. Yeh, before we finish out and we'll have other opportunities afterwards, but I'll try to keep on time, as well.

So I've got Dr. Borer, Dr. Connor, and then Dr. Yeh.

Jeff, you're -- that's right, you're muted. Now we've got you. Go ahead, Jeff.

DR. BORER: Thank you. The one question I have left that hasn't already been dealt with relates to Slide 49 and it has to do with what I think is our fundamental issue here. We're dealing with the capacity of a device to minimize the magnitude of a subjective symptom in a population that we have to define. In Slide 49, as I understand it, the judgment as to whether the patients were of limited options was made by the investigator, who, if I'm understanding correctly, was unblinded and was determining -- outcomes that were being determined where angina classes improved, which is pretty subjective.

So I'd like to have some comment about that. Were the investigators actually unblinded and would that have any impact on the assessment of the outcomes here? Is it likely that they would be, because ultimately what we're talking about is assessing the magnitude of effect of a device on subjective symptoms, so I'd like a comment on that.

DR. LANGE: Okay, Jeff. So the question again, were the investigators unblinded with

the assessment both of the inclusion of the patient and also the assessment of the outcome, as well? Great.

DR. BORER: Right.

DR. LANGE: Okay, Dr. Connor and then Dr. Yeh.

DR. CONNOR: Yeah, I'm Jason Connor.

Two quick easy questions. So the first, I apologize if I missed, but is there an explanation as to why the trial stopped short of planned enrollment?

And then second question is I would love to see the primary outcomes for the main trial by site. I know a bunch of sites are small, but you have at least multiple sites with a decent number of patients to show the sham group, the treatment group by site, just so we can see the consistency of effect with different providers.

DR. LANGE: Great. Okay, Dr. Connor, again to summarize: Why did the trial stop prematurely, an explanation for that, and then outcomes by site. Thank you.

And, Dr. Yeh, you have the final question, at least during this part. And then we'll take a break.

DR. YEH: Thank you. Robert Yeh.

Two quick comments/questions. One is I know the trial was conducted, COSIRA was conducted in a time where maybe modern complex coronary revascularization techniques, depending on where the trial was conducted and who were the operators that are involved, may not have necessarily been there. So have the angiograms been reviewed, I'm curious, by a complex coronary interventionalist or a cardiac surgeon, as Dr. Allen stated earlier, by 2020 standards or by today's standards as opposed to at the time the trial was conducted, which may be different.

The second is a question related to mechanism, which is I know that the trial, COSIRA, enrolled patients who had ischemia attributable only to the left coronary arterial

system, yet there's not a comment about that in the proposed indications for use about limiting it to only those patients with ischemia attributable to the left coronary system and how does that -- if the Sponsor can speak a little bit to the mechanism of why that was limited to that, what should be the expectation based on location of the occluder, of the placement of the Reducer, etc., related to coronary venous outflow. Just more on mechanism as it's been previously stated already by many.

DR. LANGE: Okay, so that would be the last one. So again -- okay, John, I'll get to you in just one moment. You'll have the last word, John.

Two questions was, were the angiographies reviewed by interventionalists and surgeons apropos to what's going on? And then finally, mechanism of occluder of the left versus non-left, to have them address it.

So Bram, you'll get the final word, if that's okay. The final final word. So John, you get the final word. Bram, you get the final final word.

So Dr. Somberg.

DR. SOMBERG: Well, actually, a question to add is could the Sponsor also discuss why they decided to use aspirin, a P2Y12 inhibitor. Since it's on the venous side, the occluder, why wasn't anticoagulation considered for this type of patient? How was it distinctly different, for instance, someone who has embolizations from the legs and they put in one of those filters, when you talk about Coumadin, heparin and Coumadin, not aspirin or P2Y12. Thank you.

DR. LANGE: Thank you, Dr. Somberg.

And then Dr. Zuckerman.

DR. ZUCKERMAN: Yes, I think Dr. Batchelor may have a final question for the Sponsor. Dr. Batchelor.

DR. LANGE: Are you -- there you are, I'm sorry, in the bottom left. I'm sorry I missed

you, Wayne. If you'll unmute, you get the last question, Dr. Batchelor. My apologies. You're muted right now. So, Dr. Batchelor, can you hear me?

DR. BATCHELOR: Yeah. Sorry, can you hear me now? Sorry, I was muted.

DR. LANGE: We can hear you now, sir. Yes, sir.

DR. BATCHELOR: Thanks. And I apologize this morning, with the log-in issues, but this is Wayne Batchelor from Inova.

A couple of quick questions. One that deals with logistical robustness of the results. You know, a trial like this is very prone to regression to the mean and there were a few more patients numerically in the Reducer arm that were Class IV angina versus the control arm. A lot of speakers have discussed the issues around blinding, but also regression to the mean could play a role here. So I just looked at this quickly and when you look at the chi-squared tables, in the control arm there were eight who got better out of 52 and that number is less than 10. So when we can get to these cells that have smaller numbers you've got to question whether or not to do a Yates correction or other statistical correction.

So my question is can we maybe see if one patient, for example, was misclassified? I did the calculation and if one was misclassified in each arm, the statistical results would've been completely removed. And, in fact, if one was misclassified in the Reducer arm, with the Yates correction also statistical significance would be lost. I think this is important when you're dealing with a trial that's naturally prone to regression to the mean, placebo effects, and also blinding concerns. So I'd like them to address that.

And then the other question relates to downstream, once this device is in I presume you can't take it out, so some of these patients are going to need coronary sinus intervention. So if a patient needs a biventricular AICD in the future, that completely precludes, I presume, this?

DR. LANGE: Okay.

DR. BATCHELOR: Thank you.

DR. LANGE: Great. So with that, we'll close with those two questions. One is to have the Sponsor address regression to the mean and just changing the one patient. And then finally, does this exclude use of CS for future procedures?

We're just about 5 minutes behind, so let's take -- instead of a 15-minute break, if we could take a 10-minute break. We'll call this our bio break and I'll ask everybody to join -- it's now 9:21, let's join back at 9:31. Thank you.

(Off the record at 11:22 a.m.)

(On the record at 11:32 a.m.)

DR. LANGE: Before we proceed with the FDA presentation, I failed to see two hands that were up, so I'd like to ask Dr. Starling, to give him the opportunity to pose his questions to the Sponsor and then Dr. Gersh.

So Dr. Starling.

DR. STARLING: Yeah, thank you very much, Dr. Lange, and thank you to the Sponsor for the presentation. This is Randall Starling.

And just for the record, I'd like to acknowledge that "no option" patients do have an option that hasn't been discussed, which is cardiac transplantation and of course, we know that's a highly restricted option but it is an indicated option for refractory angina. So my questions fall into three different categories.

The first is physiologic mechanisms, which have been addressed already, but my specific question relates to any pressure measurements as well as coronary sinus oxygen content, and we know that, and the third physiologic would be coronary vascular resistance. It seems the mechanism of this is related to coronary flow.

Second comment has to do with patient populations for which this is indicated, and

in the 2015 *New England Journal* article that was referenced in the appendix, it indicates that an exclusion is a right atrial pressure over 15 as well as a right atrial or a right ventricular or a coronary sinus lead. So I would like to know the specific patient populations with refractory angina that this is going to be applicable to and which are excluded.

And thirdly would be with durability. So we're told how many improve, but any information related to the durability and movement of the patients, which has already been alluded to by other questions, would be appreciated. Thank you.

DR. LANGE: Great. Thank you for those questions, Dr. Starling.

And then Dr. Gersh.

DR. GERSH: Thank you, Dr. Lange, I'll keep my comments very short.

The first one is to reiterate what others have stated and that is it does bother me that zero -- I think 25% of patients were on zero or one antianginal agent and how does that fit with the definition of refractory angina?

Number two. Again, it's been pointed out, I'd like to know more about the early termination. It's hard for me to understand, having served on many DSMBs, why you would terminate the trial prematurely when 65% of patients in one group didn't respond versus 80% in the other and the endpoint is one symptom, not mortality or morbidity.

Thirdly, I think it may have been Dr. Yeh, but I would like to see more -- I'd like to see the data that show clinical correlations with mechanistic findings. We've seen the animal studies, and I tried to look them up, and one or two clinical studies have shown redistribution of coronary blood flow, but it would have been nice to hear a summary of clinical data in regard to the mechanisms.

And then my last question is really just a comment, it's not a criticism, but it is interesting to me to look at the treatment satisfaction data. Now, I realize that it's a

secondary endpoint but, as Dr. Stone pointed out, both groups were pretty satisfied with their treatment. It is actually a very small difference between the two groups and that just seems discordant and what it may suggest -- and I'd be interested in their interpretation and it may be that, you know, with any sham-control trial, 50% of patients will receive the device and 50% won't and the patients going into this trial know that. So why were they so happy with their treatment if, in fact, there was quite a marked discrepancy in terms of angina relief? And I think this just points to some of the difficulties even with a sham-control trial of ensuring blinding. Thank you.

DR. LANGE: Okay. And I think the Sponsor has those.

Again, in addition to Dr. Starling's questions, the issue of whether this is a refractory angina group when a fourth of patients had zero or one antianginal. Why it was terminated early. What is the correlation between the clinical results and any mechanism. And why the discordance between angina relief and satisfaction with treatment. So thank you.

All right. And again, there will be additional time if we have additional issues that need to be brought up.

At this time I'd like to give the FDA an opportunity to provide their presentation.

Again, I would like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

At this time the FDA will also have 90 minutes for their presentation and please proceed.

DR. RABEN: Good morning, my name is Sam Raben and I'm a mechanical engineer/team leader in the Coronary Interventional Devices Team in the Office of Cardiovascular Devices in the Center for Devices and Radiological Health at FDA. We welcome you to the cardiovascular panel of the Medical Devices Advisory Committee

meeting to discuss the premarket approval application for the Neovasc Reducer System. Today's FDA presentation will be presented by myself along with Drs. Anabelle Crusan, Rona Tang, and Tara Ryan.

Briefly, I would like to acknowledge the complete review team for this submission. These team members helped review all of the information provided by the Sponsor, including the preclinical and clinical data and analyses.

The Sponsor has requested an indication for patients suffering from refractory angina pectoris despite guideline-directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention.

Based on this proposed indication for use, the Panel will be asked to comment on whether a reasonable assurance of safety and effectiveness has been established for the proposed indication for use based on the totality of the evidence provided herein. Additionally, the Panel will be asked to comment and make recommendations on whether the evidence provided adequately defines the patient population proposed to support the IFU.

Here is an outline of FDA's presentation. I will give a short introduction on the regulatory history and regulatory considerations, a brief description of the device, followed by an overview of the device principle of operation, as well as the nonclinical evaluations conducted in support of the submission. Dr. Annabelle Crusan will discuss the animal studies performed by the Sponsor, while Dr. Rona Tang will discuss the statistical information regarding the study design and statistical analysis plan. Then Dr. Tara Ryan will provide a presentation of the clinical study results from the primary COSIRA clinical trial performed by the Sponsor. Finally, I will provide a brief discussion of the proposed post-approval study along with a summary of today's presentation.

I would now like to briefly talk about FDA's breakthrough device designation program. This program is intended to provide the American public with timely access to new devices with the potential for significant impact by speeding up the development, assessment, and review while preserving the statutory standards. One of the key benefits of this program is that it offers increased interaction with FDA through several different mechanisms to help provide timely feedback in an effort to speed up the developmental process.

The Reducer device received a breakthrough designation from FDA, as it has the potential to provide benefit to a patient population that currently has limited treatment options.

It is important for the Panel to note that while the Breakthrough Devices Program offers increased communication and collaboration with FDA, it does not modify or reduce the statutory requirements for device approval. FDA still requires that the Reducer device demonstrate a reasonable assurance of safety and effectiveness.

In August 2019, FDA published a guidance document that discussed considerations of uncertainty in making benefit-risk determinations and premarket requests for medical devices. In this guidance document FDA indicates that it is willing to accept greater uncertainty of the benefit-risk profile if this uncertainty can be balanced by other factors. These other factors include the probable benefit to patients from earlier access to the device, timely postmarket data collection, or transparency and accountability in the device labeling.

Again, it should be noted that while FDA is willing to accept greater uncertainty in the benefit-risk profile, its statutory requirements of reasonable assurance of safety and effectiveness still hold. Additionally, FDA considers uncertainty of the benefit-risk profile based on the novelty and unique characteristics of each device. While breakthrough

devices have been acknowledged to have the potential to offer increased benefit, the breakthrough designation is not required to be considered under this framework.

During today's presentation we will highlight some of the key considerations and limitations FDA believed are present in the information provided by the Sponsor. These considerations and limitations include the preclinical animal study data's ability to demonstrate a trans-reducer pressure gradient or coronary sinus narrowing, clinical uncertainty of the primary study endpoint results for effectiveness due to study design, execution, and analysis issues. Interpretation of the secondary endpoints present challenges due to the limited sample size, high levels of missing data, and lack of pre-specified hypotheses for these endpoints. FDA is concerned about the uncertainty in the benefit-risk profile for a chronic cardiovascular implant in a population with a low mortality rate. Breakthrough devices, while offering potential benefit to patients, are still required to meet the statutory standards of a reasonable assurance of safety and effectiveness. And finally, the proposed post-approval study attempts to clarify major questions about the current clinical data; however, execution may be difficult.

Now, I would like to briefly discuss the device description, proposed principle of operation, and regulatory history.

The Neovasc Reducer is a metallic stent that is provided pre-mounted on the delivery balloon. The Reducer is designed to establish a narrowing of the coronary sinus with the goal of creating an upstream pressure gradient capable of improving perfusion to the ischemic myocardium.

While the COSIRA data was collected with the current device generation, the earlier first-in-human trial was performed using the prior device model. The difference between these generations were changes to the delivery system catheter, changes to the implant design, and changes to supply the device pre-mounted on the delivery balloon and no

longer requiring hand-crimping of the device.

As discussed, the Reducer device is intended to treat refractory angina. It is proposed that after implantation, local fluid disruption and vascular reaction will induce a neointimal proliferative response that will occlude the fenestrations in the metal mesh. However, while demonstration is not required as part of the PMA approval process, FDA believes that this proposed mechanism of action remains unclear and contributes to the overall uncertainty of the data provided. Additional information regarding this uncertainty will be provided later in the presentation by Dr. Crusan and Dr. Ryan.

Regarding the regulatory history of the Reducer device, an original IDE was submitted in 2010. FDA and the Sponsor could not agree on certain aspects of the study design and the Sponsor chose to conduct the COSIRA trial outside the U.S. In 2016, the Sponsor returned to FDA and sought approval for a new IDE seeking to build on the knowledge obtained during the COSIRA trial. This new trial, referred to here as COSIRA-II, was again proposed to be a double-blind, sham-controlled trial seeking to enroll refractory angina patients. COSIRA-II included a primary endpoint with an objective assessment of ischemic change using a Bruce treadmill exercise test, a larger sample size, powered secondary endpoints, and included a longer assessment duration with primary endpoints evaluated at 1 year with consent for follow-up going out to a total of 5 years.

However, during the review of the information provided in the IDE application, which included the COSIRA OUS data, FDA noted a few concerns that resulted in the FDA conveying to the Sponsor that additional data beyond what was proposed in COSIRA-II may be required to support a future PMA. FDA continues to believe that due to the novelty of this device and the current data limitations, a more direct observation of the device's performance is necessary. Ultimately, the COSIRA-II IDE was approved by FDA and remains open; however, the Sponsor has chosen to forego initiation of the trial, believing that the

current COSIRA data is sufficient to support their PMA.

Regarding the nonclinical testing provided as part of the submission, the Sponsor has provided several nonclinical bench tests in support of their device. The nonclinical engineering testing, biocompatibility, sterilization, shelf life, and packaging tests were all found to be acceptable.

I would now like to turn the presentation over to Dr. Annabelle Crusan to discuss the animal study information provided in this submission.

DR. CRUSAN: I'm Annabelle Crusan, a veterinary medical officer in the Office of Cardiovascular Devices. I am a laboratory animal veterinarian with training and experience in laboratory animal medicine, including cardiovascular device implantation and in laboratory animal pathology. I will be presenting FDA's review of the Neovasc Reducer non-GLP porcine studies.

Typically, a fundamental objective of an in vivo animal study in device evaluation are to provide insights into device proof of principle in support of a scientific rationale for treatment and to provide information on the basic safety of devices and the procedures. Large animal models are often utilized in cardiovascular studies because their anatomy and physiology can provide pathophysiologic insights into human device use. The animal studies that will be discussed today utilized a pig as the large animal model.

Good laboratory practices for animal care and study conduct, as specified in 21 C.F.R. Part 68, assures the quality and integrity of animal study data. GLP animal studies are typically submitted to support premarket approval applications to FDA. The Sponsor submitted three non-GLP studies to FDA.

In Study CA04001 and R01, their first generation Reducer device was implanted in the coronary sinus of miniature pigs. Study REDACL003 used farm pigs and mini-pigs and the finalized model of the Reducer device that was implanted in the human COSIRA trial

was used. These animal studies were intended to evaluate the safety and efficacy of coronary sinus narrowing with the Reducer when implanted in the model that simulated human use.

FDA has concerns with the overall quality and integrity of the Reducer animal study data. Final reports were incomplete and there was a 6-year delay in the final pathology report submission. There were missing data on findings in some of the study animals. We were unable to verify that the protocols were followed due to the missing protocol information and the lack of amendment and deviation records. Minimum quality assurance requirements to ensure data validity and completeness were not verified due to the lack of independent audits for all three animal studies.

For a postulated principle of operation, the Reducer is intended to create a functional coronary sinus stenosis by a process that occurs when metallic stents are implanted in blood vessels. As depicted in the middle figure, intimal smooth muscle cells migrate and proliferate in areas in which the device is opposed to the vessel wall. As shown in the bottom figure, the Sponsor postulates that near-intimal growth covers enough of the Reducer to restrict coronary sinus blood flow to the stenotic central orifice of the device. Consequently, if the Reducer performs as intended, a pressure gradient is produced across the device resulting in elevated coronary sinus pressure.

It's important to note that the Sponsor performed a limited histological evaluation of coronary sinus stenosis and Reducer neointimal coverage. Specifically, for each Reducer device, only three histological transverse sections from the proximal, middle, and distal portions of the device were evaluated. Coronary sinus stenosis was assessed by light microscopy, qualitatively guided visually or by a quantitative morphometry in selected animals. Quantitative morphometry raw data were not entirely provided for FDA review. In addition, scanning electron microscopy is required to fully assess tissue coverage of

intravascular devices. It is notable that scanning electron microscopy was not performed in the animal studies.

An additional important consideration of coronary sinus stenosis and Reducer neointimal coverage is the limited histology reports provided from pigs with a device implanted for 2 to 6 months, when healing would be expected to be complete. In the finalized pathology reports there were a total of 12 animals implanted with a first generation device and seven animals implanted with the finalized device. Not all animals were accounted for in the pathology reports and photos were not provided for all animals, so FDA could not independently review all reported gross and histologic findings. Of note, photomicrographs were provided only for the chronic animals implanted with the final device.

In the evaluation of coronary sinus stenosis and neointimal growth, limited assessments showed that the Reducer did not create a significant vessel narrowing; 17 of 19 or 89% of specimens demonstrated a less than or equal to 50% coronary sinus stenosis and no vessel had a more than 75% stenosis. Qualitatively, the study pathology noted there is an incomplete endothelial cell coverage of the device, variable to low levels of neointimal proliferation, and no appreciable coronary sinus luminal stenosis.

It is well established that there are limits to smooth muscle cell migration and proliferation in response to vascular injuries. Here are representative photomicrographs submitted to FDA from three pigs representing 57 days, 104 days, and 140-day time points from animal studies that used the finalized version of the Reducer. Note that there is very limited or very mild to at most moderate in-device neointimal thickening in the proximal and distal sections, and there is minimal eccentric neointimal or no neointimal in the midsection in which the Reducer is not opposed to the coronary sinus wall. Most importantly, there is no significant coronary sinus stenosis along the entire length of the

device.

In the study CA04001, the Sponsor reported a coronary sinus trans-reducer pressure gradient measured 15 minutes post-implantation of 3.71 ± 1.75 mm/Hg. The coronary sinus pressure gradient across the Reducer at 2 to 6 months remained low and similar to baseline; that is, there was no evident coronary sinus stenosis. Of note, information on number of animals studied with evaluable data and information on pressure wire measurement methods were not provided to FDA.

In the CA04001 study using the first generation Reducer, there were eight pigs that developed myocardial ischemia after placement of an ameroid constrictor on the left complex artery. Four pigs underwent Reducer implantation in the coronary sinus and four ischemic pigs did not receive Reducer and served as controls. The Sponsor reported improved left ventricular contractility by dobutamine stress echo and myocardial perfusion by myocardial contrast echo in pigs treated with the Reducer at 6 weeks and at 6 months assessment. However, FDA could not confirm improvements in the left ventricular contractility and myocardial perfusion in Reducer animals due to the lack of data for review and there is only one control animal that was available for assessment at 6 months.

So in summary, in contrast to the postulated device mechanism of action shown in the upper figure, neointimal proliferation, as depicted in the bottom figure, was not sufficient to cover the Reducer and restrict coronary sinus blood flow to the central orifice of the device. Specifically, there was no confirmation of sufficient device coverage by neointima to restrict coronary sinus blood flow to the narrowed device central orifice, no confirmation of coronary sinus stenosis or elevated coronary sinus pressure, and limited evidence of improved myocardial contractility and blood flow.

I will now turn FDA's presentation over to Dr. Rona Tang, who will discuss the statistical aspects of the COSIRA trial.

DR. TANG: Good morning, my name is Dr. Rona Tang, FDA statistician. My presentation focuses on the study design, statistical method, and analysis results of the COSIRA study.

The COSIRA study is a prospective, multicenter, randomized, double-blinded, and sham-controlled study. It was conducted at 11 OUS sites. Subjects were randomized to two study arms. The treatment arm received the Reducer device while the control had a sham procedure. The originally planned sample size was 124 patients with 62 patients per arm.

The primary effectiveness endpoint of the COSIRA study is change of two or more CCS angina grades from the baseline to 6 months. There are several safety endpoints, but there's no primary safety endpoints nor any statistical hypotheses.

The primary effectiveness endpoint was evaluated in a hypothesis where the proportion of patients with improvement of two or more CCS grades was compared between the two arms.

The pre-specified test was a Pearson chi-squared test with continuity correction at a two-side alpha level of 5%.

One interim analysis was planned after 50% of the cohort completed their 6-month follow-up. The Lan-DeMets method using O'Brien-Fleming function was used to account for this interim look. The alpha level allocated to the interim analysis was 0.0031 and the alpha allocated to the final analysis was 0.0469.

Secondary effectiveness endpoints for the COSIRA study include change of one or more CCS grades, dobutamine echo wall motion score index, Seattle Angina Questionnaire score, and exercise tolerance testing. There's no pre-specified statistical hypotheses.

The study populations of the COSIRA study include the following: the intent-to-treat population has all randomized patients. The per-protocol population contains all randomized patients except patients who did not complete the study or treatment group

patients who did not receive the Reducer device. The as-treated population is all randomized patients; however, patients were analyzed based on the actual treatment received, regardless of the treatment assignment.

The enrollment period for the COSIRA study was 2010 to 2013. The originally planned sample size was 124 and the patient enrollment was stopped after 104 patients. The ITT population has exactly 52 patients per arm. Two patients randomized to the treatment arm did not have a Reducer implanted and they were removed from the treatment group in the per-protocol analysis and these two patients were counted as control in the as-treated analysis.

An interim analysis was performed for the primary outcome after 50% of the originally planned cohort completed 6-month follow-up. The Sponsor decided to continue the study after the interim analysis.

For the final analysis in the ITT population, the Reducer group has 18 out of 52 subjects showing two or more CCS improvement, while the control group has eight successes. A p-value of 0.024 was obtained using Pearson chi-squared test without continuity correction. The per-protocol and as-treated analyses had similar results.

For the secondary endpoints, because there is no pre-specified statistical hypothesis, the descriptive results will be presented and discussed by FDA clinician Dr. Ryan in her presentation. I will discuss the missing data observed in the ITT cohort for the secondary endpoints.

For the DSE and SAQ endpoints, the control group has higher missing rates comparing to the treatment group as shown in the graph.

For the ETT endpoints, the missing rates in the treated and the control groups are both high. There are more than 71% missing data for endpoints timed to 1 mm and the maximum ST depression.

For the secondary data analysis, three missing data imputation methods were used, including the last observation carried forward, multiple imputation, and a tipping point analysis. Both LOCF and the multiple imputation methods require specific assumptions about missing pattern. In particular, the LOCF assumes patients are stable with their angina status during the follow-up period, which may not be true in this situation. As for the tipping point method, this is usually used when there are pre-specified hypotheses. Overall, due to high percentage and imbalance of missing data, the robustness of all secondary endpoint analyses are open to question.

In summary, the primary effectiveness endpoint was met for the COSIRA study. However, this study does not have a primary safety endpoint and there is no statistical hypothesis for the secondary endpoints. With a large number of secondary endpoints and no multiplicity adjustment, there is a real potential for false positive findings. Therefore, statistical inference such as p-value should be interpreted with caution. Additionally, there is a high percentage of missing data and the potential missing pattern issue in the secondary endpoints. The interpretation of the secondary endpoint analysis is challenging.

This concludes my presentation and I will now hand over to Dr. Ryan.

DR. RYAN: Good morning, my name is Dr. Tara Ryan. I am a medical officer in the Office of Cardiovascular Devices at FDA, and I will be presenting the clinical data on the Neovasc Reducer device.

The proposed indications for use for the Neovasc Reducer device is, "The Reducer System is intended for patients suffering from refractory angina despite guideline-directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting or by percutaneous coronary intervention."

Refractory angina is a debilitating chronic condition in patients with coronary artery disease. It's characterized by severe unremitting cardiac pain, significantly limiting the

patient's daily activities. The pain in these patients cannot be controlled by optimal drug therapy, and these patients are not candidates for percutaneous coronary intervention or bypass surgery.

The number of patients with true refractory angina is difficult to quantify, but it's thought that the incidence and prevalence of refractory angina will continue to rise as coronary artery disease survival rates improve and the populations age.

So this morning I will discuss the clinical data provided to support the PMA application. The primary dataset in support of this PMA is from the COSIRA study. This is the study that the Sponsor believes confirms the safety and effectiveness of the Reducer device. Also provided in the FDA Executive Summary is supportive clinical data from the first-in-man pilot study and the REDUCER-I observational study. My presentation will focus on the results from the COSIRA trial.

The COSIRA study was a multicenter, randomized, double-blind, sham-controlled trial conducted at 11 sites outside of the U.S. Of note, this study was not an IDE study approved by FDA. The results from the COSIRA trial were published in 2015 in the *New England Journal of Medicine*, and a copy of that article has been provided in the panel pack.

The objective of the COSIRA trial was to evaluate whether the implantation of the coronary sinus-reducing device could effectively improve angina symptoms in patients with obstructive coronary artery disease who had concomitant evidence of reversible myocardial ischemia and who were not considered to be candidates for revascularization.

The data collected in the study was managed and analyzed by a contract research organization. The trial was overseen by an independent steering committee, a clinical events committee, and a data and safety monitoring board. Also incorporated in the study were core labs for the testing outlined in this slide.

Key inclusion criteria included adult patients with Canadian Cardiovascular Society

Class III or Class IV angina, despite efforts to control symptoms with medical therapy for a minimum of 30 days before screening. Medical therapy included beta blockers, calcium channel blockers, nicroandil, ivabradine, and short-acting and long-acting nitrates used at maximum tolerated doses.

With reference made to the Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines, all patients were required to have evidence of reversible myocardial ischemia and a left ventricular ejection fraction of more than 25%. Only patients who were not considered to be candidates for coronary revascularization were eligible to participate in the study. This eligibility was decided by the heart team at each institution.

Only patients with coronary sinus anatomy that was suitable for implantation of the device were eligible to undergo randomization and the relevant anatomical features are summarized here.

Patients were not eligible for participation if they had had a successful PCI or CABG procedure in the previous 6 months, patients with unstable angina, decompensated congestive heart failure, severe COPD, or arrhythmias requiring placement of a pacemaker or internal defibrillator.

Other exclusion patients were those who had a pacemaker or defibrillator electrode in the right atrium, right ventricle, or coronary sinus, patients with chronic renal failure, or patients who had undergone tricuspid valve surgery.

This figure outlines the flow of patients. A hundred and sixty-six patients were consented and ultimately a hundred and four patients were enrolled in the study. Of note, the original COSIRA protocol planned to randomize a hundred and twenty-four patients in order to generate an evaluable cohort of a hundred and twelve patients at 6 months post-procedure. In 2013, enrollment was stopped. This decision was based on difficulty enrolling patients as well as a less-than-expected loss to follow-up. It was not safety

related.

This figure outlines the flow of patients after randomization took place. A total of 52 patients were in the treatment group and 52 patients were in the control group. One patient died before reaching the 6-month follow-up period leaving a hundred and three patients available for follow-up.

Enrollment in the study began in September of 2010. A total of a hundred and four patients were enrolled in the study. Enrollment stopped in May of 2013 and 6-month follow-up was completed on all patients by November of 2013.

So very briefly, patient demographics show that 85% of the patients were male and 87% were Caucasian. The average age of patients enrolled was 68. The COSIRA study was not representative for the minority or female population as evidenced by the gender and ethnic information summarized on this slide.

The Reducer group had numerically fewer diabetics, 40.4% versus 48.1%, but the two groups were comparable with regard to smoking history.

The two groups were also comparable with respect to hypertension, family history of cardiovascular disease, hypercholesteremia, hypertension, and other relevant medical history. Of the total 104 subjects, 73.1% had a history of a previous PCI, 76.9% had a history of a prior CABG, and 54.8% had a history of a previous myocardial infarction.

Dobutamine echo testing was done in 50 patients in each group. Eighty-eight percent of Reducer patients were positive for reversible ischemia and 58% had wall motion abnormalities at rest. The ejection fraction was 53.5% in the Reducer group and 54.8% in the control group.

SPECT testing was done at baseline in 48 Reducer patients and 45 control patients. This testing was positive for reversible ischemia in 86% of Reducer patients and 77% of control patients. Irreversible defects were also noted in a percentage of each group.

As noted previously, a CCS score of III or greater was required for patients to be included in the COSIRA study. Eighty-one percent of Reducer patients were CCS Class III and 19% were Class IV. With respect to control patients, 87% of patients were Class III and 13% were Class IV.

The table presented in this slide shows the number of antianginal medications that patients in each group were on at the time of enrollment. Thirty-eight percent of patients in the Reducer group were on three or more antianginal medications and 31% of control patients were also on three or more antianginal medications. Twenty-seven percent of Reducer patients were on less than or equal to one antianginal medication and 25% of control patients were on less than or equal to one antianginal medication.

The table presented in this slide shows the baseline cardiovascular medications that the COSIRA patients were on at the time of enrollment. Of note, 77% of patients in each group were on beta blockers, 55% were on calcium channel blockers. For a pivotal IDE trial of a device intended for the refractory angina population, FDA would typically request data to assure that patients were on maximally tolerated, guideline-directed antianginal medications, including drug dosages used and the rationale if patients were not on maximal therapy.

The primary endpoint for the COSIRA study was an improvement of two or more CCS grades from baseline to 6 months post-procedural evaluation in the Reducer group. Of note, this was an efficacy endpoint. There was not a primary safety endpoint specified, but periprocedural serious adverse events and major adverse events were recorded.

The study was powered to detect a difference in the proportion of patients improving greater than or equal to two CCS angina classes at 6 months after the implantation. The hypothesis corresponding to the primary objective as well as assumptions are summarized on this slide. The statistical analysis of the primary endpoint

used the intention-to-treat population. My FDA colleague, statistician Dr. Rona Tang, has provided additional details and the FDA perspective regarding the statistical methodology and analyses that were completed, including an interim analysis that was performed on the primary effectiveness endpoint.

So, for the primary endpoint in the treatment Reducer group, 18 out of 52 patients, that is 34.6%, experienced a decrease in two or more CCS grades from baseline to 6 months versus 8 out of 52 patients or 15.4% in the control group. This corresponds to a p-value of 0.024. The primary endpoint was therefore met. Of note, while 34.6% of the Reducer group demonstrated success using the protocol definition, 65.4% did not. Also of note, the response/success rate in the control group was almost half that noted in the treatment group, highlighting the potential for a placebo effect, which I will discuss later in my presentation.

Secondary endpoint success in the COSIRA trial included a CCS classification decrease of one or more CCS grades, dobutamine echo wall motion score index, Seattle Angina Questionnaire scores, and exercise tolerance testing which included total exercise duration, time to ST-segment depression, and maximal ST-segment depression. It is important to note that there were no pre-specified hypotheses for any of these secondary endpoints.

So, for the secondary endpoint of improvement of one or more CCS grades from baseline to 6 months, the proportion of subjects experiencing an improvement of one or more CCS classes from baseline to 6 months in the intention-to-treat population was 71.2% in the Reducer group compared to 42.3% in the control group.

Based on the clinical data in the submission, FDA performed an analysis of the individual changes in CCS grades and this table provides an overview of the analysis. This table illustrates the number of patients who did not show a response at all or got worse. More specifically 13 out of 52, or 25%, of Reducer patients showed no change from baseline

and 24 out of 51, or 47.1%, of control patients showed no change. With respect to an increase in CCS grade at 6 months, 2 out of 52, or 3.8%, of Reducer patients got worse, while 5 out of 51, or 9.8%, of control patients got worse.

Dobutamine echo wall motion index was calculated using a total of 16 segments. The scores for each segment were summed and the total was divided by the number of segments analyzed. Additionally, since the Reducer is placed in the coronary sinus distal to the right coronary artery, venous drainage, and modified left coronary artery, WMSI was calculated using only the 11 segments attributed to the LCA system. The WMSI and the modified LCA WMSI were calculated both at rest and during stress.

Testing was conducted using an acquisition protocol established by the core lab. Changes from baseline to 6 months in the wall motion indices are outlined in this slide. Given that there were no pre-specified hypotheses, any inferences must be drawn with caution. Also of note is a significant amount of missing data, which I will touch upon again later.

The Seattle Angina Questionnaire quantifies the physical and emotional effects of coronary artery disease. The questionnaire is a 19-item self-administered tool and provides results in five scales that measure clinically important dimensions of coronary artery disease, physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception/quality of life.

The current slide shows the data for the intention-to-treat analysis using paired data for physical limitations, anginal stability, and anginal frequency. Results for both anginal stability and anginal frequency favor the Reducer device. As mentioned previously, there was no hypothesis specified and any inferences should be drawn with caution.

And this slide shows summary data for the treatment satisfaction and quality of life component of the Seattle Angina Questionnaire. Once again, this is ITT paired data. A

change in the score for quality of life from baseline to 6 months was 18.6 in the Reducer group and 8.7 in the control group, favoring the Reducer group in improving quality of life scores.

A bicycle ergometry stress test was performed by the ETT core lab using standard operating procedures. Multiple parameters were intended to be recorded at baseline and 6-month follow-up for a comparative analysis. This included total exercise duration, time to 1 mm ST-segment depression, and maximal ST-segment depression.

The table on the current slide shows that the paired data analysis trended in favor of the Reducer group with the total exercise duration mean increasing by 65 seconds in the Reducer group versus a mean increase in the control group of 4.31 seconds.

However, it is important that we look at the issue of missing data. While all subjects were expected to have dobutamine stress echo testing, Seattle Angina Questionnaire data, and exercise tolerance testing as part of their baseline and 6-month follow-up, some of these analyses had a substantial amount of missing data, particularly related to the ETT analysis. This table shows an overview of the missing information. It's noted that there's more missing data in the control group as compared to the treatment group in the dobutamine stress echocardiography data and the Seattle Angina Questionnaire data. The missing data is problematic with respect to being able to draw conclusions regarding efficacy of the Reducer device in the improvement of functional ischemia.

There were also measures that were considered to be observational in the COSIRA study, including SPECT segmental analyses and CT angiographic analysis. The current slide shows differences in SPECT data. There were no significant trends noted.

With respect to CT angiographic follow-up, 27 patients in the Reducer group underwent angiographic follow-up. There were no signs of migration of the device. Contrast flow was noted in 94% of patients who underwent imaging. Thrombus was

reported in 43.2% of patients.

A total of 62 devices were prepared for use in the COSIRA study. Fifty-two were used in patients randomized to the treatment group. Ten were discarded due to what the Sponsor terms a device "deficiency" or a device malfunction.

For the sake of consistency with respect to characterization of device performance, this slide summarizes the events as device malfunctions. Eight of these were listed as operator mishandling events. In one case, the operator had to use a second device due to clots that were noted in the guide catheter and on the wire. In one patient, the Reducer device slipped on the balloon while advancing. The physician did not notice this until the device was inflated and deployed without essential narrowing. A peripheral balloon was inserted and expanded within the mal-deployed Reducer.

Technical success was assessed in the Reducer group only and defined as successful delivery and deployment of the Reducer device to the intended site as assessed by the investigator. In the 52 patients who were randomized to the Reducer group, 50 out of 52, or 96.2%, had a Reducer successfully implanted.

Periprocedural serious adverse events were assessed in both the Reducer and control groups. In the control group, periprocedural serious adverse events were defined as a composite of death; MI; life-threatening arrhythmias, that is ventricular tachycardia or ventricular fibrillation; and respiratory failure through 30 days post-procedure as adjudicated by the CEC.

In the Reducer group, periprocedural serious adverse events were defined as the same, with the addition of cardiac tamponade and clinically driven re-dilation of a failed Reducer as qualifying events. In the current slide, we see that there was one documented case of a non-STEMI. Of note, cardiac enzyme data was not captured in all patients post-procedure.

Major adverse events were defined as a composite of cardiac death, major stroke, and MI in the Reducer and control groups through hospital discharge and at 30 days, 3 months, and 6 months post-procedure evaluation. There were a total of five major adverse events as adjudicated by the CEC. There was one myocardial infarction in the Reducer group and three myocardial infarctions and a cardiac death in the control group. None of the five events occurring after 30 days post-procedure were attributed to the procedure or the investigational device. Only one MI was considered by the CEC to be related to a study specific assessment as it occurred during the study-required dobutamine stress echo at the 6-month follow-up.

As noted several times in my discussion, the primary dataset that has been presented as supportive of safety and effectiveness is the COSIRA study. Additional clinical data has been provided in the PMA application, including a first-in-man study using a first generation Reducer device at three sites in India and Germany. A total of 15 patients were treated.

Also ongoing is an observational study called the REDUCER-I and this slide presents summary information on this study. First, I would like to emphasize that the REDUCER-I is an observational study. There is no control group and therefore FDA is unable to interpret the data and it is difficult to draw conclusions with respect to effectiveness.

The study is currently continuing to enroll patients. The goal is to enroll 400 patients. There are three patient groups in the REDUCER-I study. FDA has received interim reports, the most recent having been provided in May of 2020. As of March 12th, 2020, there had been 241 subjects enrolled in the study.

With respect to adverse events in REDUCER-I, not all events had been adjudicated by the CEC as of the last data lock in March of 2020. There had been 13 deaths of study subjects reported. Ten events have been adjudicated by the CEC as unrelated to the device

and/or the procedure. Three events are pending adjudication. There's been one reported case of cardiac tamponade. An MI rate of 6.6% has been reported. There have been four stroke events, corresponding to a rate of 1.7% reported in the REDUCER-I study.

So to conclude my presentation, I will discuss limitations of the COSIRA study with respect to consideration as a pivotal study to demonstrate safety and effectiveness, and also comment on the adjunctive clinical data presented. First, we would like to relate to Panel members that study limitations have been discussed with the Sponsor, both in writing and during multiple in-person and teleconference interactions. FDA worked with the Sponsor to develop a protocol called COSIRA-II, a study protocol that was approved under an IDE application in November of 2017.

That being said, I would like to begin by commenting on the placebo effect. There's substantial clinical trial evidence for the placebo effect, especially for the relief of pain. Angina is known to be a placebo-responsive condition as evidenced in previous blinded studies in the field of refractory angina, including myocardial revascularization studies. We've also seen the placebo effects highlighted in other recent cardiac trials such as ORBITA.

The importance of exercise tolerance testing as a measure of functional capacity and predictable ischemic threshold has resulted in its use as a primary efficacy endpoint in clinical trials that have evaluated anti-ischemic treatments. And in appropriate control studies, it remains a valid endpoint with the ability to discriminate among effective and likely ineffective therapies. The COSIRA trial utilized a subjective endpoint of angina.

The relatively small sample size for the COSIRA study is problematic. Small sample size limits our ability to draw conclusions regarding the effectiveness of the coronary sinus Reducer device. A small positive trial does not negate of the possibility of negative results in a larger adequately powered study.

With respect to blinding in the sham-controlled trial, methods were incorporated during the procedure to help ensure that the patient and family remained blinded as to what group the patient was randomized to. However, there was no formal assessment or analysis regarding the success of blinding throughout the entire study.

As noted previously, the COSIRA study was not statistically powered to detect an improvement in ischemia by objective measures such as stress testing or wall motion index. Objective criteria of exercise time and stress wall motion could not be shown to improve significantly given the underpowered nature of the study.

As illustrated in my next slide, there was a significant amount of missing data for the secondary endpoints. Outlined previously in 32, we see there was a significant amount of missing data for the secondary endpoints. For the DSE and SAQ data, missing data were approximately twice as common in the control group as compared to the Reducer group. For the exercise tolerance testing, the data for time to 1 mm depression and maximal ST depression were mostly missing.

With respect to the statistical methodologies employed for data analysis, you heard from FDA statistician Dr. Tang regarding some of the limitations involving the analyses. Because optimal medical therapy was not clearly defined, it's difficult to know whether all patients were comparable with respect to being truly "no option," that is medication compliance, maximally tolerated doses of medications, and patient-specific conditions precluding revascularization.

Long-term safety data in the controlled COSIRA trial is limited. Seven patients from the first-in-man study had been reported at a site in India and 20 patients had follow-up data at 5 years in the REDUCER-I observational study. Given that the Reducer is a permanent implant, the long-term risks versus benefits cannot be determined. The long-term angiographic data collected does not assess the device stenosis and/or the resulting

increase in coronary sinus pressure.

Another limitation is the fact that the demographics of the study, who have been implanted with the Reducer device, is not representative of the U.S. coronary artery disease population. More specifically, no African American or Hispanic patients were enrolled in the COSIRA trial and the majority of patients enrolled were male.

Finally, the high non-responder rate noted in the COSIRA trial highlights the need to be able to identify patients who would likely benefit from receiving this permanent implant. Baldetti and others in *EuroIntervention* discuss that the presence of alternative venous drainage systems to the coronary sinus may be crucial in determining whether a patient is likely to benefit from the Reducer. Other tools may prove to be important. This is an item that we would like the Panel to consider.

So this concludes my presentation regarding the clinical data for the Neovasc Reducer device. Dr. Raben will continue now with comments regarding the Sponsor's proposed post-approval study and then concluding FDA remarks. Thank you for your attention.

DR. RABEN: Now I would like to briefly discuss the Sponsor's proposed post-approval study along with providing some concluding remarks for the presentation.

It is common for new and novel PMA devices to have a post-approval study identified as a condition of approval. These post-approval studies are conducted to provide additional information required to further support labeling for these new devices and can be used as a way to address remaining uncertainties identified during the review. Please note that the discussion of a post-approval study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA.

For this device, the Sponsor is proposing a randomized, double-blind, sham-controlled trial to be performed in a country where the Reducer device has not been

approved. Given the concerns identified regarding the statistical and clinical data as discussed earlier in the presentation, we intend to ask the Panel if a post-approval study that is randomized and sham controlled is appropriate and feasible.

In conclusion, today's presentation has discussed the data and information provided by the Sponsor to support the Reducer system. We have discussed the regulatory history, the COSIRA trial along with COSIRA-II. We have discussed some of the regulatory considerations regarding the Breakthrough Devices Program and FDA's uncertainty guidance. FDA provided a brief overview of the nonclinical bench testing provided by the Sponsor.

Dr. Crusan provided the discussion of the animal study data collected in support of this device. Drs. Tang and Ryan provided a detailed discussion of the statistical and clinical results regarding the COSIRA trial that the Sponsor believes demonstrates sufficient performance of their device. Dr. Ryan also discussed the currently ongoing REDUCER-I observational trial and some of the information that has been provided from the study. And lastly, we discussed the Sponsor's proposed post-approval study.

Additionally, as part of FDA's presentation, we have also highlighted some of the key considerations and limitations FDA believes are present in this information. These considerations and limitations include significant limitations regarding the preclinical animal studies' data's ability to demonstrate a trans-reducer pressure gradient in coronary sinus narrowing; substantial clinical uncertainty of the primary study endpoint results or effectiveness due to study design execution and analysis issues.

Interpretation of the secondary endpoints present major challenges due to limited sample size, high levels of missing data, and a lack of the pre-specified hypotheses for these endpoints; uncertainty in benefit-risk profile for a chronic cardiovascular implant in a population with a low mortality rate. And while this device is a breakthrough device, it is

still required to meet the statutory requirements for a reasonable assurance of safety and effectiveness.

And finally, the post-approval study provided by the Sponsor attempts to clarify major questions about the current clinical data; however, execution of this trial may be difficult. We believe these issues should be considered as you begin your deliberations this afternoon.

This concludes FDA's presentation and we thank you for your attention and are happy to answer any questions you may have.

DR. LANGE: Great. I would like to thank the FDA speakers for their presentation and this portion of our Panel deliberation is for us to ask any clarifying questions. And again, I'll ask you to raise your hand and I'll try to notify. I think Dr. Cigarroa I saw first and if I'm not mistaken, then Dr. Somberg and Dr. Allen.

DR. CIGARROA: Thank you, Dr. Lange.

Two questions for FDA, one on Slide 22, point 3, with regards to the statement that FDA could not confirm improvements in LV contractility nor perfusion and I just want a clarification from FDA if the data was reviewed and they could not confirm it, if primary data was reviewed, I'm just a little confused on that point.

The second question is a statistical question and would like the perspective from FDA on the probability of Type 1 error given the number of patients enrolled at a hundred and four versus the planned statistical analysis at the outset of a hundred and twenty-four. Thank you.

DR. LANGE: Okay. And as we pose questions, there will be some questions we may ask the Sponsor to address because they've got the primary data and this may be one of those and so Sponsor, if you'll -- I do think the FDA needs to explain why data could not be confirmed, so I'll ask them to address that and then I'll ask the Sponsor to address the

probability of a Type 1 error in a hundred and four versus a hundred and twenty-four patients.

Dr. Somberg.

DR. SOMBERG: A couple of questions to the FDA. One is they talked about missing data, but the primary endpoint of the COSIRA study is the CCS data. Was there missing data in that? I didn't see that on the table they listed.

Two is, there's been a lot of talk of were these patients refractory angina. The FDA pointed out a table of -- with about 25% not receiving anginal therapy. Is it the FDA's conclusion that this was not a refractory angina patient population?

And my third question is about the COSIRA-II trial, which my question is, is there a procedure in that trial that would ensure that the patients are a "no option" resistant population for both drugs and intervention?

DR. LANGE: Okay, I'm going to -- so I'll ask Dr. Zuckerman to address any one of those three, whether missing CCS data -- I'm not sure the FDA is going to render an opinion about whether they believe there was refractory angina or not, other than just presenting the data, but -- and then COSIRA-II.

So Dr. Zuckerman.

I see your hand, Dr. Vetrovec, as well.

So Dr. Zuckerman.

DR. ZUCKERMAN: Yes, Dr. Lange, thank you for your points.

With regard to Dr. Somberg's question number two, I would ask that you direct the Sponsor to present their interpretation regarding that question after lunch. The data that FDA has received on medications is extremely difficult for us to decipher and that was the best that we could do with that slide, Dr. Somberg.

DR. LANGE: Great.

DR. SOMBERG: What about the missing data? Was there any missing data on the primary endpoint for the COSIRA --

DR. ZUCKERMAN: We'll be able to answer that, but the Sponsor also can quickly answer that question for sake of efficiency.

DR. LANGE: Great. I've got Dr. Allen, Dr. Vetrovec, and Dr. Yeh and then Dr. Mathew. Verghese, pardon me.

So Keith, go.

DR. ALLEN: Yeah, hi. Keith Allen.

Can the FDA maybe comment on -- normally they would make suggestions on how to manage missing data and it may be since the secondary endpoints, which is where most of the missing data was, weren't pre-specified, the FDA just didn't go there. But can the FDA make any recommendations on how they could analyze the missing data in those key endpoints and shed light on different imputations, worst-case scenario, for example?

DR. LANGE: I see Dr. Zuckerman's hand. That may be a question we'll ask Dr. Connor to address. And Dr. Wittes.

DR. ZUCKERMAN: Yes. In general, missing data are extremely bad. I think that Drs. Connor and Wittes, in the afternoon, can talk about the missing data problem, especially when there's a sense that the missing data may not be missing at random as reflected in several of the datasets, such as the DSE and SAQ datasets.

DR. LANGE: Great. I've got Dr. Vetrovec, Dr. Yuh, Dr. Mathew and then Dr. Starling. Thank you, Randy.

So Dr. Vetrovec.

DR. VETROVEC: Yes, I have a quick question and Bram may be able to clear this up. It's pretty clear that the mechanism of action is not clear, but is that a requirement for approval? What is the definition of that?

DR. ZUCKERMAN: Yes. Underlined in the FDA presentation, a clear understanding of the mechanism of action is not required to conclude that a device is safe and effective. However, it may be helpful sometimes to know something about the mechanism of action when there is uncertainty regarding some of the other variables where there is uncertainty. But you are absolutely correct, Dr. Vetrovec.

DR. LANGE: Great. I've got Dr. Yuh. Go ahead.

DR. YUH: Yes, one question. FDA made a point of emphasizing the potential placebo effect in this patient population based -- was there any review of the literature to indicate the magnitude of the placebo effect we would expect from this type of a study? I mean, 15% positive response in the control group, at least, seems to me qualitative to be high, but I just want to scale it or calibrate it to what FDA may have gleaned in terms of what would be the expected placebo rate.

DR. LANGE: And I'll hold that for after lunch if the FDA would like to address that and if not, either myself or other panelists may want to address that, as well.

I see Dr. Mathew, Dr. Starling. And then I think, Dr. Connor, I think you had your hand up, as well.

Okay, so Dr. Mathew.

DR. MATHEW: Thank you, Dr. Lange.

A couple questions. One is the post-approval study that's being discussed is a randomized trial, and my question is are we married to that particular version if this goes to that degree or are there alternate models, such as a well-defined pre-specified registry after approval, that might be considered in our discussion?

The second point had to do with missingness of data, but based on Dr. Zuckerman's comment, I presume we're going to have to further discussion on that this afternoon, so that's fine.

Thirdly is just really just a statement, that part of the inclusion criteria here is demonstration of ischemia by dobutamine stress echocardiogram, which may exclude some patients in real life from a pragmatic perspective for this sort of therapy, and then demonstrating improved ischemia similarly over the course of the trial may also exclude some patients that may symptomatically benefit. Again, that might be heretical when we're talking about approval here, but I think in the real world, since almost exclusively this -- the goal here is improvement of symptoms, not really ischemia, I think, in the patient population that we see, it's just something to consider as we talk about this later this afternoon. Thank you.

DR. LANGE: Thank you, Dr. Mathew. And with regard to a post-approval study, we'll have the opportunity to provide our opinions and recommendations to the FDA during our discussion.

DR. MATHEW: Great, thank you.

DR. LANGE: Yeah, it's not a fait accompli. Actually, we'll be interested in this.

Dr. Zuckerman from the FDA.

DR. ZUCKERMAN: Yeah, I'd really like to underline the point that Dr. Lange just made, we're married to no specific post-approval study design. The point is that the Sponsor believes that the uncertainty present in the current data can be adequately addressed with a post-approval randomized controlled trial called COSIRA-II. The Panel, in the afternoon, will be needed to address that particular point under Dr. Lange's direction.

DR. LANGE: Great. I've got Dr. Starling, Dr. Connor, Dr. Cigarroa, and Dr. Page.

So Dr. Starling.

DR. STARLING: Thank you, Dr. Lange. Randall Starling speaking.

During the FDA presentation, when Slide 45 was up, a comment was made regarding the heart team. My question is do we have any specific information on what the heart

team was composed of?

My second question for the FDA is, does the FDA have information that they have received from the Sponsor regarding anginal relief beyond the 6-month primary endpoint?

DR. LANGE: Okay. So I'll ask the Sponsor to address the heart team issue and that is who decided -- and we asked this before, who adjudicated that the individual was not eligible to be revascularized? And then I don't believe there's any other data, but Bram, if you want to address that.

DR. ZUCKERMAN: Well, I think the Sponsor did give us this morning some longer-term data, Dr. Starling, but the subscript on the slide indicated -- on most of those slides, FDA hadn't reviewed the data. So perhaps the Sponsor can again review those data with you, but begin with the proviso of what has and has not been reviewed by FDA for your determinations.

DR. LANGE: Apropos to the question, I think, is there longer-term data on COSIRA and other than those 11 patients that may be in the Reducer study, there are no additional data available. Okay.

Dr. Connor.

DR. CONNOR: Yeah, Jason Connor here.

My question or comment is kind of a follow-up to Dr. Yuh's when he asked for maybe a lit review or comment on placebo effect. So I would basically ask the same question but ask it about natural variability. I'm hesitant to call many things placebo effects. So really, I assume patients just live with the disease. When they're worse is when they go to the doctor and when they go to the doctor is when they get invited to a clinical trial. So just in the variability of their disease they only enter here, which means they can only get better, or natural variability means they're likely to get better than worse.

So what we're seeing in the sham responders is really just regression to their own

mean. So that's what I would like to understand, is there any history on these patients or other patients in the literature just so we can understand, on the scale for the primary outcome, how likely patients are to change by two or more steps over a 6-month period, keeping in mind that, by design, they enrolled patients when they were at a random high.

DR. LANGE: Okay. So again, we'll ask the Sponsor to address that, that is the natural variability of the regression to mean either among these patients or history of life (ph.) patients. Is that correct, Dr. Connor?

DR. CONNOR: That's right, thanks.

DR. LANGE: All right, very good.

Dr. Cigarroa, I think you had your hand up next.

DR. CIGARROA: Thank you, Dr. Lange. For the record, this is Joaquin Cigarroa.

A question with regards to potential safety concerns for FDA. Did FDA consider and/or were they concerned about the potential for an elevation in coronary sinus pressure potentially having a deleterious effect on diastolic function? Early data from the 1970s and early '80s suggested that as a possibility.

DR. LANGE: All right. And I'll throw that back to the Sponsor and that is, were they concerned about it, did they assess it in any way, can they provide any information about diastolic function with CS? Is that fair, Dr. Cigarroa?

DR. CIGARROA: Yes, sir.

DR. LANGE: Okay, great.

Dr. Page.

DR. PAGE: Thank you, Dr. Lange. For the record, Richard Page.

My question is actually to Dr. Zuckerman with regard to his comment about understanding the mechanism of action of devices. A number of us have been through a number of these panels where we see statistics reaching barely significance or just missing

significance and while we don't necessarily need to understand fully the mechanism of a device's action, aren't we obligated to consider scientific plausibility as we assess the data overall and come to a conclusion as to a reasonable assurance of effectiveness?

DR. ZUCKERMAN: I think you've summarized some key points well, Dr. Page, that would be worthwhile to further explain this afternoon, especially since there's been mention of the recent FDA uncertainty guidance and how we're directed to look at and make a final determination of safety and effectiveness. But the basic scientific and logical points you're pointing to are correct. We generally want to look at the totality of data such that we can, at the end of the day, conclude that there's a reasonable benefit-risk profile.

Now, while it is not absolutely required that a mechanism of action be shown definitively, it can be helpful in that determination. On the other hand, though, I think you can fully appreciate other cases whereby you might be looking at a thousand-patient cardiovascular trial where a substantial decrement in mortality is shown at a p-value less than 0.001 and the mechanism of action is unknown and still, because you believe the clinical trial was well executed, that you would conclude safety and effectiveness. So the good common sense in scientific principles that you just enumerated are the ones that the Panel will be utilizing this afternoon in a thorough discussion.

DR. LANGE: Great. I've got Dr. Vetrovec, Dr. Ohman, and Dr. Gersh and then Dr. Allen again.

So Dr. Vetrovec.

DR. VETROVEC: Mine was an accidental hand raise.

DR. LANGE: I'll wave back at you, George.

All right, Magnus.

DR. OHMAN: Magnus Ohman here.

I have a question, if the FDA has looked at the discrepancy between the change in

the Canadian classification and the SAQ frequency of angina questions. In other words, it looks to me that these two are not quite aligned and I would be interested in the FDA's position of why they might not be aligned.

DR. LANGE: I'm happy to allow them to talk about that over lunch and come back and so this is asking their opinion. Bram, are you comfortable with that?

DR. ZUCKERMAN: That's an excellent question the Sponsor may want to opine also.

DR. LANGE: We'll ask both parties to do so. Thank you. Thank you, Bram.

Dr. Gersh.

DR. GERSH: For the record, Bernard Gersh.

A quick comment and a question. The comment relates to what Dr. Connor said about regression to the mean. You know, one of the pivotal, I think, sham-controlled trials is SIMPLICITY -- and after the trial was published, we did an analysis with Dr. Stewart Pocock, the statistician, and showed unequivocally and published in *JACC* that there clearly was regression to the mean and it occurred in both groups. So I think it's -- I wouldn't be at all surprised if there's regression to the mean. At least in SIMPLICITY it was quite easy to show it statistically.

The other comment is I know the measurement -- this comment about contractility increased with dobutamine stress echo, I think we've been looking for measurements of contractility for about the last 30 to 40 years and no one has really come up with a clear measure, but one thing is clear to me, in someone with an ejection fraction that is normal, which it is in the vast majority of patients here, I don't see how you can assess contractility with a dobutamine stress echo in someone beginning with an EF of 55 to 60%. It doesn't make sense to me.

DR. LANGE: Thank you, Dr. Gersh.

I've got Dr. Allen and then Dr. Wittes and then Dr. Connor.

So Dr. Allen.

DR. ALLEN: Thank you. Keith Allen.

Dr. Zuckerman can probably answer this very easily, but I understand that the COSIRA trial is not an IDE trial, the company chose to conduct this trial outside the United States and the FDA either wasn't privy or certainly didn't agree to how the COSIRA trial was designed. But educate me a little bit, Dr. Zuckerman. I'm struck by -- for an intravascular permanent device, safety at 6 months means quite short. What would be the normal standard that the FDA would hold a company to for a permanent intravascular device looking at safety?

DR. ZUCKERMAN: I think that's an excellent point that you're making, Dr. Allen. It would certainly be longer than 6 months and, in fact, we'll be asking the Panel that question this afternoon and what should be done to ensure that safety is verified.

DR. LANGE: Great. I've got Dr. Wittes and then Dr. Connor.

I'm sorry, you're on mute.

DR. WITTES: Yeah, Janet Wittes.

So my question is actually related a little bit to Dr. Allen's and then I have another one. The question related to Dr. Allen's is what aspects of this study did you not -- did the FDA not approve going forward? So that's a question for the FDA.

The other question I have, and I'm struggling a lot with the kind of -- the numerically marginal results. If I do a p-value in a different way, if I do a Fisher's exact test, that 0.024 becomes a 0.04. If I look at the secondaries, they're not really very strong.

And then there's the issue about the 104 and the 124. And this question goes to the Sponsor. What did the DMC tell you? They had an interim analysis, they said to go on, which meant that you had some sense that there was probable benefit. What did you know when you decided to stop at 104?

DR. LANGE: Great. So we had asked that before and that is, why stop prematurely? I'll ask the Sponsor again to address that.

Dr. Zuckerman.

DR. ZUCKERMAN: Yes. So Dr. Wittes has asked a number of good questions and it's important to remember that initial negotiations for this trial began around 2010. So for the sake of being truly transparent and factual, in addition to the FDA explaining some of the negotiations around 2010, I think Dr. Wittes would benefit also from the Sponsor recounting what their interpretation of events was.

DR. LANGE: Okay, we'll do that.

Dr. Wittes, just to save the Sponsor some time, you asked some questions before that the FDA had in their presentation and if you've got a pen there, you asked about how many countries were involved, Slide 25 has that. Number of current smokers, Slide 53. And the movement is Slide 64 from the FDA. I'm sorry, you're on mute, Janet.

DR. WITTES: The movement was a little hard to -- I can figure it out. It would be so much nicer if it was just a table that showed the cross-classification, but I can figure this out.

DR. LANGE: Okay. Well, the Sponsor may still want to do that, but you may want to look at Slide 64 from the FDA, they had some of that information. But we'll still ask the Sponsor to address that to your satisfaction.

Dr. Connor.

DR. CONNOR: Yeah. And I had asked why they stopped. Janet, Dr. Wittes, had asked what they knew at the interim, which I think are two subtly but very importantly different questions. So I just wanted to point that out.

But then my question was actually it seems like the missing data issue is largely an issue with secondary analyses, but I assume that the primary outcome and the secondaries

were all collected at the same visit, you know, at the end of the trial, like the 6-month visit. So my question is one to the Sponsor, which is operationally, how do you have all this missing data in secondaries but not in the primary?

DR. LANGE: Okay, excellent point, so let me -- again, for the Sponsor, what did they know at the interim that may or may not have influenced their decision to stop prematurely? I appreciate that nuance. And then how do we have missing data when it was an in-person interview at 6 months and we have CCS but we don't have SAQ, which is a question.

DR. CONNOR: Yeah.

DR. LANGE: Okay, we'll ask the Sponsor to address that.

All right, Dr. Batchelor, I see your hand. And then I see Dr. Hirshfeld.

DR. BATCHELOR: Thank you, Dr. Lange.

So, you know, we've discussed the fact that we may not have to absolutely have a clear mechanistic explanation for this device and for any device for that matter, as long as safety and efficacy reaches certain thresholds. The animal data that was presented by the FDA was obviously inadequate. I think that was nicely presented, there was missing data and not all the data was presented in a fashion that the FDA is satisfied with. Furthermore, the gradients across this device were relatively small, 2-3 mm/Hg, which I suppose we would expect with this device. We don't have any sense for what would be a normal response.

Two quick questions. Number one, is myocardial information -- you know, they just presented data on histopathologic assessments related to the coronary sinus. If one of these things occluded and you're going to have healing in a neointimal fashion, it's going to be sort of a bell-shaped curve and some are going to heal, I'm sure, worse than others and some will even develop thrombus, and this study is too small to detect this stuff. I'm just

thinking, worst-case scenario, is the FDA satisfied with having very little animal data and just putting all of their eggs in the basket of clinical trial information and further studies, whether they're -- it's an observational registry or randomized trial? Or is it important to have sound animal data to come up with some sense for how this device actually, really, truly heals and whether or not it affects the myocardium in any way, shape or form? If you look at case reports of coronary sinus occlusion, it can lead to myocardial edema, pericardial effusions, and death in the extreme cases. So I'm trying to understand and understand how this device really heals in the absence -- to Keith Allen's point, in the absence of safety data that goes long enough in enough patients enrolled.

DR. LANGE: So, Dr. Batchelor, I'm going to turn that back around for a second. I think to ask the question is FDA satisfied with the animal data, I think the answer to that is no. The next question is do they need additional animal data, and I think they're going to direct that question to us and say are we satisfied and do we want additional data, and I know we're going to be talking about that in our discussion. The FDA is specifically not offering an opinion but actually soliciting ours for this particular thing.

Am I speaking -- I'm speaking on behalf of the FDA, Dr. Zuckerman. Dr. Zuckerman, did I speak correctly?

DR. ZUCKERMAN: I just want to underline the points that Dr. Lange has made. Today is not a time for FDA discussion. These are the questions on the table, Dr. Batchelor, among others, and we and the Sponsor look forward to a robust discussion by this very august, independent advisory panel.

DR. LANGE: Speaking of august, that goes to Dr. Hirshfeld. You're on mute, John.

DR. HIRSHFELD: So I guess that's my signal to leave.

DR. LANGE: No.

(Laughter.)

DR. HIRSHFELD: So I've been thinking a lot about the efficacy issue of this and the mechanism and I'd like clarification. It would seem logical that as part of this study one would get systematic imaging of the device at follow-up to determine to what degree the device has actually done what it's intended to do. A CT angio at 6 months would seem like a very logical way to figure this out and I don't recall seeing that in any of the panel material and I just want to be certain that that data is not available, because it would seem like such logical data to include.

DR. LANGE: Okay. So again, thank you, Dr. Hirshfeld, for that insight. We'll ask the Sponsor if they collected CT angio data on the patients in the COSIRA study and if so, to present that. Great.

Any other hands up? Any other -- all right. Let me propose, we're 10 minutes early. I think the robustness -- the discussion is going to be very robust and I'd like to preserve as much time for that. So with your permission, instead of a 45-minute lunch, could we -- would you all -- I'm going to ask you to vote on a 45-minute lunch or a 30-minute lunch and I'll ask for a raise of hands and of course, I'm only going to see the ones that I'm voting for, but if you would prefer a 45-minute lunch at this point, can I see your hands?

(Show of hands.)

DR. LANGE: One, two, three. If you would prefer a 30-minute lunch.

(Show of hands.)

DR. LANGE: Okay, there are more, so it means that three of you will come back in 45 minutes, the rest of you will come back in 30. All right.

George, do you want to say something?

DR. VETROVEC: Yes. The question is, does that allow enough time for the Sponsor to answer the questions and for the FDA? That seems to me to be an important question. There were a lot of questions raised. We'd all like a quicker lunch, but is that going to

interfere with the information we have asked for?

DR. LANGE: And I think I appreciate you bringing that up, Dr. Vetrovec.

With the FDA, will a shorter lunch be okay for the FDA? There were very few questions posed to the FDA.

DR. ZUCKERMAN: The FDA is okay with the shorter lunch, but we need to hear from the Sponsor.

DR. LANGE: And I'm going to ask them next.

Vicki --

DR. BEBEAU: Yes.

DR. LANGE: -- what would be your preference?

DR. BEBEAU: In lieu of the number of questions that we have, I'd really appreciate the 45 minutes.

DR. LANGE: We'd be happy to do that, okay.

DR. BEBEAU: Thank you so much.

DR. LANGE: I'm going to say it's 11:10, so if we could convene at 11:55, would that be okay with everybody? I'm sorry, it's 11:55 my time, but those of you on the East Coast, you're probably getting hunger pains right now because it's 1:05, so let's reconvene in 45 minutes at -- yeah. Fifty-five, 1:55, 12:55, 11:55, and 10:55. All right. See you guys in 45 minutes. And please turn off -- and I'll remind you not to discuss this among yourselves or with anybody else, and I'll also ask you to turn off your video and mute yourself and we'll see you in about 45 minutes. Thank you.

(Whereupon, at 1:09 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:58 p.m.)

DR. LANGE: Great, it's just now a hair past 11:55 Mountain Time or 1:15 Eastern Time, 12:15 Central Time, and 10:15 -- 10:55 Pacific Time. My apologies.

We'd like to proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. These are all prerecorded, but before then, Aden will read the Open Public Hearing Disclosure Process Statement.

MS. ASEFA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. LANGE: Great. Thank you very much, Ms. Asefa.

FDA has received 13 requests to speak prior to the final date published in the *Federal Register*. Each speaker will be given 3 to 5 minutes to speak.

The first speaker is Meg Seymour from the National Center for Health Research Cancer Prevention and Treatment Fund. Erroneously in the agenda it lists her as being -- this is a nonprofit organization, I just want to state that for the record. And with that, we'll ask 3D Communications to roll with the public hearing portion of these deliberations.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

This Committee is being asked numerous questions regarding whether the data presented is sufficient to support the safety and effectiveness of the Reducer device and if so, for whom. The device in question is permanent and therefore should be held to a high standard when considering approval for a permanent device.

The FDA Executive Summary points out that there's a large placebo effect that has been shown in previous blinded studies in the field of refractory angina, including 42% of the sham group in the COSIRA trial. Given this strong placebo effect, a permanent device should not be implanted in patients without demonstrating meaningful improvements for patients compared to an effective sham-controlled group. And as FDA pointed out, it is important to know if the sham control is effective in blinding most of the patients where they did not know if they had the Reducer device. Moreover, studies must be conducted on a representative sample of patients.

Let's start with the shortcomings of the patients enrolled in the study. The patients studied are not a representative sample of refractory angina patients. Number one, more than 25% of patients in the study were on either one or no antianginal medications. In other words, they did not have refractory angina.

Number two, there was no information about medication compliance.

Number three, zero black or Hispanic patients in the COSIRA trial and more than 80% of the patients were white, male, or both. White males do not comprise most patients, so it would not be ethical to claim safety and effectiveness for a device that was not tested on most of the types of patients who will use it. And yet I don't think the Sponsor would be satisfied if the Reducer device was approved only for white men.

In addition to enrollment, the data provided by the Sponsor is severely lacking. Number one, although there's a statistically significant improvement in the primary efficacy endpoint, we agree with the FDA that the sample is too small to provide reasonable assurance that the results reflect the outcomes for most patients. This raises questions about whether the improvement occurred by chance.

Number two, only one-third of the patients achieved the level of effectiveness required by the primary endpoint, and almost 30% of the patients experienced no change at all from the implant.

Number three, the 6-month follow-up period was too short to evaluate safety or effectiveness for a permanent implant.

Number four, as I previously noted, there was a large placebo effect which, according to the FDA, presents challenges for interpreting the data given the limited sample size.

The bottom line is that the true effectiveness of the device is unknown. We agree with the FDA review that additional data are needed to identify the patient population most likely to have a clinically meaningful benefit with the Reducer device, considering risk for the implant procedure and the device.

Now let's talk a bit more about the safety of the Reducer device. I'm sure you share my concerns and that of the FDA that the Sponsor did not define the pre-specified primary

endpoint for safety and instead relied on secondary safety endpoints, which is the successful implant of the device without a need for intervention.

To address some of the shortcomings in the data, the FDA has asked you to discuss and make recommendations regarding the Sponsor's proposal to perform a post-approval randomized sham-controlled trial in a country where Reducer is not approved. That would basically mean that U.S. patients would be the experimental test subjects for a product whose risks and benefits are not quite proven for them, especially for women and non-whites. Instead, the FDA should require the Sponsor applying for approval to do a better job of recruiting patients with refractory angina, as well as patients who are female and/or people of color. If they didn't achieve that when they were trying to get approval, we know the chances are even lower in a postmarket study.

In summary, we urge the Committee to require additional premarket data from a randomized, properly blinded, sham-controlled study with a representative patient population. Such data are necessary to determine the effectiveness of the device and whether it is worthy of approval and if so, for whom. The data it provided thus far simply do not provide enough data evidence that there are benefits outweighing the risks for this permanent device. Additional data are necessary before such consequential conclusions can be drawn. Thank you.

DR. LERMAN: My name is Dr. Amir Lerman, I'm Professor of Medicine in the Department of Cardiovascular Disease at the Mayo Clinic in Rochester, Minnesota. I serve as the vice chair for the department, but also the director of the Chest Pain and Coronary Physiology Clinic at the Mayo Clinic. I would like to talk to you today about the urgent need for a new therapy for patients with intractable angina.

In our chest pain clinic, in the last more than a decade we focused on patients that have intractable angina that has several phenotypes. One of them is the group of patients

that had that severe underlying coronary disease and already underwent several procedures and are not technically amenable to any new procedure. The other group of patients are patients that have intractable angina not responsive to treatment and these are the patients that have non-obstructive coronary disease and fall under the category of microvascular angina. Both of these patients have increased evidence of cardiovascular events, decreased quality of life, and increased cost of care. We are coming to your meeting in the need of therapy for this group of patients.

Current medical therapy is not designed and currently there are no guidelines for treating of patients with intractable angina. The current device, the coronary sinus reducer, in my opinion, what I've seen from the data and what I've seen of the device, it's a safe, easy-to-use and insert device that can bring us with solution to treat these patients. We currently have requested an FDA approval and have an IDE approval to use this device with patients with microvascular angina and we are planning to start this study in the next few weeks.

Thus, I think this is the right time for the approval of this relatively noninvasive device to treat this highly prevalent number of patients.

DR. KOENING: Good afternoon, my name is Gerald Koening. I'm a general and interventional cardiologist at Henry Ford Hospital, which is a large tertiary medical center in Detroit, Michigan with a wide referral base in the state. I've been in practice for nearly 15 years and a good portion of my patient population has either coronary or peripheral arterial disease, which I medically treat and manage and, when clinically appropriate, also treat with invasive interventions.

Since medical school at Harvard and my residency and fellowship at the University of Michigan, I've had the opportunity of encountering a countless number of patients with a diagnosis of refractory stable angina. With the prevalence in the United States of nearly 1.8

million patients with such a diagnosis, and an annual incidence of nearly 75,000 patients, that would be not surprising.

Currently, my arsenal of treatments for those no longer having a percutaneous or even a surgical option for revascularization, it's typically medications. Only a general category of four medication groups have shown clinical efficacy. But this option is not uncommonly limited; a patient's ability to tolerate the medications, all the pharmacy issues with interactions with other medications, and the overall effectiveness of the treatments.

Additional treatment options exist, such as the external enhanced counterpulsation, stem cell therapy, extracorporeal shockwave treatment, or previously excimer laser therapy. But they've been fraught with limited clinical success or cost effectiveness over prior years, as well as the limitations of the ability for patients to tolerate these regimens. At that point I find myself and my patients to be significantly debilitated by their limitations. This frequently leads them to become physically de-conditioned and in a worsened clinical state for their overall cardiovascular health. In addition, they frequently have a significant decline in their mental well-being, being more depressed, anxious, and oftentimes withdrawn.

Fortunately, more recently I've had the opportunity to be one of the only U.S. cardiologists to actually use the coronary sinus Reducer device by Neovasc. This was done through the FDA and our institutional IRB approval on a compassionate use basis for two patients that had severe limitations and markedly reduced quality of life with refractory and persistent stable angina. Both had residual ischemia demonstrated on stress testing and had been exhausted of current therapeutic options. They were quite miserable and depressed as a result.

This therapeutic option was initially brought to my attention already back in 2015 when the COSIRA clinical trial results were published in the *New England Journal of*

Medicine and carried out through about 11 centers in the world. However, we've yet to access these therapeutic technologies in the United States despite having CE mark approval in Europe and regular success in treating patients based upon registry data.

These two patients, which I believe will also be providing their own testaments, have had quite a significant response in reducing their angina classification category and have much improved quality of life. Their success has brought a new ray of hope, really, to potentially treating a number of my other patients, and this also opened up referrals for my institutional colleagues as well as others at institutions across the street.

Again, having had the experience of implanting this device, I can attest to the relatively low-risk nature of the procedure and really any significant complications, and the relatively limited training and proctoring that's needed for a high rate of successful implantation.

Patient tolerance of the procedure is exceptional and much like that of a standard right heart catheterization procedure, and certainly much less than that of an arterial coronary or peripheral stent implantation. Recovery is rapid and results begin to become evident after about 6 weeks when the device has had a chance to endothelialize and actually form the narrowing or stenosis within the coronary sinus.

From my experience as a general cardiologist in both medical management to these challenging medically refractory stable angina patients, to an interventional cardiologist perspective in performing such a low-risk, high-yield procedure, I definitely feel this technology would make a significant impact in the quality of life in a countless number of patients in the U.S., and also be relatively cost effective, especially in the backdrop of the high healthcare cost associated with treating these patients with relatively few effective options. Thanks for the opportunity to speak with you today, and I'm always available to answer any further questions you may have.

DR. GINDI: My name is Dr. Ryan Gindi and I'm a clinical and noninvasive cardiologist at Henry Ford Hospital. I completed my cardiology fellowship a little over 2 years ago and during my training, I frequently encountered patients with angina refractory to medical therapy. The most common and best evidence-based treatment we had at the time was ranolazine, which in my experience has been marginally efficacious. There were multiple mechanical attempts to help these patients, such as mechanical counterpulsation and transmyocardial laser revascularization. This became a subject of interest to me and I had read about the coronary sinus Reducer, but it wasn't available in the U.S.

In my last year of fellowship I cathed a patient who had severe coronary disease and multiple prior interventions and he was suffering from severe anginal symptoms refractory to medical therapy including ranolazine. He had no targets for revascularization. It occurred to me that this would be an ideal patient for a coronary sinus Reducer and I had mentioned this to my attending during the cath. I was then challenged with obtaining FDA approval for compassionate use.

To make a long story short, I succeeded, and this patient improved from having chest pain while walking to his mailbox, to 3 months later walking around Washington, D.C. for several hours without any symptoms. He recently rode a bicycle 35 miles and was symptom free.

I have since obtained FDA approval on a total of six patients. However, we only implanted one additional patient who had similar positive results. The other five patients were postponed due to COVID-19. These patients are all suffering and all would have been implanted over 1 year ago if it wasn't for delays related to obtaining FDA and IRB approval.

Following my experience, there are cardiologists throughout our organization and even the entire country who have reached out for help with their patients suffering from refractory angina. Angina refractory to medical therapy is a common dilemma we face in

cardiology. There have been multiple mechanical interventions proposed; however, none have panned out over the past several decades and some have only posed higher risks to our patients. I am baffled that a high-risk CTO intervention that carries significant mortality risk is acceptable for treating refractory angina and a low-risk coronary sinus Reducer implantation that has quality data supporting its use and is in the European Society of Cardiology guidelines, remains unavailable to the majority of our patients. I strongly urge the FDA to consider approval of this device, which has the potential to help many patients across the country with a very low risk of even minor adverse outcomes.

MR. CASCIANO: My name is Fred Casciano. I'm 58 years old, I live in Traverse City, Michigan, and was diagnosed with heart disease at the age of 38, with five-way bypass at 41. I had angioplasty with three stents placed within 6 weeks of my bypass surgery. I was then free of angina until 51.

Prior to angina, I was very active, I worked 60 to 70 hours a week, started my own painting business with a crew of four to six employees. I built five homes, I maintained a home and a cabin, mowed an acre and a half of lawn with a walk-behind mower and snow-blowed 300 feet of driveway with a walk-behind blower. I cut and stacked firewood, enjoyed snowmobiling, bowling, and waterskiing.

But my life disappeared after angina diagnosis. I suffered severe depression not knowing from day to day if I was going to live or die. I constantly worried about dying. I worried about my wife if I was to die. I felt guilty for stress and responsibility put on my wife. I worried about the cost of medications and medical bills. I also had anxiety for each time I went to the hospital for a procedure or surgeries, that I would not wake up. Unable to sleep more than an hour at a time, I was afraid I would not wake up. I was unable to walk 300 feet to the mailbox, unable to snowmobile, snow-blow, or mow the lawn. I consistently was reminded of my heart disease with every episode of angina.

Under the care of Dr. William O'Neill, Dr. Ryan Gindi, Dr. Gerald Koening at Henry Ford Hospital in Detroit, I was informed there was a new procedure that might help people with my condition. I had the procedure January 2018 and since then my quality of life has returned. I know that I still have heart disease, but since I received the Reducer I am able to get back to walking. Six months after the surgery, I went for a 35-mile bike ride. I am able to get back to doing things around the house, I have been able to paint rooms at my home and for my mother. I feel my depression is decreasing and I am enjoying life again. I feel very lucky I received this device, it has given me hope again. Please consider my story as you make your decision today. There are many other people out there like me suffering from angina who need this kind of hope, too.

MS. CASCIANO: My name is Annette Casciano. My husband is Fred Casciano. We have been together for 33 years, married for 18 years. Fred was diagnosed with heart disease at the age of 38. By 41, he had survived several heart attacks and a five-way bypass. About 6 weeks after his bypass surgery, he had to undergo angioplasty with three additional stents. Fred was always very active, extremely driven to succeed in his goals. We always enjoyed boating, snowmobiling, spending time with family and friends. Fred started his own painting business with several employees and we built five houses.

When Fred began to suffer with chronic angina at age 51, you could see him decline physically and mentally. He became angry that he was unable to do things around the house. The simple task of walking 300 feet to the mailbox was a struggle. He felt like he was a burden to me. He worried about the cost of medications, medical insurance, and procedures. While he was worrying about these things, I worried about him constantly. I watched the toughest guy I know giving up on life at 57. I was always afraid I would get a phone call or I would come home to find him suffering a massive heart attack or find that he had passed away.

When we were told about the opportunity for Fred to receive the coronary sinus Reducer, we were given something we haven't had in a long time, which was hope. We understand that Fred's cardiac disease would still be there, but having the hope that Fred could possibly be able to do things he used to do and we could get back to a life that we had before, one without so much fear.

Since the coronary sinus Reducer, Fred's energy has improved, he's become more confident, he is able to do things without the constant reminder of his heart disease. His depression has decreased, he's laughing again. Family and friends have noticed a big improvement. I feel that I have my husband back and the stress that I had been living with all this time is also becoming less. I don't worry about losing him on a daily basis. I am so thankful Fred was given this opportunity for this device. It has definitely made an improvement in our lives and brought us renewed hope for the future. I hope that you can find it in your wisdom today to bring this kind of improvement and hope to patients and their families that struggle with angina. Thank you for your time.

MR. SOBERANO: My name is Mark Soberano, I worked as a nurse anesthetist for special needs families at Cincinnati Children's Hospital for 20 years. Now my life is far different. On January 18th, 2016, after ignoring 18 hours of chest pain, I had a cardiac arrest. I was revived by my wife and children and taken to a regional hospital where I received one stent.

Since then, I have continued to have 8 out of 10 chest pain with any kind of activity and continually need nitroglycerin. I am on disability. I cannot walk for more than 50 feet without having 6 out of 10 chest pain. I take nitroglycerin at least five times a day. Although I'd like to take more, the side effects preclude that. I am a husband, father of seven children with ages 28 to 11. But as time goes by, my condition gets worse. I feel like my family's life is moving forward while mine is standing still. My five sons are all in

scouting and we used to go camping with the scout troop at least once a month. Now I am unable to join them for even one night. As a family, we would take hikes in the parks near our home. Now I get chest pain when I walk anywhere outdoors. I have had trouble walking my service dog. My daughter's a gymnast and I cannot attend a full meet without being exhausted.

This treatment will not change my diagnosis. I will still have complex microvascular cardiac disease for the rest of my life, but it will give me back some quality in life, the kind of life that I can only dream of where I actually used to be part of my family, like seeing my kids participate in a favorite sport and enjoying the outdoors. I beg you to remember that this treatment has a high potential to change my life so that I can be an active participant in my world and the world of my family, something that you take for granted, but I cannot. Thank you.

MR. SUMMERS: My name is Steven Summers, I'm 58 years old and I live in Macomb, Michigan. My first heart attack was in 2012 at the age of 50. I experienced chest pain and angina as well as chest pressure. I believe at that time I had two stents placed during the catheterization procedure. The year prior to the first heart attack, I had started seminary with the goal of becoming a full-time minister. As a result of the heart attack and subsequent periods of angina and continued procedures, I was unable to continue the pursuit of a master's degree.

My cardiologist has, I believe, run out of options, that is, room for any additional stents for controlling the angina. I am also not a candidate for bypass surgery. I'm currently on disability as a result of a mild stroke in 2018, combined with the continuing heart issues. Prior to the cardiac sinus Reducer procedure, I relied on the nitroglycerin tablets to ease any chest pain. Any exertion, including taking the garbage to the curb, mowing the lawn, going for a walk around the block, going up stairs, would have caused

chest pain. My cardiologist mentioned the sinus Reducer as a possibility in 2017 and got approval in 2018. The first 6 months following the procedure, I was still experiencing angina pretty regularly. The past year and a half have been nearly angina free. I still use the nitroglycerin occasionally. Rarely, actually, two to three times a month, but the pain is not nearly as intense and is rare.

The angina I experienced prior to the sinus Reducer procedure was tough on my wife, especially. But now the angina has subsided considerably as a result of the sinus Reducer procedure. My wife and I were recently on a weekend and we're able to bike ride, horseback ride, and walk with only one instance of needing a nitro pill. It's actually pretty rare now that I even think about angina, but when I do, I'm reminded of the life-changing sinus Reducer procedure and the remarkable improvement of my life. Please remember my story as you make a decision. Thank you.

MS. SUMMERS: Hello, my name is Donna Summers and I have been married to Steven Summers for 33 years. Steven had his first heart attack at 50 years of age, 8 years ago, and was diagnosed with diffuse narrowing of his cardiac artery. Before his diagnosis, we lived active and a busy life with work, church, family, activities, and vacations. And all of that changed 8 years ago.

Living with a husband with angina is worrisome, constantly aware of the need for potential medical care. I've lost count of the number of stents Steven has had placed and the number of hospitalizations. Our life changed from being able to just pick up and go to needing to remind Steven as we leave the house on meds, insulin, nitro. The anxiety and fear of the nitro not working, the fear of the limiting impact on our family was our constant companion.

Steven took a lot of medications and any activity would trigger the chest pain. Simple things lots of people would take for granted, like enjoying a walk with the grandkids,

that was gone. And other things could trigger it, as well, that were out of our control. Basically, our family and our church activities revolved silently around Steven's limitation. We'd always try, but we could tell he was struggling and because he could not work any longer, he needed to apply for disability, something we never thought would happen. The sadness that our life was becoming was so limited by this disability and it was profound for Steven. He struggled with depression and feeling useless and feeling old at a young age.

Thankfully, we were told about this procedure, a device that could help Steven's quality of life and so we talked it over at length with the team and decided it would help. For the most part now, Steven can do daily work without chest pain and care, it's very rare for him to have to and he can take walks with the dog and play with the grandkids and we've gone on two vacations recently and gone on long walks without any chest pain. He is more hopeful and so am I, as we've just had a 1-year anniversary without any hospitalization.

We know that his cardiac condition is serious, but are appreciative of every moment we get together. But with this procedure, our quality of life has improved exponentially since it has allowed us some semblance of normality and enjoyment of basic abilities. Without this procedure, we were becoming very limited to our home. This procedure gave us hope for a life maximized instead of a life limited by his heart issues. This would not have been possible without the procedure and I hope other families are given this opportunity, as well. This illness impacts the health and well-being of the spouse, too.

MS. VANDENBOSSCHE: Good afternoon, my name is Laurie Vandenbossche. I live in Port Huron, Michigan, and I'm 59 years old. In the past two and a half years I've had two heart attacks and was diagnosed with angina. In those two and a half years I've been hospitalized several times and had six heart catheterizations, angioplasty, and stents. In spite of these health issues, I've had an absolutely wonderfully blessed active life with my

husband and children. Unfortunately, since suffering from angina, my life has changed dramatically. I truly hope by sharing some details you will gain a better understanding of what it's like to live with angina.

I had planned on working for another 5 years, but had to take an early retirement from a very rewarding job that I loved, teaching struggling first graders how to read. In my retirement, I was hoping to be involved in volunteer work, but I'm afraid to commit for fear I won't be physically able to fulfill the duties expected of me. Although I've always been a positive person, I now struggle with anxiety and depression. I would love to wake up in the morning and not have the feeling of being stressed about whether I'll have angina today on my morning walk or throughout the day or after I eat or doing yard work or household chores or even running errands like grocery shopping.

I was very social, but now I'm often withdrawn and fearful. I've always enjoyed walking with friends, but now I make excuses because one of my angina triggers is the feeling of indigestion and belching, which is not only uncomfortable but embarrassing. I'm fearful to make any travel plans because of the frequency of my hospitalizations.

Last year while on vacation in Chicago, I wound up spending 4 days at Rush Medical University Hospital. It breaks my heart that our family vacations have had to drastically change because of my angina.

Although I realize this procedure will not cure my cardiovascular disease, I'm very hopeful it will provide some relief from the deep anxiety I experience every day and help restore some normality to my life and the lives of my family. After consulting with my cardiologist, I know this may be my only option to enhance and improve my quality of life. It has the potential of being a life-changing experience for all those suffering from this debilitating disease. Thank you for allowing me to speak to you today. I hope and pray you seriously consider approving this procedure.

MR. SCOTT: Hello, my name is Don Scott and I am here to talk to you today about my experience living with angina. I am 76 years old and was working full time until I was 71. I started cutting grass as a teenager, worked as a union teamster on a dock at a trucking company loading and unloading trucks, and then I spent the last 30 years of my career working as maintenance and grounds manager at a retirement apartment complex. In all the time I worked, I carried things, fixed things, and was able to help people.

Since retiring for medical reasons, I am no longer able to do even some of the most basic things that I have done my entire life. My wife cuts the grass at our home and I can barely walk up or down a flight of steps without being winded or having to take a break. Even walking from my car to the baseball field where my grandson plays is a challenge. I really miss the quality of life that I used to have and I'd love to be able to help take care of my own home and my own family and pick up my grandchildren without fear of getting light headed or dizzy.

I believe I am a good candidate for this procedure and hope you approve it so I can bring back some of those things that I used to be able to do. Please remember my story as you make your decision today.

MS. HOPKINS: Hi, my name is Tammy Hopkins. I am a 42-year-old female that lives in Cincinnati, Ohio with my husband. I was diagnosed with angina at the age of 29 and had a massive heart attack 6 months later that required me to undergo a CABG, which led to having a stent placed several months later and every year after that, for 4 years, with continuous hospitalization every 3 to 4 months in between having my stent reopened and countless surgeries, or just having pain from angina with excruciating pain and being very short of breath.

Before having angina, I used to swim all the time and enjoy life with my dogs and my family, but now my quality of life is limited because I'm short of breath all the time, never

know when my angina is going to come on or how long it's going to last. It limits me to do a lot of activities like going to Six Flags, riding rides, playing and running with my grand babies or just normal day walks with my husband and my dogs. I am a nurse and love what I do, but I have a lot -- I have to give up my passion and life because my everyday normal life of living with angina is too much for me. Just regular everyday breathing and watching TV or walking devastates me because of my excruciating pain.

I realize that a treatment like this won't change the fact that I have a cardiac condition, but it can give me a better quality of life that's vibrant, joyful, and worth living. My mother and sister died at a young age of a massive heart attack, as with myself with no other options available to me, I live with the same fear. So when I heard of this procedure, I thought it could be a helpful option of what it could bring to me and my family, as well as others like me in the same space. I always say if there is a will, there's a way. So please take into consideration of what this would mean to a lot of people like me and our loved ones because all we ask for is a chance for a better life. Thank you.

MR. HART: Good afternoon and thank you for allowing me to be one of the speakers today. My name is Clyde Hart and I'm a 74-year-old heart patient with stable angina and severe breathing issues, and I know I have the best cardiology team trying to guide me through these issues and help to improve my quality of life. I have had one open heart surgery in 2014, numerous tests, 14 stents, a triple A surgery, high blood pressure, and diabetes. My doctors tell me I am not really a viable candidate for any re-vascular procedures.

My cardiologist heard of this procedure and began to research the possibility of getting this done. He knew it had not been approved in the United States but was being used overseas and had some promising results. He asked me if he could apply to our FDA for compassion use approval. He sent in a request and after a short period of time, we

were approved. I am not sure how many others across the U.S. were approved, but I do know there were several. In this process the COVID pandemic came up and a doctor from Israel has not been able to come, he is going to proctor the procedure with Dr. Balarn (ph.) and therefore, even though approved, we will have to wait for the infection rate to diminish prior to getting the device implanted.

The quality of life for me has been lessened in the past 3 months, mostly in the ability to breathe well, and also the angina issue. I think I'm a pretty tough old guy who can get along with the angina, but the breathing issue really hinders my ability to get around. I have always been a very active person and honestly, at this point, I would rate my quality of life about a two. I realize I am not supposed to feel like I did when I was 25, but not being able to do things with my grandson, not being able to walk into my church and having to take three times as long for my wife if I have to go anywhere, I would love to be able to go my grandson's ball games, but would not be able to walk from the parking lot to the field and it would be too much of a burden on the rest of the family.

I would urge you to help with getting this device approved and our doctors trained to help patients like myself to hopefully have a little better quality of life. Again, thanks for trying to give me a reason to go on with my life.

DR. LANGE: I want to thank each of the 13 speakers. Your perspective and your experience is valuable, and so thank you for taking the time to share that with this Panel. I now pronounce the Open Public Hearing to be officially closed and we will proceed with today's agenda.

We'll now begin the Panel deliberations. Although this portion is also open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

During the next approximately hour and a half or so, we will open the floor to questions for both the Sponsor and the FDA. We have a number of questions that have already been posed and what I'll do is take this opportunity to repeat the question from each of the panelists and allow the Sponsor an opportunity to respond to those questions.

So is the Sponsor prepared, are they ready? Great.

DR. BEBEAU: This is Vicki Bebeau.

Yes, we are. I'm actually going to turn it over to Dr. Stone, who will moderate for us.

DR. LANGE: Okay. All right, Dr. Stone.

DR. STONE: Well, thank you very much. We really appreciate the effort and the time you're taking today to hear all of the details about the Reducer and I do think that the patient summaries were actually very powerful.

But we have spent the entire lunch period and we will try to address every single one of your questions. What we're going to do is kind of -- some of them overlap each other, so we're kind of bunching them in groups. So we may not specifically say who addressed the question, but we'll try to address every single one and if there are any we have not addressed at the end, please ask us.

DR. LANGE: All right. So, Gregg, let me say, I'm going to do this the opposite. I'm going to go by the speakers and pose the question and allow you to answer and that way --

DR. STONE: I see.

DR. LANGE: Yeah, but I agree, that's great to have additional clarifications. But I thank you very much.

DR. STONE: Okay, so that's fine. So yes, we are ready, and myself and Ms. Bebeau and Dr. Shmuel Banai will be answering the questions, as well as the statistician.

DR. LANGE: Terrific. Let me start with Dr. Somberg's question, he asked about what you can tell us about the pharmacologic maximization for the 30 days prior to the

procedure.

DR. STONE: Yes. So most of these patients had had chronic refractory angina. The inclusion criteria were, yes, just greater than 30 days and I will say it was not collected in the case report form as to the number of months or years that they had refractory angina, but they had to be on stable medical regimen for at least 30 days, and that was also reflected in the Seattle Angina Questionnaire forms. So we do have a lot of stability data on medications post-randomization which we can show you, if you'd like to see that now or wait until later.

DR. LANGE: No, please, now would be a good time.

DR. STONE: Okay, so let us -- let's pull up those. Let's see, let me look here. So first let me show you this slide. We've got, I think, three separate slides I can show you. So this slide shows you the antianginal medications at baseline and at 6 months, and you can see the Reducer arm compared to control at baseline, Reducer arm compared to control. This is just a number of antianginal medications. And basically, what you can see that is in both arms, just being on a class of medication was fairly stable. Perhaps one exception was nitrates, there tended to be perhaps slightly greater control group patients taking nitrates at follow-up compared to the Reducer patients, but pretty much it shows stability in the number of angina medications and the classes of angina medications. So now I think that we can --

DR. LANGE: Can you go back to that slide? Dr. Somberg, you had asked for this information. Can you go back to that slide, please? Dr. Somberg.

DR. STONE: Yeah. Can you pull up that slide again, please?

DR. SOMBERG: Can you hear me?

DR. STONE: Yes, John.

DR. SOMBERG: Okay. Well, two points. One is, so you're saying that there was

really no attempt at maximization of therapy in the pre-randomization and --

DR. STONE: Well, no, no. No, no, I'll get to that. That actually was not the case.

DR. SOMBERG: Okay, so then -- okay, you'll get to it. And the second thing is do we have any idea -- I mean, we know the class of drugs, but we don't know the dosages and the -- you know, was there any up-titration over the course of the study?

DR. STONE: Both of those two issues will be in the next two slides. So let me show you these next two slides and then we can address whether there are any other questions. So first, here I'll show you this slide, which is the mean antianginal medication dosages at baseline and 6 months.

And before even talking to this slide, let me just state that all the sites in the investigational protocol and the discussions with the sites, before the patients were enrolled, was that they and the general cardiologist, the interventional cardiologist and the cardiac surgeons, had to optimize the medications that these patients were on and they had to optimize all the revascularization options.

So as you can see, most of the patients had had -- almost all the patients had prior revascularization, most of them had had multiple revascularization procedures. All of these patients were being evaluated constantly for years in their lives by interventional cardiologists and cardiac surgeons and they still had Class III or IV angina. All of them were also constantly being evaluated for maximal medical therapy.

Now, when we get to it, and I'll show this in the next slide after this one, the reason that many of these patients were not on what you might consider four or five drugs is multiple reasons. As you know, the more drugs you're on and these patients are on not only antianginal drugs but drugs for diabetes, drugs for hypertension, drugs for hyperlipidemia and multiple other conditions, it's very difficult to take 8 or 9 or 10 drugs a day. Number one. Number two, these drugs, and in particular, beta blockers and nitrates,

have a lot of side effects and the patients were almost uniformly tried on these drugs, but many of them could not tolerate the drugs. And as I'll show you, the usage of the drugs were very similar to what we've seen in every other refractory angina study. So let me show you these two slides and then I can address any other questions.

First of all, this slide that you're seeing right now speaks to the constancy of the drug dose over time and you can see, basically, this is just a very simple counting up milligrams of beta blockers at baseline and in the Reducer baseline and then at 6 months.

DR. SOMBERG: What does this mean?

DR. LANGE: Yeah, I mean, the people are on 10 mg of a beta blocker? What does that mean?

DR. STONE: So as you know, there are different beta blockers and -- you know, from bisoprolol to metoprolol, etc., these are the means and there -- and I'll be the first one to acknowledge that there are tables where you avert the average daily doses from one to the other, that was not --

DR. SOMBERG: That's well established.

DR. STONE: And that's well established, but that was not done here. This was to try to get you whatever information was available at short notice and here you can see what we're able to show you.

DR. LANGE: Okay. Gregg, that's fine. Let's go to the next slide. In other words --

DR. STONE: Okay.

DR. LANGE: -- here's what I'm saying, we have a lot of questions and I want to get through them.

DR. STONE: Yes.

DR. LANGE: And so I want to keep our answers short and succinct.

DR. STONE: I appreciate that. At least what this shows you is similar doses in both

groups and constancy over 6 months, at least with the manner that these data were calculated.

Now let me show you this next slide, and this is a slide that I don't believe FDA has seen or been able to adequately evaluate, but what this shows you is a literature review of the principal or the largest refractory angina trials that have been done, RENEW, ACT34, AGENT-3 and 4, the OPTIMIST registry, and COSIRA, and these are all refractory angina patients. And here you can see just the -- at baseline, the medications that were used, nitrates, calcium channel blockers, and beta blockers.

Now, in those other four studies, those studies were actually performed before there were other antianginal drugs available with the exception in RENEW of ranolazine, so those asterisks basically are drugs not available. You can also see in COSIRA that there are patients on other antianginal drugs, as well.

So I think when you add all of this up, it's approximately similar to all refractory angina trials, the drugs that patients are taking and able to tolerate, given side effects, hypotension, etc.

DR. LANGE: So Dr. Somberg, do you have enough -- I think you --

DR. SOMBERG: Well, I appreciate the Sponsor going to this effort, but I do not think either of these slides answered the question.

DR. LANGE: Okay, all right. Sufficient.

Dr. Page had asked about the mechanism of action with regard to the Beck, knowing if there was both CS narrowing at the procedure and also asbestos applied to the pericardium and occluder rods, but the comments from the Sponsor that it was -- relief of angina was due to CS, is there any data that the Sponsor can offer to document that?

DR. STONE: Dr. Banai will address that.

DR. BANAI: Hi, Shmuel Banai here. Thank you for the opportunity to answer a few

of your questions.

The Beck operation included several different operations. The Beck 1 operation in human included both narrowing of the coronary sinus, as you see here, with a metal stylet in the diameter of 3 mm, within the ligature, around the coronary sinus and the metal stylet and then taking out the metal stylet and leaving out with the ligature that narrowing the coronary sinus for 3 mm. This was done in human with -- in some of the patients scrubbing with asbestos the pericardium, and the thought was to promote angiogenesis inflammatory response and more blood vessels coming from the chest wall into the myocardium.

But Claude Beck also performed experiments in animal, in dog model, of severed circumflex artery and he showed that only with increasing the pressure in the coronary sinus by his operation he can double the amount of backflow coming from the distal cut of the severed circumflex artery by increasing the pressure or relieving the pressure in the coronary sinus. So even without asbestos, scrubbing of the pericardium, just the narrowing of the coronary sinus, he's shown in animal models that it preserves myocardium and improves ischemia.

DR. LANGE: Dr. Page also had asked about the narrowing in the coronary sinus, it looked like a reverse hourglass and was that -- that's on Slide 45. Was that the intended result of the procedure or something unexpected?

DR. BANAI: Yeah, let me take you through the mechanism of action and what really happens when you implant the Reducer, and I'll also address the question that was about the pressure gradient across the Reducer.

So when you implant the Reducer in the coronary sinus, you intentionally oversize it by 10%. The intention of over-sizing has two reasons. One reason is to uncork (ph.) the device in the coronary sinus and prevent migration and the other reason is that both ends, both wide ends of the Reducer are engaged into the vessel wall and the interaction

between that embedment of the struts into the vessel wall start a process of tissue proliferation, what we call injury induced smooth muscle cell proliferation, tissue proliferation. And this process takes a few weeks, sometimes 8 or 6 to 8 weeks and this tissue proliferation grows over the struts to cover the struts and the gaps between the struts, and in the histology cuts that you see below from an animal model, you see the proximal end, the distal end, and the midsection.

Now, sometimes the midsection is not covered with tissue, which is fine. The narrowing is caused by tissue proliferation mainly at both ends and what you end up in this specific example is a tube-like narrowing. But really it doesn't matter, it can be both sides throughout the Reducer, only one spot. The idea is to get the pressure gradient across the Reducer, which does the work.

And this is an example of a pressure gradient measured in animals 6 months after implantation of the Reducer, you see almost 3 mm/Hg pressure gradient. Remember that in the pig there is azygos, big azygos vein, so it might not be representative of what we have in human. In human, we haven't measured the coronary sinus pressure because we felt it is unethical to expose this patient for another right heart catheterization 2 months after the procedure, but we do have CT angiography. May I have Slide AE-10, please? We have CT angiography done in more than 44 patients, both from the COSIRA trial and from the first-in-man trial. All of the CT angiography were analyzed by an independent core lab.

What you can see here is a CT image showing a contrast flow through the coronary sinus, coming from 12 o'clock and draining into the right atrium, which is at 6 o'clock. The central narrowing of the Reducer is clearly seen and contrast is flowing only through the center. You don't see contrast around the struts or outside the center and you clearly can see that the Reducer is not occluded.

Now, out of the 44 CT angiography analyzed, there was no device fracture, all

devices were patent, there was no thrombosis at all in none of them. Also, there was no distinguishable differences in the CT angio findings between the COSIRA Reducer and the 12 years follow-up of the first-in-man Reducer. Additionally, there were 11 CT angio from the first-in-human that was performed at 3 years follow-up with similar results.

One more thing I wanted to show you, this is another example of 3-D reconstruction of the heart, the back of the heart, showing the Reducer and a cross-sectional area. And maybe I'll show another example talking about the tissue growth and the neointimal growth in the Reducer.

If you will pay attention to the bottom picture on the left, if we look at the most left image, you will be able to see -- I don't know if you see it large enough -- you'll be able to see a transverse cut of the proximal segment of the Reducer and you will see the white struts, which is the outer circle which is whitish. At the center you will see a contrast of the true or residual lumen and in between the struts, the white strut and the gray lumen where we see the contrast, you see a black circle aligning in between and separating the true residual lumen and the struts. This is actually the tissue growth that grow in response to the interaction between the stretching of the vessel wall by the Reducer and the vessel wall. So this tissue growth caused the narrowing along the Reducer.

DR. LANGE: Okay.

DR. BANAI: May I have also --

DR. LANGE: Dr. Banai. Dr. Banai, I'll get to those things. I just want to make sure that for each of the questioners, their questions were answered and so we'll talk a little bit more about this, the CT angio, in just a moment. But Dr. Page had asked previous questions about the Beck and the CS narrowing.

Dr. Page, have they adequately --

DR. PAGE: Well, yeah, the Beck wasn't as much a question as a comment, but I

appreciate the response and the confirmation was that the human procedure included the pericardial asbestos and whatever happened in pigs or dogs or whatever it is, I haven't looked at those data, but the humans all received both procedures is what my understanding was and I just heard confirmed.

The issue of the blood flow I thought was really interesting from the pig, but as was pointed out, that has significant drainage to the coronary sinus that humans don't enjoy.

And then finally, the CTA, I think, is interesting. I'm not an angiographer. I'm an electrician, not a plumber, so I'll leave it to my plumbing colleagues to comment on what they're seeing there. I do wonder whether that perfect hourglass is typical of the 44 angios that were obtained or whether that is, as most of us would do, a really good example of one case where the perfect hourglass is provided, and I'll leave my comments for the later discussion.

DR. LANGE: Okay, so keep those comments because we will come back, there's more issues about the CT and the thrombosis that was reported in the Reducer study, so we'll get around to that. So thank you, Dr. Page.

But Dr. Banai, thank you for answering his questions regarding --

DR. BANAI: Just a moment on the comment.

DR. LANGE: No, no. I mean, there will be additional time, in other words, we'll make sure that you have -- I just want to address it by each speaker so we don't leave anything out and so you'll have an opportunity to speak, I promise.

Dr. Allen asked, in terms of the evaluation of whether people were revascularization candidates or not, did a surgeon -- was involved with that decision, that the patient had no other options? And/or an interventional cardiologist?

DR. STONE: This is Gregg.

So in general, the answer is yes. Again, the instructions that were given to the

investigation team is that these patients had to truly be refractory to all revascularization options, both PCI and surgery. These patients had been evaluated for surgery multiple times in their lives and as you saw, a majority of patients had actually had prior surgery, some had had two surgeries and many of the patients had multiple PCIs. So while this study was done before the concept of a heart team was really formalized in the world, in general, yes, these patients were seen by a general cardiologist and a comprehensive care team also consisting of an interventionalist and a surgeon before they were felt to be eligible for enrollment in the trial.

DR. LANGE: Gregg, let me go -- let me ask a question. That's documented or it's just presumed that because they got in the trial, that's what happened?

DR. STONE: Yes, just presumed. There is not detailed documentation about it.

DR. LANGE: Thank you, sir.

There was a question about how the blinding was confirmed. And both the FDA and the Sponsor talked about what measures were taken to try to do it. Were there any measures taken to confirm the blinding was successful?

DR. STONE: Yeah, that's a great question. You know, this is one of the first sham-controlled randomized trials that have been done in interventional cardiology and in fact, I think, as you know, there's actually even to date been very few of them that have been done and the procedures that were put in place when this trial was performed are not as robust today, and they did not include a blinding or what I would even call a perception questionnaire.

So we are left to look back at the robustness of the study procedures, but I think that even more important than that, we do have evidence that there was effective blinding, and I'll just bring this up again because it is one thing to have somebody say yes, I know or I don't know, but I do think we actually have pathophysiologic evidence that there indeed

was blinding. I think you got these 30-day results that do show a combination of placebo effect and yes, I would certainly say there may be some regression to the mean phenomenon here. And importantly, I think you see that that was balanced between the Reducer group and the sham-control group. Then I think you see, over 3 months and 6 months, you've got a separation of the groups of patients here and I think very important is actually the control group. Because they had the control group become unblinded, I don't think you would see the same maintenance of their improvement. And the same thing happened for just one-class improvement in angina, as well. This goes along with the mechanism of the Reducer, that that neointima develops over about a 2-month period, which is when you would expect the pressure gradient to be created.

DR. LANGE: And I appreciate that.

DR. STONE: Thank you.

DR. LANGE: But the answer is -- and I agree, the study was done differently, it's not as robust, but the answer to the question is we have no -- I mean, we can surmise based upon this data but the answer to, I guess, Dr. Allen's question is that we have no confirmation.

DR. STONE: There was no formal blinding questionnaire.

DR. LANGE: All right, thank you.

Dr. Zuckerman.

DR. ZUCKERMAN: Yes. Important data are being discussed and as I mentioned after the Panel's initial Sponsor presentation, the Sponsor does have the ability to show data that has not been independently reviewed by the FDA. But I would again ask the Sponsor, when they are showing data that has not been independently reviewed by the FDA, such as the last important slide discussion, that this be mentioned such that panelists are made aware and also that these comments are appropriately put into the official government record.

Thank you.

DR. LANGE: Thank you. And if we fail to do so, please remind us, Dr. Zuckerman. Thank you, I appreciate that.

Dr. Allen also asked who was managing the post-op medications and any change in medications and was that person blinded to the treatment.

DR. STONE: Yes, all the post-op evaluations and management were performed by blinded investigators.

DR. LANGE: Terrific. And then there was a question about pressure measurements in animals. Dr. Banai, you showed one graph. How many animals actually had pressure measurements done?

DR. BANAI: In this graph that I showed, this is the mean of six animals to 6 months after implantation of the Reducer.

DR. LANGE: Terrific, terrific.

So Dr. Allen, does that address the questions that you had?

DR. ALLEN: Yes.

DR. LANGE: Great. So thank you for the responsiveness of the Sponsor, I appreciate it.

Dr. Yuh asked about microvascular disease in a broader general -- about the presence of coronary disease because none of that data was shown for either group, the extent of coronary disease, or there was microvascular disease and did this exclude women. So let me turn it over to you, Gregg, to address that.

DR. STONE: Yeah, thank you.

To get into the trial, the patients had to have severe coronary artery disease and there was no core lab analysis and there was no formal evaluation of the extent of coronary disease. The patients with microvascular angina or INOCA, ischemia with normal coronary

arteries, were not enrolled in this study and I can tell you, speaking for myself and Dr. Henry, we certainly believe the trial results speak to the patients that were enrolled, which were patients with severe coronary disease, again, almost all of whom had multiple coronary revascularization procedures, there's evidence of that. And while we think this should be effective for patients with microvascular disease, that would need to be the topic of a future study and I don't believe the Sponsor is asking for approval in that patient subgroup.

DR. LANGE: Great. Dr. Yuh had also asked about the procedure times for the sham procedures and the control -- I mean the sham procedures and the device procedures. Do we have that information?

DR. STONE: Yeah. As we sit here, I don't have that information, but these are relatively short procedures, usually on the order of 30 to 45 minutes. It's basically implanting a stent in a normal vein, which, for any interventionlist with a little bit of training, is quite easy. And of course these patients, again, were mostly heavily sedated and I can't imagine that there was a major difference in the procedures, but I don't have that data.

DR. LANGE: All right, great.

So Dr. Yuh, to the extent possible, did the Sponsor address both of your questions?

DR. YUH: For the most part. The first part was more out of curiosity in terms of the putative mechanism of this intervention, it would seem to favor those patients that had microvascular disease with a redistribution of blood flow. So I was just curious as to why that population was not included at all. There must have been some conscious reason why you wouldn't include that and I was just curious as to what that was.

DR. STONE: No, I mean, I think it's a great question and I think those patients should respond well. I will show this one additional slide because you also asked about women. It

is true that women have a higher incidence of INOCA and the fact that those patients were excluded is probably one of the reasons why it was a male-predominant population.

So initially it was decided to study the Reducer in the population of patients with, again, obliterative coronary artery disease with no revascularization options, especially left coronary distribution ischemia, and that led to the population that we studied. You can see here regarding the number of women, and we've put here the major refractory angina studies. And again, all of these studies did require coronary artery disease, as well, and you can see it was 19% women in the Reducer and actually 12 to 16% women in the other studies. So this seems to be quite typical in terms of both race, sex, and age for refractory angina populations due to coronary disease.

DR. LANGE: Great.

DR. YUH: Thank you.

DR. LANGE: Dr. Cigarroa had asked about whether the individuals that were adjusting meds and those that were assessing angina, were they independent, were they blinded, were they interactive in any way?

DR. STONE: No, all of the investigators and personnel who were seeing the patients during follow-up, who were assessing their angina class, who were adjusting their medications, who were administering their exercise tests, were blinded.

DR. LANGE: Right, but were the people who changed the medications blinded to how they responded to the SAQ or the CCS?

DR. STONE: Oh, you mean were the same people that were taking the CCS, were they the ones who were adjusting medications?

DR. LANGE: I believe that's the question.

DR. STONE: So I don't know the answer to that, but I would imagine so, because you have to ask the patient about their angina before you decide whether to change their

medications over time.

DR. LANGE: All right, thank you. He had also asked about whether, in the 34 of 52 treated patients that had no change, no improvement in their angina, and the 44 of 52 in the sham group, was there any difference or change in the diastolic filling period?

DR. STONE: Dr. Banai will address this.

DR. BANAI: Hi, Shmuel Banai here.

May I have Slide MO-11, please? The issue of diastolic function was -- is a question we ask our self because when you narrow the coronary sinus and you increase coronary sinus pressure, one might suspect that you can cause interstitial edema and affect diastolic dysfunction. This was not tested during the COSIRA trial, but it was evaluated later by two clinical trials.

The first one that I'm showing you here is an echo study which tested the diastolic function in 24 patients with severe grade III and IV angina, who were treated with a Reducer and diastolic function, was evaluated 6 months later and actually, it showed that the diastolic function improves at 6 months. And the idea why does it improve is because you improve perfusion and when you improve perfusion, you improve diastolic function.

Lately, it was also tested, and this is a slide that was represented in a manuscript that was published in May, so the FDA might have not the chance to see it. Nevertheless, this study was done by perfusion MRI and by perfusion MRI, they took 20 patients with severe angina, implanted the Reducer and repeated that perfusion MRI at 4 months and they showed that at 4 months the Reducer implantation improved myocardial contractility, ejection fraction improved, it improved myocardial longitudinal and circumferential strain and maybe most importantly with the fact of diastolic function, it is improved ischemic burden and improved intramural perfusion balance and redistribution of blood into the ischemic subendocardium, which goes along with animal data that we have previously.

Thank you.

DR. LANGE: Dr. Banai, thank you for sharing that and thank you for identifying that the FDA hadn't seen that yet. Thank you.

Dr. Cigarroa, does that address your questions or additional clarification to your questions?

DR. CIGARROA: So that addressed two out of the three. The one that I had specifically asked the Sponsors to clarify were between the responders and non-responders, was there a difference in the diastolic filling period?

DR. STONE: So as measured by heart rate, I presume.

DR. CIGARROA: That would be --

DR. STONE: Yeah.

DR. CIGARROA: -- one surrogate for it. Yes, sir.

DR. STONE: As we sit here, I don't have that information. The baseline heart rates were 60 to 65 beats per minute. At baseline, the beta blockers and ivabradine dosage didn't change over time, but we'll see if before the next break we can get you any of the follow-up heart rate information, specifically in the responders and non-responders.

DR. CIGARROA: And the reason I'd like clarification of that goes back to the impact of shorter diastolic filling periods on the ratio of epicardial to endocardial blood flow.

DR. STONE: No, I understand, that's a great question.

DR. LANGE: Thank you. Thank you for addressing that. Dr. Banai and Dr. Stone, thank you. Thank you, Joaquin.

Dr. Wittes had asked about what countries were involved, 11 countries, and I think you have that information now, Janet, and the current smoking rate I think we have as well, the FDA. You did ask about showing movement between treatment and controls and I don't know if the Sponsor would like to address that.

DR. STONE: Yes, we can. We can show you the individual patient data and from baseline to 6 months. If we can pull up those slides, I can show it to you either in the standard point by point, patient by patient, or in tabular form. I'm waiting for those slides to come up.

(Pause.)

DR. STONE: Okay, here we go. Now we've got it. Okay. So here you see point by point, and the Reducer patients on the left and the control patients on the right, the Class IV and Class III patients, at which they all started at and then Class 0, I, II, III, IV at 6 months. And again, I could -- if you want to see this in tabular form, I can --

DR. WITTES: Yeah, tabular form is much easier to see.

DR. STONE: Okay, let me bring that up.

DR. WITTES: Thanks.

DR. STONE: Okay, so here you can see the baseline, the Reducer on the left, control on the right, baseline Class III/IV are the two columns and then the follow-up 6-month classes are shown in the rows.

DR. WITTES: Okay, that doesn't really show it, but the combination of that and what the FDA showed, one can reconstruct it.

DR. LANGE: Okay, great. Great.

DR. CONNOR: Dr. Lange, can I ask a question here, a follow-up to that? This is Jason.

DR. LANGE: Yes, sir.

DR. STONE: And it's possible that the FDA did not see those slides before.

DR. LANGE: Okay. Thank you, Gregg.

Go ahead, Dr. Connor.

DR. CONNOR: Yeah, on the last slide I was worried because you kind of showed that

quickly -- if you can put the last slide up -- during the core presentation, that there were actually two control patients who went, I guess, from Class III all the way to no angina at 6 months, which is amazing and great for those two patients. I was wondering if you had any of those in your observational study, I guess, the REDUCER trial, your second trial that you had a bigger *n* on it. Did you have anyone go from like a III to a zero in that trial, either?

DR. STONE: So go from a III to a zero. In the REDUCER-I there were only -- only four classes were captured, so the zeroes were put into Class I. So we certainly had many patients that went from Class III to Class 0/I, but I can't break it out from Class 0 and Class I in REDUCER.

DR. CONNOR: Okay. Yeah, that kind of went fast during the core and I was just wondering about that, given that the only two patients we have who had none whatsoever were controls. Okay, thank you.

DR. WITTES: And let me just say that it really is easier if you see the number of people who were in III who went into I, II, III, and IV rather than having these two cross-sectionals, but we can figure it out.

DR. LANGE: All right. And they may be able to get that during a break, Dr. Wittes. And I appreciate trying to read our minds to know exactly what we want, so if they can provide that information, that will be great.

And also, Dr. Wittes had asked, the last slides, 75, 77, 78, 81, that were shown, it talked about people that were -- results at 6 months, 1 year and 2 years, were those all the patients? In other words, were there --

DR. STONE: Yeah.

DR. LANGE: You reported on a 181. Were there only a 181 at 6 months or were there a larger group and only 181 reported?

DR. STONE: Yeah. No, we looked at that and I can show you those data. It's

approximately at each time period all the way out to 5 years. It was 90 to 95% of all the patients represented in the CCS angina class. So I can show you these data here, these are the -- I'm not sure that this has been seen, too, this has not been seen by FDA before, but here are -- this is the patient visit compliance, all the patients eligible and all the ones that actually had their visit, and then if you actually cross-correlate this to that actual slide that showed the number of data with CCS angina classes, you could see that it's basically 90 to 95% at each time period.

DR. LANGE: So go back to that one slide just so that we can hit it for Janet.

DR. STONE: So here, I'll show you now the original slide. You know, so for example, if you look at -- what would you like? If you look at --

DR. LANGE: Just the slide you showed previous to this.

DR. STONE: Yeah, okay. Yeah, I was going to help you. It's easier if there's two slides up at once, but here's the slide we showed previously.

DR. LANGE: So at 6 months there were -- go back where you were, please.

DR. STONE: Right. So go back and forth between the two slides.

DR. LANGE: Right there, stay right there. There were 199, Janet, at 6 months. They have data on 181. There are 166 at 12 months, they're reporting data on 140. And there are 117 at 2 years and they're reporting data on 98.

DR. WITTES: Yeah. So I have to say that bothers me because by not showing what's missing, we interpret the data as if it's not -- the data are not missing. But thanks for showing.

DR. HIRSHFELD: So actually before we leave this, it looks like these percentages add up to more than a hundred percent.

(Audio feedback.)

DR. LANGE: The greater than one class improvement includes those with greater

than one and greater than two.

DR. HIRSHFELD: Okay. All right, got you.

DR. LANGE: All right. So Janet, does that answer the questions that you had? And we can talk about --

DR. WITTES: Yes.

DR. LANGE: -- the limitations, okay. Great, thank you.

Dr. Mathew had wanted to -- and as did many Panel members, wanted to address the fact that these were people that were -- had refractory chest pain but 25% were on zero or one medication.

DR. STONE: Right. So as I showed you, again, there's a lot of reasons why these patients who do truly have refractory angina are on only zero or one medication. It's not by choice, if you will, because they are really having severe angina and they are quite limited. But in general, it's because there were side effects from those medications, there was hypotension, dizziness, renal insufficiency, etc.. They're taking many other medications and as I showed you, I can show it again if you'd like, the angina, number of angina medications in the classes are really pretty consistent with what you've seen in every truly refractory angina trial before. I can put it up quickly if you'd like to see it again because it went fast the last time.

DR. LANGE: So Gregg, again, my question that I'll pose to you all, were these things that were documented or do we just assume that because a patient was only on one medication, that's all they could tolerate?

DR. STONE: Right. So there was not a detailed questionnaire in the case report form saying for each possible antianginal class, of which there are about seven of them, why was the patient on it or not on it, or only on that dose and what other side effects in the last 1, 10, 20 years that they had from those medications, that data was not collected in COSIRA.

DR. LANGE: Okay. And the other question that Dr. Mathew had asked was what do we know about the adherence to medical therapy in both COSIRA and the REDUCER trial?

DR. STONE: Right. So as I showed you from the other prior two slides the other time, the classes of medications were consistent in both groups, at least as reported by the patients. There certainly were no pill counts or anything that were done in COSIRA, that's really been done in any study. But from patient-reported compliance of medication, I can put it up, and with the quick and dirty dose equivalence that was assessed, it also was consistent and similar in both groups. So this just shows you, again, whether the patients were taking them at baseline and at 6 months in both groups and you can see, in general, I would say it's pretty similar between the two groups. And this slide may not have been seen by FDA before.

DR. LANGE: Great. And so I guess what you're saying on that is we don't have any information regarding adherence or compliance.

DR. STONE: Right, I think within the limitation reported, right, we didn't have pill counts or bottle openings from electronic bottles or anything like that.

DR. LANGE: The last question Dr. Mathew asked, and we'll make sure he has -- he asked about that there were 8 of 50 devices that were technically -- there was some difficulty handling these with technical difficulties and I'll allow the Sponsor to address that.

DR. STONE: Well, I will let Dr. Bebeau address it, but I will say that as with any new procedure, there's always a learning curve. There's a learning curve for interventionalists working in the coronary sinus, working with this device, and I think as you saw as we went from COSIRA to REDUCER-I to the commercial experience, the outcomes in terms of coronary sinus events, etc., were going down in general. So I think some of this is due to the early learning curve, some are operator errors, some are training experience. As you can see, the procedures were quite uncomplicated, though, and the Reducer was implanted

in 50 of 52. The only times it wasn't implanted was because of poor guide catheter support and that can be improved by future guides.

Ms. Bebeau, I don't know if you want to further address that. You might be on mute.

MS. BEBEAU: So sorry, I'm trying to click on here and I apologize. Vicki Bebeau here.

For the technical success rate, as you spoke about, we had the 50 of 52 patients with successful implant. I would have to go to another slide as far as the mishandling, but typically in the protector that's on the device, sometimes in the handling, I think there was a case where it caught the -- the strut caught on some gauze. I mean, there's been just a learning curve with some of the technical successes. But the procedure successes, as we talked about, it was just the two patients that they had difficulty with the guide catheter.

DR. ALLEN: Can I ask a number-counting question because it doesn't make sense. I've heard you say 50 of 52 were successful, but you had a 3.9% embolization rate. So something, either you didn't count -- I'm not sure where your numbers are coming from. You had a 3.9% embolization rate, but yet you state you had 50 out of 52 were successfully implanted.

DR. STONE: So Dr. Banai was at the procedures and I think can address this.

DR. ALLEN: I just want to know the -- no, I don't want it addressed, I just want to know the numbers, so they don't add up.

DR. STONE: Well, they were ultimately -- the procedures were ultimately successfully implanted. So I mean, it's not uncommon at all that in interventional cardiology you try one thing, it doesn't work, you take the stent out, you try something else. Some of these --

DR. ALLEN: I guess I have a problem, though, with an embolization of a device being counted as a successful procedure.

DR. STONE: I understand. I think it all depends on the definition. In terms of the

definition -- you know, interestingly, for those non-interventional cardiologists, believe it or not, most embolizations don't cause a problem, either the stent can be retrieved or even when they're not retrieved, it's almost never caused an issue, which is interesting. It's not desirable and of course, we would try to avoid it and the rate of that has gone down over time with greater learning with the Reducer. That said, ultimately, the procedures were successful in 50 of 52, but I share your comment and your concern.

DR. BANAI: Shmuel Banai here.

They're called embolization when the Reducer moved either on the balloon backwards, dislodged or it was on the wire. In every case, the Reducer was taken out as it was on the wire and a new Reducer was implanted successfully. So there was no embolization to another organ.

DR. LANGE: So I'm sorry, I'm looking at this slide and it says all but one occurred during a procedure and one embolization was reported 3 hours post-procedure and it was a pulmonary artery. So did I miss that?

DR. ALLEN: You missed the same thing I missed.

DR. BANAI: This is in the REDUCER-I or COSIRA? Are we talking about COSIRA or REDUCER-I?

DR. LANGE: Yeah, COSIRA.

DR. STONE: I think if we put up -- we can put up this slide. Here, I think you can see COSIRA is at the bottom and there were these two cases where the device was dislodged from the balloon catheter but did not embolize. The pulmonary artery cases you see were in the commercial experience of several thousand cases.

DR. LANGE: Okay. Thank you, Gregg. Thanks for clarifying that. Okay.

Dr. Mathew, did they address the questions that you had?

DR. MATHEW: Yeah, I think within the limits of what's possible and I think that

addresses it, yes. Thanks, Gregg.

Just one other point that I brought up or asked about, maybe this is an administrative question, but the IFU, proposed IFU, as written, it said patients not eligible for CABG or PCI, and while it's clear that microvascular angina is not included in this subset of patients nor included for the approval, I guess maybe I'm being a little overly cautious, but could somebody interpret that proposed IFU as including somebody with microvascular angina who obviously wouldn't be a candidate for CABG or PCI? So it would just be a matter of clarifying the phraseology if it comes to that.

DR. STONE: Yeah, I can speak quickly about indication and then Ms. Bebeau can also speak about why it turns out that was the IFU. I think there's the full expectation that based on the advice from this Panel and in working with the FDA, that that proposed IFU and central indication would be changed. I'm a firm believer that the results of any trial apply to the patients that were enrolled, which were patients here with severe coronary artery disease who did not have coronary revascularization options with Class III or IV angina. That's what I would expect. Ms. Bebeau can speak to as to why that ended up as the initial submission.

MS. BEBEAU: Yeah, Vicki Bebeau here.

As I mentioned earlier in my presentation, we submitted that indication for use based on the fact that that was the indication we were provided for the breakthrough designation, fully understanding, as it was clear from the Agency and the guidance document, that it would likely require to have some further discussions with FDA. We are open to any changes that the Panel or FDA would recommend, if the device would be approved, to add to the IFU and amend it.

DR. MATHEW: Okay, thank you.

DR. LANGE: Dr. Ohman had some questions regarding the early termination of the

study and whether that introduces some bias and could you provide a sensitivity analysis of how that might influence the trial.

DR. STONE: Yes. Let me ask Chris to address that.

MR. MULLIN: Good afternoon. Chris Mullin, I'm a statistician with NAMSA. So the trial did have the pre-specified analysis plan for potential early stopping with an alpha spending function. The trial was not stopped at that point, so the decision was made to continue. Subsequently, though, there was the decision made to end enrollment, but that was based on logistical concerns, not safety concerns and not crossing the pre-specified boundary. So really, the effect was reduced power relative to the originally planned sample size.

DR. LANGE: Chris, regarding premature or early termination and the possibility of bias towards a positive result.

MR. MULLIN: Yeah. So because it's not stopped due to awareness of the efficacy data, I would argue that there's no issue with that. The pre-specified stopping would've handled that if that boundary had been crossed, but that wasn't the case.

DR. STONE: I can also address, importantly, that the Sponsor -- and Ms. Bebeau can verify this -- had no knowledge of the outcomes data when the decision was made to stop the trial. The data remained blinded and they just -- they stopped because the enrollment had slowed down at that point and they were getting better follow-up than anticipated, so they felt they would likely have enough data for a robust and hopefully a positive conclusion to the study, if it was going to be positive, so they elected to stop.

DR. LANGE: Dr. Connor.

DR. CONNOR: And I would just say, from the stats perspective, if it truly is just logistically you're not enrolling and you stop short, that you're not increasing Type 1 error because you're not stopping because you have a success. So in theory, it's not increasing

Type 1 error if they stop for that reason.

DR. WITTES: Can I ask a question? This is Janet.

DR. LANGE: Please, Janet. Go ahead.

DR. WITTES: And that's related to the slight difference between the question that's being addressed and the question that I asked. Or that I tried to ask. What was conveyed by the DMC to the Sponsor and did the Sponsor, when the Sponsor said we're going to stop the trial because we can't recruit, did they ask the DMC whether that was okay or did they just do it?

DR. STONE: I'll let Ms. Bebeau and Dr. Banai answer that.

MS. BEBEAU: Yes, Vicki Bebeau here.

The decision to stop the study was made by the board of directors and the board of directors had no knowledge of the analysis that was -- any of the data, they had no exposure to the data. It was a decision based off of the difficulty in recruiting and how long the recruitment had gone on, as well as the small number of lost to follow-up patients.

DR. WITTES: But did they ask the DMC for whether that was okay with the DMC?

MS. BEBEAU: I don't know the answer to that, so I honestly can't answer that statement.

DR. WITTES: All right, so let me just tell you why that's important, because if they didn't, then I'm fine, I agree totally with what everybody says, it has no effect on Type 1 error rate. If they asked and got some kind of a signal back, then you wonder whether there was some bias.

DR. LANGE: Thank you, Doctor.

Dr. Ohman had also asked about a sensitivity analysis and I don't know, Dr. Mullin, if you had an opportunity to do such or thought it was worthwhile.

MR. MULLIN: Sure, thank you. Chris Mullin again.

So I think, if I recall the question, that was the one if the enrollment had continued to the full originally planned sample size, how sensitive the results would be and of course, since we did these calculations over lunch, FDA hasn't had a chance to verify them. But by our calculations it would be still significant, the p-value is about 0.02 if you just take the observed results and apply that proportionately to the full sample size. And then the sensitivity, if you switch two patients, two treatment patients, from successes to failures, that would flip the results so the p-value would be over 0.05. Likewise, two control patients going the other way or one in each group going the other way.

DR. LANGE: And then Dr. Ohman had also asked, if we took the COSIRA data and took out the individuals that were on minimal medications, did the results change, were they still affected?

DR. STONE: Yeah, and I can show you data in that regard. We can pull up that subgroup slide. While you're waiting, the answer is there was no interaction between the number of baseline medications and the primary endpoint results. Okay, yeah. Here we go, terrific. And I don't believe FDA has seen this slide.

So here you can see the primary endpoint on top of two or more CCS angina class improvement and the bottom half of the slide is one or more CCS angina class improvement and you see all patients, which is the first and fourth treatment differences in the 95% confidence interval, and then you see, for those patients who were on zero to one versus two or more antianginal medications, you can see the response rate and the 95% confidence intervals. The interaction p-values are 0.27 and 0.35, respectively.

I would point out, of course, this is a modest sized study and of course, all subgroups are at best hypothesis generating and there's certainly no reason to try to pull any -- too much out of these small subgroups. It is interesting, though, I will say, that the zero to one antianginal medication group, if anything, you could see the difference was a little bit more

positive, which I actually take as a good thing because these are the patients that just could not tolerate antianginal medications, who had great clinical need and they had the good response. But again, I would say there's consistency effect across the number of baseline medications.

DR. LANGE: Great.

DR. SOMBERG: This is John Somberg.

You can just take the other point of view, is that the less medications, the less treated they are, therefore they have more significant ischemia and therefore the process works. But if you took a really resistant population that was fully medicated, there would be little difference.

DR. LANGE: Dr. Ohman.

DR. STONE: Well, you could take that, but again, these patients really had severe coronary disease and even those patients on zero and one medications had a high number of prior PCIs, bypass surgeries, myocardial infarctions. I don't think there's any reason to believe that they just were fresh patients with Class III or IV angina.

DR. LANGE: Gregg, unless you're willing to show that data that shows the zero and one patient and the three and four, let's not make those comments. Unless we can put them side by side and show that's the case.

DR. STONE: Sure, we can try to get you that after the break.

DR. LANGE: Magnus, you had your hand raised.

DR. OHMAN: And I think the last slide that Dr. Stone showed is very telling. I mean, the therapeutic efficacy in the zero to one is twice as much, which makes me wonder how well the patient population is characterized. And obviously, if you took those out, out of the equation, this study will not be statistically significant. So basically, it's not reliable or the findings are not stable enough.

DR. LANGE: Okay, all right.

DR. STONE: If I can respond.

DR. LANGE: Gregg. Gregg, I'm sorry.

DR. STONE: Okay.

DR. LANGE: Yeah. I mean, with all due respect --

DR. STONE: No, no. That's fine, Richard. That's fine.

DR. LANGE: I just want to get through the questions and then the Panel will have a chance after the break --

DR. STONE: Absolutely.

DR. LANGE: -- and we will call the Sponsor and the FDA back for questions. And then Magnus also had a question on Slides 90 and 91 about the MI, just number of MIs, and I know that you all can address that.

DR. STONE: Yes, we can pull that up. Magnus is absolutely right, there were two myocardial infarctions. The other slide that Magnus was looking at was looking between 30 days and 6 months, so there was one MI before 30 days and one MI after 30 days. So I can show you this slide, Magnus, is all the events. So this is within 6 months and now I'll show you the other slide that you were looking at before. This slide was after 30 days to 6 months. We had another slide that showed all the outcomes in total and there were two myocardial infarctions, both non-STEMIs.

DR. OHMAN: Thank you.

DR. LANGE: Thank you, Gregg.

Dr. Brindis had asked about safety. The comment made is that there were over 2,000 individuals that had the Reducer implanted and there is no evidence of coronary sinus thrombosis and I think he just asked for how that was determined.

DR. STONE: Yes. So there's been no reported instances of coronary sinus

thrombosis and as we'll show you, the CT data is also consistent with that, and I know there was a question about that from PROMISE on the CT data, so if you'd like it to be now or later, but Ms. Bebeau can address that issue.

DR. LANGE: That would be great because Dr. Brindis had actually asked about the presence of thrombosis.

DR. STONE: Perfect.

DR. LANGE: And I think it had to do with the CT report in the REDUCER trial where it looked like 16 of 37, or 43%, reported a thrombus was present by the CT angio core.

DR. STONE: So Ms. Bebeau.

MS. BEBEAU: Yes, thank you.

I will pull up a slide here. I apologize. This might be a slide that FDA hasn't seen before, but when we were working through our deficiencies, when filed for our IDE, we had met with FDA and talked about concerns that they had potentially with device patency/occlusion, emboli or thrombus, fracture/durability, and in the COSIRA study there was data on the 37 CT scans that were done.

We'd been approached by the physician from India to look at CT data with his patients, so we were speaking with FDA, we talked about having the same core lab that read the CTAs in COSIRA to read the seven patients' 12-year follow-up. In talking with FDA, they did agree with us that we could reanalyze. We had Dr. Wiseman from MedStar reanalyze the CT data from the COSIRA study, which he actually then did. Let me just share another slide here. And again, FDA may not have seen this slide, also.

So when Dr. Wiseman re-reviewed the data, again, it was consistent that there were no fractures but that previously, the thrombus that had been identified was really areas of low CT density and the device coded as thrombus and the CT core lab indicated that low density area seen could represent other diagnoses and not possible to differentiate

between thrombosis and fibrosis. But in the reanalysis, the thrombosis was defined as hypoattenuation.

Working with FDA, we also had put together -- and I'll show this slide. And the FDA has seen this during our discussions with them. This was done every single CT scan, both for the eight patients from India and the 12-year follow-up in addition to the 37 patients that were analyzed by the same CT core lab during the COSIRA study. And this is an example of a patient that had been previously reported with thrombus, and I'd like to turn this over to Dr. Banai to explain further.

DR. BANAI: Thank you. Shmuel Banai here.

This is a very nice example. If you again look at the bottom pictures, and the one most to the left and the second one from the left, this is a proximal aspect of the Reducer and at 4 o'clock you can see hypoattenuation, a black spot, which was previously suspected to be a thrombus, but that is typical for neointimal formation for tissue growth occupying the area and encroaching on the lumen. There was no thrombosis seen in none of the animal studies and none of the CT angios and none reported as adverse events in all the clinical cases we had in Europe. Maybe I'll elaborate on that a little bit.

The question was asked why don't we give anticoagulation like we do to patients with venous thrombosis, and the reason is that here, although it is a low-pressure system, a venous system with a venous pressure, because of the narrowing we have a high-flow system. The funnel shape of the coronary sinus after Reducer is implanted and the narrowing is established, the funnel shape causes acceleration of blood flow through the narrowing and because of the high flow, we don't see thrombosis and dual antiplatelet therapy is probably sufficient. Only in patients with chronic arterial fibrillation we give anticoagulation and single antiplatelet therapy.

DR. SOMBERG: Can I ask why you give --

DR. LANGE: Go ahead, John. Go ahead, John.

DR. SOMBERG: No, I just asked why they give dual antiplatelet therapy for the venous side.

DR. BANAI: We decided to give that because we -- exactly like we do in bare-metal stents in the coronaries, we did the same protocol and then only single antiplatelet therapy after 6 months.

DR. ALLEN: Can I -- yeah, it's totally different on the venous side, but you call this hypoattenuation, and I guess I'm very confused because we use the same term in structural heart and this, on a transcatheter valve, would be clot not fibrosis. And it looks like clot on a CT. And I'm confused because -- and I guess I would want to have clarity from the FDA and have them weigh in at this point in this process because it's really important we get -- initially it's called thrombus and then you get somebody else to review it who then says no, it's not thrombus, and a hundred percent of them it goes away. I guess it's pretty confusing to me.

DR. LANGE: And I guess if you go back -- I think probably the best they can do is call it hypodense and they really can't tell what it is.

DR. BANAI: I can remark on this. When you do CT angiography to patients with stent in the coronary arteries, this is exactly the picture you get for diagnosis of restenosis. This is the way you diagnose restenosis in a stent, it's exactly the same picture, and that's what you see here. It's tissue proliferating into the lumen of the artery.

DR. LANGE: So Dr. Brindis, you had had some questions. And I'll get to you, Dr. Batchelor.

Dr. Brindis, does this address your questions?

DR. BRINDIS: It does.

DR. LANGE: And we'll have conversations about it. The difference, I just want the

Sponsor to answer and then we'll get involved in conversations about the value, the limitations, what we believe and don't believe.

Dr. Batchelor, you had your hand up, sir.

DR. BATCHELOR: Just a quick question. On paper the investigators adjudicating the CCS class and the outcome were supposed to be blinded, but if only the patients who received the device are on aspirin and Plavix, how were they blinded? How did you account for that?

DR. LANGE: They actually all got aspirin at once.

DR. STONE: All patients received dual antiplatelet therapy.

DR. BATCHELOR: Okay, thank you.

DR. LANGE: Actually, Dr. Cigarroa.

DR. CIGARROA: This is Joaquin Cigarroa. Thank you, Dr. Lange.

I just wanted a point of clarification on a statement that Dr. Banai made when talking about the antiplatelet versus antithrombotic. The comment regarding a high-flow state induced by the hourglass and the endothelialization is theoretical. There are no measurements where you actually measure velocity with any Doppler techniques or actual flow, correct?

DR. BANAI: Correct.

DR. CIGARROA: And at the narrowest point, there is -- that's the area where there is lack of complete endothelialization, correct?

DR. BANAI: Correct.

DR. CIGARROA: And so we actually don't know, in the narrowest point where you have endothelialization on the inlet and the outlet, whether or not there are eddies there and errors of spaces in the context of that incomplete endothelialization and what the velocity may actually be in that segment, correct?

DR. BANAI: Correct. Nevertheless we know that in all CT angiography, we see blood flow through the Reducer.

DR. CIGARROA: Understood. Thank you very much.

DR. LANGE: Thank you.

Dr. Connor, again, you had asked why they stopped the trial prematurely and they had described logistical issues and if you have a follow-up question to that and also --

DR. CONNOR: No.

DR. LANGE: Okay. And then he had asked for the outcomes by site and I don't know if the Sponsor had an opportunity to --

DR. STONE: I don't know. Chris Mullin, I don't know if you have that. We may not have that right now. We might be able to get back to you after the next break on that one.

DR. LANGE: Thank you, Dr. Stone, appreciate that.

Dr. Somberg asked about antiplatelet agent and anticoagulation and that's been addressed.

Dr. Batchelor had asked about regression to the mean and again, if a patient was assigned to one group or another. I think, Dr. Batchelor, they had addressed that. Any other clarifying questions on that? Are you comfortable with the response?

DR. BATCHELOR: No, Dr. Mullin nicely addressed to the effects of having one or two patients misclassified on the statistical significance, so thank you.

DR. LANGE: Great, thank you.

And then Dr. Batchelor also asked about the use of coronary sinus for other procedures in the future, like a bi-v lead and the recommendations from the Sponsor regarding that.

DR. STONE: Yes, I can address that. One of the nice things about the Reducer is that it's actually very easy to re-expand that central hourglass. All one has to do at any time is

just put a regular size balloon back into the Reducer and you can re-expand. Here, I'll just show you this picture. But that can easily be done. So the coronary sinus, you can have a future lead placed in the coronary sinus through the Reducer quite easily in the future.

DR. BANAI: Shmuel Banai here.

I want to comment on this. The reason we made the Reducer from stainless steel was exactly that, because you can always get rid of the narrowing. But since we have some experience now, I can tell you that it is very easy to implant a CRT-D lead into the coronary sinus through the Reducer without disrupting the Reducer.

DR. LANGE: Great.

DR. BANAI: But you can do it if needed.

DR. LANGE: Thank you, Dr. Banai.

Dr. Starling had asked, in humans, has there been any pressure measurements, any measurement of CSO2 content or resistance, coronary vascular resistance.

DR. STONE: There has not been -- I mean, I'll just clarify that to do that, we expect the Reducer to again have its maximum amount of neointimal hyperplasia at around 2 months. So it would require bringing patients back for an additional cardiac catheterization procedure and that has not been done, it's not been felt to be ethical.

DR. LANGE: Okay, great. And he had also asked about one of the exclusion criteria was an RA pressure greater than 15 mm and the explanation or rationale.

DR. STONE: I'll let Dr. Banai address that.

DR. BANAI: Yeah, this was a decision made when we were not sure that the device would work or not and we thought that the patient with very high right atrial pressure, mean pressure of 15 in the right atrium in the heart, they might also probably have high pressure in the coronary sinus that might -- you know, it might not be effective. That's why we decided to not include this patient, but we don't have any data to support that.

DR. LANGE: Just a question, Dr. Banai, in terms of physiology. Obviously, the Reducer is meant to increase coronary sinus pressure to improve the endocardial blood flow and obviously, an RA pressure of 15 increases CS pressure. Why that doesn't change blood flow and why it doesn't -- why that's not anti-ischemic.

DR. BANAI: It does, but patient with very high right arterial or right-sided pressure, they have probably other problems. They have right-sided failure, so the problem of angina is one of their problems. We, in the COSIRA, tried to take pure patients with obstructive coronary artery disease, preserved left ventricular function with no severe valvular disease or other cardiac disease that can mask the effect, the pure effect of the Reducer on angina and ischemia.

DR. LANGE: Okay, thank you.

And then lastly, Dr. Starling asked about the durability and any information regarding movement of patients over time in the COSIRA or other trials.

DR. STONE: So we don't have any data from COSIRA the past 6 months. We do have the data that we've shown you from REDUCER-I up to 5 years and from individual investigator sponsored studies, about four or five of them, in which the overall angina class appears to be approximately stable. But I agree, there are some limitations with assessment in a certain proportion of patients in all of those studies. But I don't think that we have any data that suggests that the effect is not long lasting.

DR. LANGE: Dr. Starling, does that address your questions sufficiently?

DR. STARLING: Just one last clarification. So a patient with an RA pacemaker lead or a right ventricular lead, are they eligible for the device? And currently, if the patient has a CRT device, is it not feasible?

DR. STONE: Go ahead.

DR. BANAI: Yeah. Pacemaker lead in the right atrium, in the right ventricle, are fine.

We allow the device as long as the pacemaker was implanted more than 3 months before, so there would not be a risk of moving mainly the atrial lead.

Regarding CRT-D leads in the coronary sinus, we don't allow it for two reasons. One, these patients usually have low ejection fraction, they have heart failure, and we don't know that this device is effective in heart failure patients with very low ejection fraction. The other thing, we're not sure that the Reducer implanted on a lead will not accidently break the lead. That's why until now we did not allow implantation of the Reducer in patients with a coronary sinus pacemaker lead.

DR. STARLING: Thank you.

Thank you, Dr. Lange, that answers my questions.

DR. LANGE: And then Dr. Gersh had asked about is there any correlation of the clinical results with any of the -- any mechanisms, that is, associating coronary sinus reduction with improvement in anginal class.

DR. STONE: Well, I guess the answer would be no, we don't have any such evidence because as you saw from the CTs, the hourglass shape is formed in every single patient, we've seen that in every single CT. So certainly you saw about 70% of the patients who get the Reducer do have some reduction in angina. I don't think there's been a detailed analysis done to try to understand who the non-responders are, but we don't have detailed follow-up coronary sinus data in those patients because of the need for a repeat cath for human anatomic measurements, etc. So I don't think we can address that.

DR. LANGE: Okay, great.

DR. BANAI: Shmuel Banai here.

There are data in animals showing relationship between coronary sinus pressure and regional myocardial blood flow in animals. Not in human.

DR. LANGE: Okay. Thank you, Dr. Banai.

Dr. Allen.

DR. STONE: Thank you. I assume that's --

DR. ALLEN: Dr. Banai, can you help me understand, as a vascular surgeon, if I put an AV fistula in and I narrow a vein, that vein dilates. But in every one of your CTAs, and you talk about this hourglass, I don't ever see dilated coronary sinus proximal to where the higher pressure would be. Can you explain why not?

DR. BANAI: Shmuel Banai here.

I can speculate. First of all, we do not cause edema of the heart, we do not cause very high pressure gradient going backwards. We are doing a small pressure gradient elevation just enough to dilate some arterioles in the subendocardium to reduce resistance to flow. There are reports that even if you completely occlude the coronary sinus, patients do not die because of possible alternative drainage, venous drainage of the heart to the right ventricle into the right atrium. But --

DR. ALLEN: And I appreciate the explanation, but it's not really answering my question. Because your CTAs are very impressive, if you believe the CTA, you get a very impressive narrowing of the coronary sinus and to not show any dilatation of that coronary sinus before that seems unusual, which makes me suspect of the mechanism.

DR. BANAI: Yeah, but that's a fact that in all 44 CT angios, these are the pictures we see.

DR. LANGE: Thank you.

And then Dr. Gersh's last question was the discrepancy between what appeared to be an improvement in CCS class, but people that got sham treatment had the same satisfaction, angina -- and discordant results.

DR. STONE: Yeah, I can address that. The treatment satisfaction question is very different than all the other questions in the Seattle Angina Questionnaire. It basically is

asking are you satisfied with your doctors taking care of you, are you satisfied that they're trying to do everything that they can, are you satisfied that they are explaining to you what the situation is. It's not a direct question, are you satisfied that you have no angina.

And as a result, when you look at the baseline treatment satisfaction scores, they're around 80. This a 0 to 100 scale where a hundred is perfect, and the baseline treatment satisfaction scores are usually about 80 to 85 and that's in every refractory angina trial, whereas the baseline quality of angina or amount of angina scores are usually around 40 or 45. So there's very little room to improve your treatment satisfaction in either group because they believe their doctors are doing a good job.

DR. GERSH: Thank you, that answers it.

DR. LANGE: Dr. Cigarroa had asked, the FDA showed a slide, 2020 -- or Slide 22 looking -- discussing LV contractility, perfusion, and the FDA made a comment that they were unable to confirm the results and he had inquired as to why that was.

DR. STONE: I would leave that to Dr. Banai or Ms. Bebeau.

DR. BANAI: Shmuel Banai.

Are we talking about animals or humans?

DR. LANGE: Animals.

DR. BANAI: Okay, so the animal study --

(Crosstalk.)

DR. LANGE: -- FDA slide, FDA Slide 22.

DR. BANAI: Yeah. May I have Slide AD-20 for the animal studies?

DR. LANGE: No, let me show you Slide 22 in just a second so you know what he's talking about, Dr. Banai.

(Pause.)

DR. LANGE: Jim, can you show FDA Slide 22?

MR. SWINK: Yeah. Sam, can you go ahead and share your screen? Thank you.

DR. LANGE: Yeah. So Dr. Banai, Dr. Cigarroa asked about the last statement.

DR. BANAI: Yeah. Okay, the animal study that we did with the Reducer -- can you see my slide now? Can you share my screen, please? Okay. The animal study that was done with the Reducer are ischemic pig model, pigs were implanted with an ameroid constrictor around the proximal circumflex artery and the ameroid constrictor caused gradual narrowing until complete occlusion of the circumflex artery.

This is a very difficult animal model because the pigs, unlike the dogs, do not grow collaterals and most of the pigs will either die from this procedure or develop a full-blown myocardial infarction and a scar. Those pigs who survive the procedure and did not form a scar had reversible ischemia induced by dobutamine stress and perfusion of contrast, echo contrast, into the root of the aorta. So there were four pigs in each group and you can see here -- and then after ischemia was confirmed by dobutamine echo and perfusion, the pigs were divided into two groups, one group received the treatment with a Reducer and one did not, and they were reevaluated after 6 weeks and 6 months.

What you can see here on the left are examples of two pigs under dobutamine stress with perfusion and you can see the ischemia territory; actually, black area of the lateral wall of the pigs and on the right, same pigs under same dobutamine stress, even a slightly higher heart rate. Six weeks after Reducer implantation there is marked reduction in the ischemic territory, there's actually perfusion into this area of the circumflex artery. More than that, we didn't measure contractility here, so the pressure wasn't about contractility, we showed improved perfusion. Three out of the four control pigs died of pulmonary edema and ventricular fibrillation and none of the Reducer pigs died at 6 months.

Now, we do have data about improved contractility, systolic performance in humans, both by dobutamine echo wall motion score index and by MRI, the MRI data I showed you,

and also data -- if I can show you, if you want, about the improvement in dobutamine wall motion score index in humans.

DR. LANGE: I think we've seen that.

So Dr. Cigarroa, does this answer your question?

(Off microphone response.)

DR. LANGE: It does. Okay, great.

Dr. Somberg had asked if there were missing data with regard to the Seattle questionnaire and exercise stress test and dobutamine stress echo. He asked whether there were any missing data regarding the CCS data.

DR. STONE: So in COSIRA, we have CCS data in every patient.

DR. LANGE: Okay, great.

Dr. Somberg, does that address your question?

DR. SOMBERG: Yes.

DR. LANGE: Great. And, Gregg, I think you had addressed this. Dr. Starling had asked about who the heart team was that evaluated these patients to determine whether they were refractory or not and I think what you had said is there really wasn't a heart team, they just -- they were included in the study because of the refractory angina, is that correct?

DR. STONE: Correct. This was before the formal concept of a heart team, but all these patients, again, were cared for by general cardiologists and had been seeing interventionalists and surgeons for possible relief, to see if they had a revascularization option and they didn't, which is how they qualified.

DR. LANGE: Okay. Dr. Yuh.

DR. YUH: Thank you. David Yuh.

Along those same lines, were there any guidelines distributed to these evaluation

teams or individual surgeons versus interventionalists, as to what they should be using as criteria for deeming somebody as a "no option"? And the reason I'm asking is that even amongst cardiac surgeons looking at an angiogram, there may be differences in opinion between cardiac surgeons as to what's revascularizable versus not, and I'm just worried that with such small sample size that any variation in selection mechanism could confound the data. That's what kind of is nagging me about this -- about the definition you have of "no option" patients.

DR. STONE: Well, these were all very experienced sites that the Sponsor went to. I mean, that was a criteria for them being in the trial and these are sites that were very used to taking care of patients with complex coronary artery disease. I think, again, you could see by the fact that there was bypass surgery in a large percentage of the patients already, PCIs in a large percentage of the patients already, it's not like these patients were being ignored in terms of revascularization options.

That being said, it is a real-world study and you're absolutely right, there are differences in terms of threshold for revascularization among interventionalists as well as surgeons, and it's possible that there may have been more or less aggressive interventionalists or surgeons at different sites. Nonetheless, this is a multicenter trial and I think the results do reflect a multicenter experience with revascularization. I don't think surgical revascularization has changed much over the last decade in terms of what you can and cannot revascularize. There may be a slight improvement over the last decade for some interventionalists with advanced CTO techniques but, for the most part, this is coronary revascularization as reflected in these patients.

DR. YUH: David Yuh.

Just a follow-up. So as an example, in looking at an angiogram of a potential patient that had bypass surgery, for example, were grafts evaluated? And different surgeons, I

think, would take -- may take a different approach as to whether or not that patient would likely succeed with a re-operative coronary bypass. Even though the notion of coronary bypass surgery hasn't changed much there's still a lot of variation, I think, between surgeons as to what they deem as doable versus not or too high risk.

DR. STONE: No. I mean, I can certainly say that in general, yes, all of these patients had repeat angiograms to see that there were no revascularization options. And I will say, one thing I've learned from prior studies is that while we do sometimes evaluate these patients in eligibility committees, we've learned it's never a good idea for a remote committee to tell a surgeon or an interventionalist you need to operate on that patient or you need to fix that.

So as you know, surgeons like to operate and interventionalists like to stent, and if there was anything that they could do where they thought they might help the patient, my presupposition would be that they would have offered that to the patient before putting them in a trial such as this, especially given the number of procedures they had previously had.

DR. YUH: But don't you think that there would be more consistency if you had, for example, a core group evaluating, not necessarily dictating --

DR. ZUCKERMAN: Dr. Yuh, I don't mean to completely cut you off, but --

DR. YUH: Sure.

DR. ZUCKERMAN: -- our goal here is just to get some responses from the Sponsor such that we can then allow you and the other panelists to debate these important topics. Your point is extremely critical and an additional point is that this study was completely done outside the United States, so the Sponsor and FDA will be looking for you and other expert panelists to further develop this topic among yourselves, but if we can continue with just quickly addressing these questions to the Sponsor.

DR. LANGE: Great. So I think I tried to cover everybody's questions. Was there a question previously asked that hasn't been answered? If not, I want to ask Jacqueline Alikhaani, who's got a question. So is there any question that the Sponsor did not address? I see two hands, Dr. Bonde, Dr. Batchelor. And then Jackie, I'll come to you.

So Dr. Bonde. And I'll ask you to unmute.

DR. BONDE: Hi, Pramod Bonde here.

One of the facts that we learned in cardiac surgery is that if you perfuse retrogradely a coronary sinus, you tend to protect the left side better than the right side, and there have been instances and studies published of poor protection of the right heart because perfusion of the right ventricle is not as optimal as that of the left ventricle. In your studies, were you able to see a difference in the function of the right ventricle versus the left ventricle? That's one question.

And the second question is that how will that impact patients who have a single territory non-revascularizable disease, for example, a right coronary artery? Those are my two questions.

DR. BANAI: Shmuel Banai here.

Thank you, this is a great question and the reason, the thought was that the Reducer will not affect patient with ischemia or angina due to the right coronary artery was the anatomy. The vein that drains the internal wall in the right coronary artery territory drains right at the ostium and when you do retrograde cardioplegia or when we implant the Reducer, it's further deep in by 1 or 2 cm, it's deeper, so you do not increase pressure in the vein of draining right coronary artery. That's why in the COSIRA and at the beginning of our experience we said this is good only for patient with left-sided ischemia. Having said that, recently there was data published from Europe, and I don't know if FDA ever seen this or not, but this is a study that was done on patient with CTO and they --

DR. LANGE: Dr. Banai, is this a Sponsor study? If not, we're going to move on.

DR. BANAI: No.

DR. LANGE: Okay.

DR. BANAI: No, it's not Sponsor study. It's a study coming from Europe, from several centers in Italy, the Netherlands, and Belgium, I think, and if you look at the left side, they tried to evaluate the effect of the Reducer on patients with CTO, that they couldn't open the CTO and evaluate the effect of the Reducer. And surprisingly enough, patient with isolated RCA occlusion responded to the Reducer.

DR. LANGE: Thank you, Dr. Banai. Thank you. We're here to discuss the Sponsor and the Sponsor's studies and the results, so we're going to move on rather than talking about other studies that have been published.

So Dr. Batchelor, you had a question. You're on mute, sir.

DR. BATCHELOR: My question was related to the RCA, as well, so we're covered. Thank you.

DR. LANGE: Got it. Okay, I think we addressed it.

Ms. Alikhaani, I want to give you an opportunity to ask any questions and/or make comments. And if you'll please unmute.

MS. ALIKHAANI: Yes. I did not hear much about the patient voice, particularly American patients, throughout the study process and I think it is very important, very useful to have a team of patients and family members and caregivers and nurses to help advise throughout the conduct of the study. And I just can't -- you know, also, I just can't really understand why we can't just do the study here in the United States, where we're going to be using these therapies to help patients who are American patients here in this country. And as a heart patient, I'm a heart patient, healthcare consumer, volunteer patient advocate for heart health, and my biggest concern is always safety and effectiveness for

heart patients. I know what it's like to live with chest pain. As a woman and as an African American, I know what it's like to experience disparities in care and I just feel like -- I mean, there's so many questions and issues that are so legitimate that have been raised here today during this discussion and I just resonate with all of them. Very, very good discussion.

And it seems to me that a lot of these issues should've been taken care of before the hearing. I think that there's so many questions that bother me, like incomplete data and all the discussion that we've had trying to flesh all these issues out, incomplete data, missing data, early termination issues, exclusion of patients, lack of significant diversity in the study. These are all really critical issues.

And it seems like there was, you know, just such a missed opportunity to really do some good follow-up collaboration with the FDA that wasn't done because I'm seeing that here in the hearing we're having information presented that the FDA has never even seen before. And so that's kind of bothersome for me and I just wish that we could've done a study right here in the United States. I mean, we have such a diverse community of patients and consumers here in the U.S. and we have women experiencing disparities in care, we have African Americans, other ethnic communities, traditionally underserved groups. And so these are some of the concerns I have.

DR. LANGE: That's a great, great segue, I think, to go into the Panel deliberations. Jackie, I appreciate your comments and I think those will be prescient as we head into these.

Before we do that, any last remaining questions, clarifying questions for the Sponsor? Dr. Ohman. After that we'll go into our deliberations.

Dr. Ohman.

DR. OHMAN: Yeah, I think I did ask on the FDA side of the equation, but I had a question about how you reconcile the SAQ questionnaire of angina frequency and the

response in Canadian classification improvement that we're seeing. So I'm trying to reconcile a neutral effect versus a beneficial effect.

DR. STONE: So thanks, Magnus.

So in general, first, I think that they were quite consistent. You know, the Seattle Angina Questionnaire, first of all, it's not an optimal questionnaire for refractory angina patients in particular because of the wide standard deviation and given the standard deviation, we would've needed about 200 to 230 patients depending on the scale to be powered and as you know, there was only 104 randomized patients.

That being said, in addition to the two CCS angina class reduction, there also was a statistically significant reduction in angina quality and there were relatively substantial directional differences in angina frequency and angina stability, suggesting that that was Type 2 error.

So I actually think that it was relatively consistent, and had more patients been enrolled it would likely have been positive. But I do think that to remove some of that uncertainty, that is one of the reasons that Dr. Henry and I have been very vocal that we should perform an additional post-approval randomized trial, allowing this therapy to be brought to the public because it is such a major unmet clinical need, but at the same time we will generate more data regarding safety, effectiveness, and mechanism of action.

DR. LANGE: So with that, we are about, I'd say, 10 minutes ahead of where we still got a lot of work to do. I think this is a natural breaking point before we go into our deliberations. First of all, I want to thank the Sponsor. We asked a number of questions, some easy, some difficult, but there were a number of them and in a short period of time. I think you guys have done a terrific job of addressing those, so I want to thank you for that. And for the FDA, as well.

I'm going to recommend we take a break of 10 minutes and then let's get back, let's

begin our Panel deliberations. And probably the best way to do that is to begin working through the questions.

So Dr. Zuckerman, your thoughts.

DR. ZUCKERMAN: Yes, that's an excellent plan, Dr. Lange, but prior to that you'll probably want to hear the FDA response to questions which can be posed by the Panel. That can be done very quickly when we get back from the break. Dr. Lydia Glaw, Assistant Director of the Coronary Interventional Team, will be the quarterback to help you out on that.

DR. LANGE: Great. And Dr. Zuckerman, I have no preference. Would you prefer to do those now and then take a break or take a break and then do those?

DR. ZUCKERMAN: It depends really on you and the Panel members. It can be done either way.

DR. LANGE: Let's hear the FDA response. Let's do that now and then let's take a break.

So Lydia, let me hand it over to you. And there were some questions specifically directed toward the FDA. Do you want to address those or do you want me to --

(Audio feedback.)

DR. GLAW: Yes. Thank you, Dr. Lange. I think I have -- here and I can go through all the appropriate --

DR. LANGE: So Lydia, hold on a second. I think there's some audio -- it sounds like she's on Halloween voice. Lydia, go ahead and talk again and see if we've got it corrected.

(Audio feedback.)

DR. LANGE: No.

DR. GLAW: Okay.

MR. SWINK: Lydia, maybe stop your video, mute your mike and then kind of

re-launch it again.

DR. GLAW: Hello? Is that any better? Still bad.

(Audio feedback.)

DR. GLAW: Okay, I'm going to turn it over to someone else.

DR. LANGE: I'm sorry, Lydia, I couldn't hear what you said.

(Audio feedback.)

DR. GLAW: I'm going to see if someone else can take it on --

DR. LANGE: Okay.

MR. SWINK: We have Sam.

DR. RABEN: Yes, I'm happy to do that. Lydia, if you want to try and call back in, we can see if we can address that but I can handle that in the meantime.

Dr. Lange, can you give me the first question and then I can help facilitate the address?

DR. LANGE: Sure. Dr. Allen asked how does FDA handle missing or recommend handling missing data.

DR. RABEN: For that, Dr. Rona Tang will answer that question.

DR. TANG: Sure. This is Dr. Rona Tang from the FDA.

So for the missing data question, it is challenging because there are so many, there's a large number of missing data and the missing pattern for the secondary endpoint is not clear. So actually, we look to the Panel statisticians for recommendations on this issue.

DR. LANGE: Okay. And then Dr. Connor had asked whether we have -- because of the regression to the mean, do we have a history of information regarding these patients or similar patients?

DR. RABEN: Dr. Ryan can answer this question.

DR. RYAN: We don't have, with respect to -- are you asking about the placebo effect

or a statistical regression to the mean?

DR. LANGE: Dr. Connor?

DR. CONNOR: Well, I think the question was everyone was throwing around placebo effect and I'm calling it regression to the mean.

DR. RYAN: Okay.

DR. CONNOR: So I think the question is any historical evidence that says it's more one than the other. I would bet regression to the mean, but I always do.

DR. RYAN: I got you, okay. So yeah, we did do a literature search about the data that's available, specifically with respect to the placebo effect and angina. And I mean, certainly, the placebo effect can vary. We found out that there's a lot of range. Particularly with patients that are in desperate states and stress levels that are really high, the placebo effect can definitely be very high. As I mentioned before, there's been various studies that have shown that the placebo effect can vary in these -- in TMR studies, particularly, was an example that I brought up. So I don't think we're able to give you a number, we don't have a threshold that we would expect, for example, this percentage of patients we'd expect the placebo effect. So we can't really give you an upper or lower limit on that.

DR. CONNOR: Okay, thank you.

DR. LANGE: Dr. Wittes had asked what did the FDA not approve going forward.

Janet, do you want to expand on that? Yeah, it looks like she's frozen.

DR. RYAN: I think I understand -- oh, go ahead. I think Dr. Wittes was asking about what our concerns were about the COSIRA study and how that was reflected going forward. So I think, basically, for the COSIRA-II study, and I think the protocol was included or information was included in the panel pack, one of the pushes we had about COSIRA was the use of a subjective endpoint rather than objective endpoint, and the COSIRA-II study protocol would have addressed that issue. So there were other issues, as well, but without

getting into a lot of specifics, that was the major concern that we had.

DR. LANGE: Okay, great. A couple more chat questions, again, not to the FDA but to the Sponsor, and why there was so much missing data on the secondaries but not the primary outcome, again, because they were measured at the same visit. The SAQ and the CCS were supposed to be done in person at 6 months but were missing SAQ data.

DR. STONE: So there's actually relatively little SAQ data that is missing.

DR. LANGE: About 15 to 20%, Gregg?

DR. STONE: No, not that much. Let me put up the slide.

DR. LANGE: I guess, Gregg, why is any missing?

DR. STONE: Yeah. Yeah, that's a good question. So here is the data. You can see it's probably about 5 or 7%. So the SAQ is achieved differently than a CCS angina class. CCS angina class, you're talking to the patient, you're listening to nuances, etc. The Seattle Angina Questionnaire is a set series of questions that are on a written form and the patient is given the form and asked to go into a separate room and then to fill out the form. We don't have the reasons why in about 5% of those patients. You can see it's approximately 5, maybe 7% overall. Why the patients did not fill out the form, they may not have understood the questions. I don't want to speculate, but it's a relatively small percentage.

DR. LANGE: Okay, thanks. So we all know.

And then finally, again, there was information regarding CT angio. During the break, if the Sponsor could provide the summary statistics of the CTA findings rather than showing a picture. There were 44 patients that had CT angiograms done. If we could see the minimal luminal diameters, persistent flow of those signs, I think that would be lovely.

DR. RYAN: We have a slide on that, too, if you'd like to see that. We prepared a backup slide.

DR. LANGE: Go ahead and let's see it and see if --

DR. RYAN: Sam, can you share that? I think it's 154 or 155.

(Pause.)

DR. RYAN: Okay, there it is. There we go. So you see there's a total of 44 CTAs, 37 from COSIRA and then seven from the first-in-man study in India, and the minimal luminal diameters, both proximally and distally, are on this slide for your review.

DR. LANGE: Great.

Dr. Hirshfeld, does this answer the question that you have?

DR. HIRSHFELD: Well, if I interpret this correctly, I think we'd be interested in two things, what's the minimal lumen diameter in the neck of the device as opposed to the proximal and distal ends? And secondly, we saw evidence of, in the animal studies, where the neck of the device was not endothelialized and there was evidence that there would be flow around the neck of the device. And so I think the prevalence of that phenomenon in people would be answered by the CTA data and I haven't seen that, you know, specifically tabulated.

DR. LANGE: Could the Sponsor provide that during the break?

DR. STONE: We can certainly look at the break and see what we have. We showed you in a previous slide it's a hundred percent patency. I don't know what we have, as I sit here, in terms of the NLD at the neck versus elsewhere. I've not seen a case where there's flow outside the neck, but I understand you want quantitative tabulation which, of course, you're right in asking for. I'll see what we have at the break.

DR. LANGE: That sounds great.

And with that, I think all the questions that -- and a lot of them were addressed or we've offered and have been addressed. So with that, I'm going to ask that we take a 15-minute break. Let's convene at 4:45 Eastern Standard Time and we'll be ready to delve into the questions and use these answers as a platform to do that. All right, thank you

everybody. See you in 15 minutes.

(Off the record at 4:29 p.m.)

(On the record at 4:46 p.m.)

DR. LANGE: Great. I'd like to reconvene the Panel.

At this time let's focus our discussion on the FDA questions. Panel members, copies of the questions are in your folders. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate the transcription. In just a second I'm going to ask the FDA to show the first question. Although there are six or seven questions, and there's about 11 embedded in there, we have a large panel, I think about 19 of us, so what we'll try to do is get a consensus about the opinion without getting all 19 to speak on each question. I'll try to summarize. Obviously, if there are any dissenting views or any additional views you want me to relay to the FDA, we'll do so. With that, let me turn it over to the FDA to start with our first question.

DR. RABEN: Thank you. Over 90% of the COSIRA subjects were taking at least one antianginal medication and 36.5 were taking three or more at baseline. However, in a trial intended for a refractory angina population, greater than 25% of subjects were on only none or one anginal 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 calcium channel blockers in a refractory angina population. Also, no information was provided about medication compliance, or whether patients were on therapeutic or maximally tolerated doses.

So FDA's Question Number 1: 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. LANGE: I'll either look for a hand or I'll call on somebody. Dr. Batchelor and then Dr. Somberg.

DR. BATCHELOR: Yeah, so I think the Sponsor and the previous speakers tried to address this, but I think it's still an issue. I think the way that this is going to probably be best handled, in my opinion, is in the way in which the future study is handled, and I know we're going to get into that, if there's a trial that's going to be done, how is it structured, designed, etc., but I think it's going to be extremely important that this issue is addressed in another study because I think it was woefully not handled effectively in this trial. And I might add that historically, that's been an issue in prior studies, as well.

So any study moving forward should really identify what is the definition for refractory angina, who governs the medications, what's the escalation protocol for optimizing medical therapy, etc., so we've got a really good even spot to start the trial out, so I'll just make those comments and leave it at that.

DR. LANGE: Great. Dr. Somberg?

DR. SOMBERG: What I would add to that is I think it's critical that we do have a defined patient population and the patient population be resistant to medical therapy. We're dealing with an interventional procedure and a device which is semi-permanent. As we put in more, some of them may actually be permanent, so I think it's very critical that we define this population. A quarter of them were on no meds. Well, maybe they couldn't tolerate any meds, but that's very, very unusual and it's not just the number of meds, it's the pushing the meds to their maximum dose and their combinations. And we said well, some of them are symptomatic, they may be dizzy, they may be unable to tolerate the medication, but look at the large -- almost half of the people were on ACE inhibitors, ARBs,

diuretics, and we know when we treat angina patients we diminish other anti -- drugs that will reduce blood pressure and give the antianginal drugs a greater chance, and they often control the blood pressure, as well.

So I'm very disappointed in the pharmacologic determination that these are resistant patients, but I'm also saying that we need a better way to make sure that they are not interventionally treated, able to be treated by other therapies, as well. So if we're going to define a last-resort population, we've got to do it medically and we have to do it, also, interventionally.

DR. LANGE: Okay. I'm going to call on Dr. Brindis and then Dr. Mathew.

DR. BRINDIS: I agree with both comments, this is Ralph Brindis.

The only thing I would add is, to build on John's point, is we need dosages both at baseline and follow-up because that also tells an additional story.

DR. LANGE: Thank you, Ralph.

Dr. Mathew and then Dr. Cigarroa, and I think we'll close it at that.

DR. MATHEW: I agree with all the comments. I would just sort of reiterate the point that in real life as well as other clinical trials, it's been very difficult to optimize medical therapy for reasons that have been mentioned. While this proportion of patients on little to no meds is probably higher than I might have anticipated in anecdotal clinical experience in other trials, it may be that this is what it is in a small number of patients and the error of variation there, as well. So I think in a very few trials such as COURAGE, where there was dogmatic emphasis on medical therapy, or SYMPLICITY, where there was a roll-in period of aggressive medical therapy for hypertension that could achieve it, but I think this study is not necessarily an outlier in terms of aggressiveness of medical therapy.

DR. LANGE: Dr. Cigarroa. And I saw Dr. Yeh and Dr. Vetrovec, and then if we have a consensus, we'll move on, but Dr. Cigarroa.

DR. CIGARROA: My answer to Question 1 is no for two reasons. First of all, the patients studied were primarily Caucasian men, which is not reflective of the demographics of our country, and secondarily, the percentage of individuals who were intolerant to medicines without insight as to the reasons left a -- you know, which accounted for about 25%, challenges the ability to interpret these results. So for both those reasons I would say that we have not yet identified a defined patient population.

DR. LANGE: Okay. Dr. Vetrovec and Dr. Yeh, anything else to add?

DR. VETROVEC: Very quickly. While I think it's -- the number of patients who were inadequately treated is exceptionally high for this study, I would suggest the idea that some patients, say, who aren't taking the medicines and won't take the medicines and they are refractory. And so some percentage of that I don't think is a crime, but I do think it's important to have a much better balance of good medical therapy.

DR. LANGE: Okay. And then Dr. Yeh, you get the last comment here.

DR. YEH: I was going to say that I'm sort of playing devil's advocate in my own mind, but while I agree that it may not be clear that all of these patients have truly refractory angina despite a very optimal medical regimen, I do think at the same time we don't -- it's quite clear that all these patients are very symptomatic, they all had Class III or IV CCS symptoms and very low Seattle Angina Questionnaire scores. And so that being said, I wonder if, although it didn't necessarily find a refractory angina population, it does find a population with severe symptomatic coronary disease, mostly on medical therapy. So it may not be the patient population that they explicitly named here, but it is a clinically relevant patient population, so I'm just wondering how that plays out and how we think about that as a group.

DR. LANGE: Okay. So I'm going to summarize, Bram.

It seems that there is -- the feeling is that the Sponsor has identified people with

angina, severe angina, but there's insufficient documentation to define whether they actually have refractory angina or not. The data that's missing are angiographic data that's missing, medication, dosing, whether on max dose, whether patients are compliant, whether there was medication adversity or intolerance, and whether the patients were truly not amenable to revascularization, and future studies need to address this. The Panel recognized the difficulty, but feels like the Sponsor needs to make a better effort if they're going to target refractory angina as opposed to severe angina.

Dr. Zuckerman, does this address the question satisfactorily? Additional comments?

DR. ZUCKERMAN: Yes. And can you --

DR. GERSH: I'd like to make an additional comment.

DR. ZUCKERMAN: I guess, Dr. Gersh, did you want to make a comment? And then I'd like to make one.

DR. GERSH: I agree with Dr. Yeh completely. I think these are patients with severe angina. Are they truly refractory? No.

DR. LANGE: Okay.

UNIDENTIFIED SPEAKER: I think he muted himself by mistake.

DR. LANGE: I think you muted yourself, Bernie.

DR. GERSH: But in terms of revascularization, at that time, as Gregg Stone pointed out, there was no formal heart team and I believe -- and I think, moving ahead, if there's another study I would design it differently in some ways. But I think I'm comfortable that these patients -- there was a consensus that they were not revascularized. A large number had bypass surgery, even repeat bypass surgery, multiple stents, and I'm comfortable with that. You know, 25% zero to one drugs, that is surprising in terms of antianginal therapy. But I do think they've answered the question that this is a group with severe symptoms and probably not revascularizable and we have to remember, the formal heart team was not in

existence at that time.

DR. LANGE: Great. Dr. Zuckerman.

DR. ZUCKERMAN: Okay, but the question is we recognize that this is a patient with significant angina, but is it well enough defined, Dr. Lange, with respect to all the other key variables that would allow us to write an indications for use? And am I correct in noting that the majority of the Panel believes not?

DR. LANGE: I think that's correct and that is, it's severe angina. Is it refractory angina? I don't believe that the Panel has enough information to ascertain that's true, so they're uncomfortable with that.

DR. ZUCKERMAN: Thank you.

DR. LANGE: Great. Next question from the FDA.

DR. RABEN: So regarding blinding and the role of placebo effect. 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 at 6-months 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.

So Question 2a is please discuss the robustness of the trial results given the lack of a blinding assessment throughout the course of the study and the limited sample size.

DR. LANGE: Magnus, you had asked about blinding and confirmation, so do you want to address, answer this first? Then we'll let other people chime in.

DR. OHMAN: Yeah, so it's never easy to do successful blinding in sham-operated studies, so I think the study group should be congratulated for attempting, but I think some

of the key aspects to this, namely how was it assessed, in other words, was there an objective way of assessing how well the patient -- given that this is a study of symptomatic behavior rather than objective ischemia.

So I think the study design is very challenged and interpretation, therefore, is very difficult because it's on a symptomatic scale where sham-operated -- but how well blinded patients are included, it's very, very hard. Had they been combined with objective evidence of ischemia, then the story could have been told, but the lack of the latter makes it almost impossible to understand it.

DR. LANGE: Dr. Somberg.

(Pause.)

DR. LANGE: You're on mute. John, you're on mute.

DR. SOMBERG: What I was saying was given all the drawbacks of the trial, I think the blinding issue is one of the better aspects. They tried hard to blind it, and there's nothing to suggest that it wasn't blinded. So I'm less concerned of blinding, but I'm most concerned of the missing data. It wasn't in the Canadian questionnaire, so that's good, but everything else seems to be Swiss cheese.

DR. LANGE: Dr. Batchelor and then Jason, I'm going to come to you because it looks like there's twice as much missing data in one side than another and if it's blinded, what's that likelihood?

So Dr. Batchelor, let me to come to you.

DR. BATCHELOR: Just to stand on the blinding issue, you know, I've been involved in sham trials and as Magnus mentioned, they're very difficult to do in the cath lab. However, it's crucial that the manner in which the case is dictated and documented has to be done in a way you can't figure it out. Remember, all of these folks, people are going to look at the procedure report and follow-up and if the interventionalist doesn't dictate it in a

completely generic fashion, you can quickly figure out who got what. So we didn't have a chance to ask that question, but it's a very important point moving forward in terms of trial design for the future. We have to make sure that the interventionalists and all the source documentation is completely obscure in terms of treatment assignment.

DR. LANGE: Great. Jason?

DR. CONNOR: Yeah, agree on the blinding and it seems like they did a good job to attempt it. There are so many one-arm trials we see in devices that I think this is higher quality evidence than we usually see. At the same time, I think the missing data is very problematic especially given this idea that the primary is there but the secondaries aren't and it's imbalanced. Like I guess that if people are sent into a room to fill out an instrument and they miss a few items in the instrument, you can't get a complete score. It sounds like, from Dr. Stone's explanation, that's kind of what happened, but I think that's an unsatisfying answer because in theory, people just are missing questions and you can't get a whole score for the instrument. There's no reason that should be this different between groups.

So I was really hoping the answer on (a) why is there missing data in the secondary but not the primary and why is it imbalanced would be, you know, a little more thoughtful or well-studied and I think without that, that it's really hard to answer how effectively it was blind or why this imbalance, but I'd love to hear if Dr. Wittes has any insight there, too.

DR. LANGE: Dr. Brindis and Dr. Allen, I see both hands up.

DR. BRINDIS: So I want to also chime in about the missing data, I think it's a significant problem, particularly it being unbalanced between the two groups. I wanted to get back a little bit because I think we glossed over the issue that Joaquin brought up, which is the patient demographics. Because this study was so imbalanced in terms of ethnicity and gender, this is a huge step backwards and angina is not the same by gender and

ethnicity and that's sorely lacking in the study, it needs to be emphasized.

DR. LANGE: Great.

DR. ZUCKERMAN: Okay, can I pause the Panel a moment? We are going to get into the demographics question extensively in Question 5, but if we could try to address the questions that Dr. Lange is posing to us, that is most helpful to the FDA.

DR. LANGE: Great. Dr. Allen and then Dr. Starling.

DR. ALLEN: Yeah, Keith Allen.

You know, I think the Sponsor is to really to be congratulated on doing a sham procedure. As somebody who was in Gregg Stone's position in 1998 presenting to the FDA on TMR data, I understand the constraints and concerns of doing studies like this. Nonetheless, the investigators and the consultants for the Sponsor have all been involved in sham trials and they clearly understand what's needed to make that successful.

I am really concerned about the imbalance and the missing data for the simple reason that I'm concerned that the patients did know what they got and usually if the imbalance was on the treated side, I would be less concerned. But normally the group that doesn't get the therapy, they lose the flip of the coin or so they perceive they lose the flip of the coin, are less likely to participate in follow-up studies, particularly ones that require time and effort, like a treadmill test or a thallium study or extended answering of questionnaires. So it does really concern me.

DR. LANGE: Great. So what I'm hearing, and I'm going to summarize, if there are additional comments, please add them.

Dr. Zuckerman, what I'm hearing is that the blinding is absolutely essential, that the panelists applaud the Sponsor for attempting to do so. Unfortunately, we don't know how successful they were at doing that because there was no objective assessment of that and for some studies it may be easy to figure out, and the missing data imbalance makes

individuals concerned that despite the Sponsor's attempt is that the patient and/or the caring physicians may have figured out which treatment they received and as Dr. Brindis said, having evidence of ischemia, which is much more objective as opposed to a subjective symptom, would've been essential to help in this particular trial.

But Dr. Brindis, an additional comment to that?

DR. BRINDIS: Yeah, the only other point which I thought was excellent, and I can't remember which panelist made it, the ability of actually picking up the presence of the device on a chest X-ray, and Keith gets the credit for that --

(Crosstalk.)

DR. BRINDIS: -- and I know that would be in a X-ray report or anybody who's following the patient would certainly be looking at that chest X-ray potentially with interest.

DR. LANGE: Or an echo that shows a metal device in the coronary sinus because they all had DSEs, so it would be very difficult. So again --

DR. ZUCKERMAN: Thank you, that's an excellent response.

DR. STARLING: Dr. Lange, could I make a comment, please? He's muted. You're muted.

DR. PAGE: You're muted, Rick.

DR. LANGE: I'm sorry. Someone asked if they can make a comment, I didn't see who made that -- Dr. Starling, I'm sorry.

DR. STARLING: Please. I just wanted to reiterate, having participated in at least a half dozen sham-controlled trials going back to the ACORN era to the most recent trial with an interatrial shunt, there are numerous safeguards that can be put in place including having the investigator sign a document at every visit to verify that they have not been unblinded to the treatment. So yes, this trial was a bit dated from a few years back, but I don't think we have any assurances as to appropriate blinding in addition to the other

issues related to an outside U.S. study with missing data.

DR. LANGE: Very nice. So if a future study is done, having that objective evidence of blinding documented, that will be quite important. Thank you.

DR. GERSH: Richard, I think it's important to bring up the interatrial shunt study because this is an example of where blinding was verified at the time of the procedure, but it has been verified throughout the follow-up. I think it's critically important.

DR. LANGE: Thank you. And both times, you're right, Dr. Gersh.

DR. GERSH: I think we just have to think about it in future trial design, I mean, this was several years ago.

DR. LANGE: Yes, thank you.

Next question from the FDA.

DR. RABEN: Question 2b is, given that some patients did 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. LANGE: Dr. Yuh.

DR. YUH: Thank you, David Yuh.

I think this is one question where we're somewhat handicapped by, at least for me, not being clear on the mechanism of action. I think that mechanism can speak towards who would benefit and what the limitations of the procedure are. For example, if the putative mechanism is really at the micro -- redistribution at the microvascular level, you would think that patients with primarily microvascular disease would stand to benefit the most and I think for future studies or future investigation, that that sort of patient population be included as a subset, at least, in addition to the subsets that were used already.

DR. LANGE: Great. Dr. Starling.

DR. STARLING: Yeah, I think that we don't know the answer to this question and ironically, the data that we were shown indicated that those that had the lower anginal class were most likely to respond. Dr. Stone attempted to provide us with an explanation for that, but I think the answer to this question is we don't know who will derive the most benefit.

DR. LANGE: Okay. Before I ask for any other hands, does anybody feel like they know, from the data we have, who would receive a significant clinical benefit?

(No response.)

DR. LANGE: Does anybody -- okay, I don't think -- I'll go to Dr. Somberg, Dr. Page, and Dr. Ohman.

Dr. Somberg.

DR. SOMBERG: Yes, I think there's one anatomic/physiologic characteristic that we're just not focusing in on and that is that the coronary sinus, for the most part, only does about half the drainage of the myocardium, the total myocardium, and I think we should assume that the benefit of this device has something to do with its implantation in the coronary sinus increasing pressure and therefore more proximal profusion.

So I think it would be useful, and I'm surprised preliminary work wasn't done on this to try to define where the ischemia is coming from in a stress thallium or wall motion study and then trying to see if that is a plausible area, that the coronary sinus in that patient will drain because, for instance, the -- what was it, the Bayesian drainage has anything from 30 to 60% of alternative venous drainage. So I think we're not correlating the plausible intervention with the physiology of the heart and maybe some studies looking at the distribution of the drainage compared to where the ischemia's coming from could be used to try to identify patients who would benefit.

DR. LANGE: So at this point, you propose that that's a possible thing to look at but you don't -- you're not saying at this particular point you know which distribution --

DR. SOMBERG: Of course not, nobody knows because it's not been explored, but I think it's a hypothesis to generate and to try to test instead of putting it to everybody who has something to do with the circumflex in the LAD and only getting a fraction of those responding.

DR. LANGE: Dr. Page and then Dr. Ohman.

DR. PAGE: Yeah, I don't think I have a good enough understanding of the nature of the patients and the mechanism of action to really say that we can predict who will benefit from this. I'm always struck when I hear testimonials from patients, and this time their significant others, and the fact that they're looking for something, but at best, 34% would have a positive response as defined by two levels of improvement in class and almost half that many who got a sham procedure had a similar response. So I think the answer to the question is we can't predict which of those patients are going to respond favorably.

DR. LANGE: Okay. Dr. Ohman, I think you have the last word on this.

DR. OHMAN: Yeah. I want to echo what others have said, I think it's unclear. But unfortunate for this study and the very limited sample size, the best therapeutic data seem to be in those who took the minimal amount of medication, zero or one, which is rather paradoxical, so there may be some clue there to the future but it may actually not address the refractory angina.

DR. LANGE: Okay. And Dr. Borer, I'll let you have the last word on this, sir. Unmute yourself, Jeff.

DR. BORER: Okay, can you hear me?

DR. LANGE: Yes, sir.

DR. BORER: Great. Okay, I'm disturbed by what I think is a fundamental problem

here. Some patients did not appear to be receiving benefit from the treatment, only a third achieved a primary endpoint success of a change in CCS of at least two grades. This is an angina study. For 50 years the standard for angina for success or magnitude of success in minimizing angina, preventing angina, has been a quantitative exercise test, how many minutes will a patient be able to go on a quantitative exercise test, and that's not what we're talking about here, we're talking about a subjective endpoint and I don't -- I think that that's a real problem. It just magnifies all the other problems that have been discussed already. I think in developing a new study there has to be a much greater emphasis on quantitative assessment.

DR. LANGE: Okay. So I'm going to summarize.

Bram, I think the consensus of the Committee is no, we don't know the answer to this, we don't know who would benefit. And some information that's lacking is the mechanism, the correlation of the mechanism with any clinical benefit. There's a lot about the native patients, we don't know demographics, nature, distribution of coronary anatomy, so that's ill defined. And then finally, as Dr. Borer mentioned, we don't have any quantitative data to ascertain which patients received it and so all of those things are limitations that prevent us from saying who would benefit from this.

DR. ZUCKERMAN: Okay, so Dr. Lange, that's an excellent summary after a great Panel discussion. Just a quick comment to respond to Dr. Borer. In 2010, when this study was being discussed with FDA, not unexpectedly, Dr. Borer, FDA did recommend the treadmill endpoint that has been used as a standard. The Sponsor disagreed and was one of the reasons why the study was done overseas, the Sponsor was confident that this was an objective enough endpoint. Certainly with COSIRA-II, again, the FDA has really tried to urge the Sponsor to use the exercise treadmill endpoint as the primary endpoint and when we get further into the questions, I'd like you to further expand with other Panel members

on how objective some of these angina endpoints are. Thank you.

DR. LANGE: All right. I think we can move on to the next question. Thanks to the Panel for opining on that.

DR. RABEN: Thank you, Dr. Lange.

So the next question is regarding the primary effectiveness endpoint. A two or greater CCS grade change at 6 months was the primary effectiveness endpoint of the COSIRA trial. Primary endpoint success was observed in 34.6% of subjects treated with the Reducer device, while 15.4% of subjects achieved success in the control group. In 28.8% of the Reducer group and 57.7% of the control group, no change in CCS was observed. However, angina can be a placebo-responsive condition. Exercise tolerance testing provides an objective measure of functional capacity in myocardial ischemia. Other clinical trials evaluating anti-ischemic treatments have used exercise testing results as a primary effectiveness endpoint.

So 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. LANGE: Dr. Borer. And again, unmute yourself, Jeff.

DR. BORER: Yeah, a change in CCS grade is certainly not an unreasonable measure of whether an intervention does something or doesn't, but it's not the best evidence. The best evidence would be a quantitative assessment that includes an electrocardiographic measure of ischemia, as well as an antianginal effect. In fact, although I don't know how the rules are written for devices for this kind of thing, for drugs, for years, an antianginal drug has to prevent angina by an anti-ischemic mechanism, there has to be a reduction in ischemia. So I would say that a reduction in CCS grade is nice, but it's not sufficient.

DR. LANGE: So I'm going to ask all Panel members to -- a yes or no vote on this, that

is going forward, either another study or a postmarket study, how many of you would -- Ralph's shaking his finger at me. I'm not assuming either, okay, I'm not assuming either, but how many would recommend that the Sponsor use only CCS grade change and would say that that would be a reasonable assurance of effectiveness? If you say yes, let me see your hand.

(Show of hands.)

DR. LANGE: If you say no, let me see your hand.

(Show of hands.)

DR. LANGE: Then I'll call on Dr. Brindis, okay?

DR. BRINDIS: One comment that hasn't been made yet is a publication showing the lack of correlation between physician reporting of CCS and SAQ scores. I might assume it might be more aligned in this study because it was blinded, but it is interesting that patient-reported outcomes is what clinicians like and we haven't mentioned that before.

DR. LANGE: Thank you, Ralph.

DR. SOMBERG: Dr. Lange, can you tell us the results of the hands? I didn't see everybody.

DR. LANGE: Yes, there were no hands up with reasonable assurance and all hands went up with they would not recommend that as the sole measure of reasonable assurance.

DR. SOMBERG: Thank you.

DR. LANGE: It was unanimous.

Dr. Yeh.

DR. YEH: I mean, I'm thinking about what is the more important endpoint here and for this category of patients, I just do want to raise the possibility that the goal is the reduction of angina, not the reduction of ischemia, and one can imagine therapies, not is the case, per se, but one can imagine future therapies that treat patients with angina not

through reduction of ischemia but via some other mechanism. And so this question as framed, I think, sort of implies that ischemia is the thing that is the gold standard for what we're trying to reduce here, but I mean, I think, arguably for this patient population, they don't care about their objective measurement of ischemia, what they care about is what they're feeling, their angina. And so among these two things about whether or not I sort of think that the exercise tolerance test is a better study versus angina class, I'm sort of more concerned about the blinding issue that we talked about previously for this particular issue.

If there were perfect blinding, I would be, I think, much more comfortable and I don't have, I think, the historical viewpoint of this that Dr. Borer does, but I'm more comfortable. We use Seattle Angina Questionnaire very frequently and I think what it's subject -- it's a very stable estimate over time and what I think I'm more concerned about when we use those types of endpoints is the blinding issue, but also exercise tolerance test, it certainly also could be a placebo-responsive condition. I just want to say that people's exercise effort may be related to also those things. I don't disagree with anything that's been said, I just wanted to put that point out there.

DR. LANGE: I appreciate it.

I've got the following hands up in this order: Dr. Cigarroa, Dr. Mathew, Dr. Borer, and Dr. Somberg.

Dr. Cigarroa.

DR. CIGARROA: So I certainly agree that there are approaches that can impact the perception of ischemia, whether it's dysthymia or classic chest discomfort through means other than mitigating ischemia. However, in this particular situation where the putative mechanism is a primary means of impacting ischemia, I think assessing ischemia in addition to the measurements of angina is critically important and I think especially even more so given the small sample size that we are looking at in this trial in which flipping two patients

in either direction on how one classifies would change the statistical significance. So not knowing the mechanism of action, having the purported mechanism of action improving symptoms via reduction in ischemia, I think one has to have a quantitative assessment of ischemia.

DR. LANGE: Okay. Dr. Mathew.

DR. MATHEW: Yeah, Verghese Mathew. Thank you, Dr. Lange.

So I just want to convey my agreement with what Dr. Yeh brought up. From a patient perspective, as we see these people in real life, I mean, they're really concerned about their symptoms and they're not coming in to sort of say we're wanting our ischemia reduced, they want their symptoms reduced, and I think it goes to the patient populations that we're testing here and what the goals are, and I think that a larger denominator would've been helpful in that regard.

But I think the limitations of measuring ischemia and the variableness of ischemia, I think there's a scientific discomfort on my part, and maybe our collective part, that not having an objective measure like that is, again, discomforting. I don't know that I would solely rely on Canadian Cardiovascular Society class, but some complement that satisfies our scientific curiosity, I think, would be important moving forward in another trial.

DR. LANGE: Thank you, Dr. Mathew.

Dr. Borer.

DR. BORER: Yeah, thank you.

There are a couple of issues here. First of all, I agree completely with the statement about blinding that I think Dr. Yeh made a few minutes ago. But the primary reason I think that the demand is made that reduction in angina as measured on an exercise tolerance test is accompanied by evidence of a reduction of ischemia is safety. If you were able, with any kind of intervention, to allow people to walk longer on a treadmill before they develop

limiting angina and you weren't limiting their ischemia, they could die while they're walking on the treadmill. That would be a bad thing and I think we'd all agree with that.

So I think that there really must be some assessment of ischemia associated and not just for purposes of completeness. In Europe the primary criterion for approving an intervention as an antianginal is evidence of a reduction in ischemia, not angina, so I think that it's very important to do both, but to quantify both.

DR. LANGE: Okay.

DR. GERSH: Richard?

DR. LANGE: Dr. Somberg, anything?

And then, Bernie, I'll come to you.

DR. SOMBERG: I would just agree with Jeff's statement, we want to do both, and I think it's very concerning that we would just put all our emphasis on CCS because we can give an analgesic and you can take an opioid and you wouldn't feel pain but you would have significant physiologic consequences. So I think we want to have something to substantiate that it's just more than a pain reliever, that it's actually an ischemic reliever, as well. So we might know the absolute mechanism of this device but we want to know that it's doing something to the ischemic process.

DR. LANGE: Okay. And then Dr. Gersh, Allen, and then I'll summarize.

DR. GERSH: I totally agree that we need both, I think both measurements of ischemia or assessments of ischemia and severity of angina have their limitation and one great example of that is the ISCHEMIA trial that's just being published. I mean, the rationale for this trial was that people with moderate to severe degrees of ischemia would benefit from revascularization and although not yet published, it's been presented. In fact, there was no relationship between the severity of ischemia and the outcome of the ISCHEMIA trial. So it has its limitations, too, as does the assessment of angina, but -- clinical

assessment, but I prefer to see both.

DR. LANGE: Great. I'm going to summarize, but -- and then Keith or Randy, if you have anything to add to it, raise your hand and I'll let you do so.

I think the consensus is, Bram, is that the Committee is recommending both. The CCS alone is not an effective way to reasonably assure effectiveness.

So Keith, if you want to go ahead. You're on mute. This is Keith Allen, Dr. Keith Allen.

DR. ALLEN: Yeah, Keith Allen.

So I think Joaquin really summarized, and I do think it's very important that mechanism play a role in when you're choosing your -- how you're going to judge your primary endpoint, and I just want to give you two examples to maybe make it clear for people listening.

You know, in this case the mechanism is improvement in profusion, it clearly is related to ischemia. Picking an endpoint like ETT makes a lot of sense. On the other hand, let's say the mechanism was de-innervation (ph.), that's how you are fixing people's angina, then improvement in profusion and reduction in ischemia wouldn't be a reasonable endpoint and perhaps CCS class in a well-blinded study is a much better endpoint. I don't think you can separate the two, but for this particular example, CCS class is not the right endpoint.

DR. LANGE: All right, great.

Dr. Starling, do you want to add anything to that, sir?

DR. STARLING: Yeah, I just wanted to say, and this is coming as being a heart failure specialist, this discussion is somewhat analogous to NYHA class and cardiopulmonary exercise testing or ejection fraction as far as gaining some objectivity, and this is sort of a patient-reported outcome, although they did have a blinded assessor, but we were never

really told, at least in COSIRA, we were never really told what the rigor was as far as that blinded assessment other than it was a blinded assessment. But fully agree, we need something more than CCS.

DR. LANGE: Okay. Bram, do you need any other additional comments from the Panel or do you feel like you have enough information?

DR. ZUCKERMAN: This was an excellent discussion, please go on to the next question.

DR. LANGE: Thank you.

Go ahead, Sam.

DR. RABEN: Thank you, Dr. Lange.

Question 3b, we would like the Panel to 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. LANGE: Dr. Borer.

DR. BORER: You know, this is a question that can only be answered in a relative way. The overall primary effectiveness rate of 34.6% using the endpoint that was used may be wonderful. Do we know anything that's better? I don't. You know, in people with refractory angina, we don't have a comparator. So I think that that's reasonable enough. Yes, the patient population is relatively vulnerable, but the goal of the therapy is to improve their quality of life, to make them feel better, and if the effectiveness endpoint is achieved, the measure that was used is achieved in a the third of the patients, that may be pretty good. So I don't think that's really an important issue. An important question, I think the important question is do most -- do people generally feel better, because that's what you're trying to get them to do. We're not talking about survival with this trial.

DR. LANGE: I've got Dr. Allen and Dr. Batchelor.

DR. ALLEN: So the 34, 35% rate compared to 15% in the control, I think that's an okay number. If you had a 34% cure rate of a Stage IV cancer drug, you would have a real winner. I think at least what concerns me with it's not so much the number, but the veracity of the number and whether the clinical trial was done in such a way with all considerations such as missing data and things like that, whether I believe that they got to that number and it was powerful. So the 34% I'm okay with, I just don't know that the trial makes me comfortable that they actually got that number.

DR. LANGE: Okay. Dr. Batchelor, Dr. Cigarroa, Dr. Brindis, and Dr. Somberg.

DR. BATCHELOR: Just to springboard off of what Keith just mentioned, I actually think the response rate is pretty good if the patient population was truly defined as truly refractory angina patients. I'm sure Dr. Gersh, Dr. Borer, and others who have a lot of wealth of experience in this thing can chime in, and I think Dr. Gersh mentioned that this is actually not that bad of a response rate. My issue is it's not -- the absolute risk reduction and the relative risk reduction is actually pretty good, it's the confidence intervals around this result and the sample size that we have concerns about where the -- you know, the confidence intervals are fairly wide. In just a little of the sample size, it only takes one or two patients to shift the statistical significance. So I think we're talking about two different things. The delta, the difference, it's a pretty good delta but the confidence around that reduction is questionable.

DR. LANGE: Great. And I've got Dr. Cigarroa, Dr. Brindis, Dr. Ohman, and Dr. Somberg before that, go ahead.

Dr. Cigarroa.

DR. CIGARROA: My points are along the same line as Dr. Batchelor and Dr. Allen's. The number itself is a reasonable effectiveness rate; however, the believability of that number, given the issues that we discussed about the trial and the sample size and blinding,

calls into question whether I believe that number.

DR. LANGE: Thank you --

(Crosstalk.)

DR. BRINDIS: Yeah, so my comment is if we believe the number, NNT is just fine for me assuming that the device is safe, you know, because that's the tradeoff. So that would be my comment.

DR. LANGE: Thank you.

Dr. Somberg and then Dr. Ohman, and then I'll try to summarize.

DR. SOMBERG: I guess I'm going to be in a minority position here that I don't think that number -- I mean, we're talking about 34% response in the intervention versus 15 in the control, you know, you're going to benefit 15 out of 100 people for a permanent device. I think that's very marginal.

DR. LANGE: Okay. I appreciate even -- especially dissenting opinions.

Dr. Ohman.

DR. OHMAN: Yes, so I'd like to turn it around and think of it in a different term. Nearly half the patients did not respond. Now, I can live with that if we showed a reduction in ischemia because of the variability in angina, but the fact of the matter, that I put in a device and about half of them are not going to have any benefit at all using this classification worries me, and that's why I think the importance of angina plus ischemia becomes critical.

DR. LANGE: So I'm going to -- and Dr. Borer.

DR. BORER: Yeah, I just want to come back to something John Somberg said a little bit earlier, he said you could use an opioid and relieve the pain, and you could. Janet Wittes and Bram will remember, the first meeting at which Janet and I participated for this Committee was when partial laser revascularization was put forward and there were no

exercise tests, there was no measure of ischemia, and I remember making a suggestion that they could've given everybody morphine. And the trial was done in Detroit at Wayne State and the progenitors of the trial were up in arms, you can't use opiates for treatment of coronary disease, that's a terrible idea. Well, no, it's not. If the idea is just to make them feel better, it may be a good idea. The problem is that the opiate won't relieve ischemia, so we have no reason to believe it would, we'd have to test it. So I think that's a key issue to remember. Chest pain isn't enough.

DR. LANGE: Keith, the last comment.

DR. WITTES: Can I jump in?

DR. ALLEN: Yeah. So let me just make -- I just want to --

(Crosstalk.)

DR. ALLEN: -- because we're not really here to debate TMR and I was involved in a lot of the TMR studies, but I would beg the issue with what was just stated because Dan Burkhoff in 1999 presented the ATLANTIC trial which was published in the *Lancet* and their FDA-mandated primary endpoint was ETT and patients that got TMR had a 111-second improvement over the control group following surgical sole therapy, TMR. So we do have objective evidence in other antianginal devices so we're not here to debate TMR but I just think we need to be careful about statements that maybe aren't correct.

DR. LANGE: All right. I'm going to summarize. Some Panel members felt like a 34% rate was -- the 34, 35% was satisfactory, others did not. Bram, that's obviously balanced with the safety and the placebo effect --

(Audio feedback.)

DR. LANGE: -- confidence in the reliability of this information and also of the patient population. I think there was less concern about the number and more concern about -- especially if there's a marginal benefit, more concern about the reliability of the patient

population and the assessment. Does that answer your question?

DR. ZUCKERMAN: Yes, it does. It's a very good summary of a very good discussion.

DR. LANGE: Thank you.

All right, Sam.

DR. RABEN: Great, thank you.

The next question, I would like to discuss secondary effectiveness analysis. In a secondary effectiveness analysis in COSIRA, the ETTs, specifically the 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 versus a mean increase of 4.3 seconds) and time to ST-segment depression versus control patients, which was 76.3 seconds versus 33.8. However, the study was (1) underpowered to detect improvements 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 30% was missing for control subjects. Total exercise duration testing was missing in about 25% of all patients, and ST depression data was missing from 70 to 88% of patients. These two factors impact the conclusions that may be drawn from these ischemia data.

Question 4a is, 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. LANGE: Dr. Gersh and Dr. Allen and Dr. Somberg.

DR. GERSH: Thank you. I want to go back to the *New England Journal* publication of this paper and the editorial that was written by Christopher Granger and myself, and

basically, what we see in there, I think -- and that is the bar that was set for the magnitude of benefit was quite on, I mean, two Canadian CCS classes, as was pointed out by Gregg Stone. If you go from four to two, that's a huge change, and if you go from three to one, that's a large change, but what we did say, the study is underpowered. If other studies show this then we may have a highly effective treatment for a very difficult group of patients, but it is an underpowered study. I do not understand still why it was stopped.

And thirdly, I think that the -- in terms of the secondary endpoints, the discrepancy and the lack of missing data and the discrepancy between the two groups totally invalidates that. I don't know what to make of the secondary endpoints at all, so I think if this degree of benefit can be substantiated by the studies, and I think we have a very interesting and effective form of treatment, and that's what we said a couple of years back.

DR. LANGE: Great. I've got Dr. Allen, Dr. Somberg, and then Dr. Wittes.

Keith, you're muted. Sorry about that.

DR. ALLEN: My fault, excuse me. Keith Allen.

Now, I have a hard time, quite honestly, putting much faith in the secondary effective analysis and obviously the company and the Sponsor didn't either because they didn't do a pre-specified hypothesis, they didn't power the study for any of these, so they clearly weren't confident they might meet these secondary effectiveness endpoints, so I'm not sure why I should be empowered to think they're positive.

DR. LANGE: Okay. Dr. Somberg and then Dr. Wittes.

DR. SOMBERG: With that degree of missing data in the control group of 30%, the data really will not be informative. I think any study that's presented to the FDA that has a critical component with that much missing data really should not be brought to the Panel.

DR. LANGE: Okay. Janet.

DR. WITTES: Yeah, so Dr. Zuckerman asked us about how Jason and I would handle

missing data, and I agree that when you have 30% in one group and 15% in the other group missing, there's no --

DR. LANGE: Janet, we just lost you.

DR. ALLEN: Janet needs to pay her Wi-Fi bills better.

UNIDENTIFIED SPEAKER: Yeah, she might want to stop sharing her video, that might help her.

DR. LANGE: Yeah. Janet, if you can hear me, turn your video off, leave your audio on.

DR. WITTES: My video is off and my audio is on, can you hear me?

DR. LANGE: We can, so I'm sorry, we lost you just at the -- go ahead.

DR. WITTES: Okay. So what I was going to say is --

(Audio feedback.)

DR. LANGE: All right. Janet, we're having trouble with your audio, as well.

DR. WITTES: Okay. Never mind.

DR. LANGE: I'm so sorry. I know what you're saying is important. As a non-statistician, I can't even help you out.

(Audio feedback.)

UNIDENTIFIED SPEAKER: -- format.

DR. LANGE: Yeah. So Bram, I'm going to summarize this.

So Dr. Zuckerman, I think everybody recognizes and the Sponsor did, too, it's underpowered, lacks a hypothesis for any of the secondary endpoints. We also acknowledge that it's missing data, as well, and I think the Panel is actually putting --

(Audio cut out.)

DR. ZUCKERMAN: I think the Sponsor was partially aware of some of these problems and that's why the Sponsor presented to the Panel the REDUCER-I observational data which

are nonrandomized data where the Sponsor believes that the same trends are being shown and that these are important data. Could someone like Dr. Allen just comment on this strategy? Do the REDUCER-I data help you at all, Dr. Allen?

DR. LANGE: And then after that, Jason, I'm going to come to you because you had your hand raised.

So Dr. Allen.

DR. ALLEN: Thanks, Dr. Zuckerman.

The short answer and very short answer is no, and I've really discounted the REDUCER-I data altogether. Those were observational studies; a lot of these are single center, some of the data they presented were single center, obviously none of it is randomized. Where the placebo effect concerning any data that's not randomized and appropriately blinded comes into suspect. Commingling randomized data like COSIRA with REDUCER-I data actually only confuses the issue, in my mind, and it draws into question a lot of the issues that we've already discussed.

DR. LANGE: Dr. Connor, you had your hand up and if you want to make a comment there, and also whether you think that the REDUCER-I data overcomes the shortcomings that we've identified.

DR. CONNOR: Yeah, my comment was just going to be regarding pre-specification of secondary endpoints, pre-specification of missing data, things like that. I had requested the SAP because I always request the SAP when I'm on this, and didn't receive it. I received the protocol but I've not seen any SAP that may have gotten into, you know, alpha spending, how secondary endpoints would be in alliance from a prospective standpoint, what order they focus on, things like that. So we don't know that, either.

Regarding the supportive study, I mean, I think it's -- you know, it just doesn't, as far as I can tell, also have at least pre-specified performance goals and things like that. If it

were a one-armed trial it would at least have those and they put a stake in the ground and see what -- so I mean, we've seen the data, but I think that's it.

DR. LANGE: Okay. Dr. Starling.

DR. STARLING: Thank you, Dr. Lange. Randall Starling.

I'd like to respond to Dr. Zuckerman's question just by saying that I think the concern raised is we have an inadequate COSIRA trial and then an open-label, non-randomized REDUCER, and I would raise the word cardiomyoplasty and just say that the placebo effect, I think, is an overwhelming consideration that we have to reflect on.

DR. LANGE: Okay. So I think what you're hearing, Dr. Zuckerman, and I appreciate you advancing the question, but I'm not -- I don't think the Panel feels like the information or data derived from REDUCER-I overcomes the shortcomings of the secondary effectiveness analysis.

DR. ZUCKERMAN: Thank you, Dr. Lange, a very helpful discussion.

DR. LANGE: Thank you.

Sam, next question, sir.

DR. RABEN: Thank you.

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

DR. LANGE: And I think addressing the previous question, we've addressed this, as well. The Panel feels like obviously anginal information and relief of angina, change in angio class is important, but it has to be combined with some objective evidence.

MS. ALIKHAANI: That's not what he asked.

DR. LANGE: Please discuss if additional premarket objectives are needed to support

Reducer effectiveness. Okay, I'm sorry, I misunderstood. In other words, whether the current data are sufficient or whether there's additional objective ischemia assessment.

Dr. Somberg. Unmute.

DR. SOMBERG: Since we haven't established the appropriate patient population, I should say -- resistant population, COSIRA-II needs to do that, and then you need to show the ischemia measurement using exercise testing or some other, dobutamine study, echo or what have you. So I think COSIRA-II needs to define the population and then show that you have a reduction in angina and that is related to ischemia, they're all tied together.

DR. LANGE: Okay. Dr. Page.

DR. PAGE: Yeah, I'm not exactly sure what the question is, whether we are asked if we think premarket objective assessment is needed or if it were done, whether we would need some objective evaluation. I think we've answered the second part, but it just seems like we're getting ahead of ourselves right now if we're saying we need further premarket data because it gets to whether we're including whether it's effective or not and we can tip our hand now or not.

DR. LANGE: Can we get some clarification from the FDA? What would you like the Panel to opine on?

DR. ZUCKERMAN: Sam, do you want to begin on that?

DR. RABEN: Although I think the Panel has done a great job of discussing the value of an ischemia assessment, I think it would also be valuable for us to understand if the current totality of the data is sufficient or if additional data is needed to further support the proposed indication.

DR. PAGE: Okay, go back to my question, so if you substitute "whether" instead of "if," we're getting into effectiveness. If you're saying it's a hypothetical if we were doing more would we need objective evidence in addition to the subjective, I think we've

answered that. So if you're changing this middle, this first "if" in the question to "whether," then we're getting into effectiveness, we can do that, but it seems like we're getting ahead of ourselves.

DR. LANGE: I agree. So can we hold off on that, Sam, until we talk about effectiveness?

DR. RABEN: I think that's reasonable. Bram, do you concur?

DR. ZUCKERMAN: Yes. Thank you, Dr. Lange and Dr. Page.

DR. LANGE: Okay, I want to have something entered into the record. Dr. Janet Wittes typed in a response to the previous question and I just want to read it so it's entered in the record.

She said, "Sorry you couldn't hear me. I find the fact that secondaries are so weak and have so much missing data really bothers me. The combination of a primary outcome that is subjective 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. is another problematic issue. Dr. Zuckerman asked whether we two statisticians should suggest what we need to do with the missing data, my response is that too much data are missing to be able to do any statistical fix." I just read that for entering into the record and thank Dr. Wittes for her comments.

All right, Sam, let's go to the next question.

DR. RABEN: Great. So now I'd like to discuss some of the study limitations. 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 stenosis or severity;
- Lack of evidence of a coronary sinus 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 coronary sinus stenosis resulting in a functionally significant increase in coronary sinus 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 coronary sinus 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 coronary sinus pressure gradient across the device;
- The association of a coronary sinus stenosis or a coronary sinus pressure gradient with reduced angina or ischemia.

So Question 5a: Please discuss and make recommendations whether additional premarket 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 current available data.

DR. LANGE: Okay, and the FDA is going to be really interested in this particular question.

Dr. Page.

DR. PAGE: Yeah, now we're getting to the "whether" question and I don't -- a number of us have been doing this for quite a while and I don't know when I've seen a litany

of problems this long and this significant, and I think I could add to them, but I won't. I think it's -- from my standpoint it's absolutely clear that we need another trial that is better performed, in the U.S., and provides both objective as well as an arguably important subjective measure of angina and ischemia.

DR. LANGE: Great. Dr. Allen. You're muted, Keith. I'm sorry. You're still muted.

DR. ALLEN: Sorry, I'm a heart surgeon, I'm a slow learner. So I agree with what Richard said completely. I find it very odd that the very postmarket study that the company is proposing actually should be their pivotal IDE trial and I find it unusual that we're asked to essentially approve a product and then do the study that we would all like to see done, and so we absolutely need more and a better study.

DR. LANGE: Dr. Batchelor and then Dr. Zuckerman.

DR. BATCHELOR: So to follow up with that question, perhaps it's the result of this being submitted as breakthrough technology, and so I would like to hear the FDA's response on is the reason for the -- was the answer to the question that Keith has proposed really related to the breakthrough technology. And to just answer the Question 5a a little bit more, I think most of us, if not all of us, feel that the current data so far is not good enough to provide any answer in terms of effectiveness that we're confident on.

However, I must say I think it's a safe procedure, I think it's relatively safe. I think we've seen 2,000 procedures; it's not 100% safe but within the realm of interventional procedures I think it's quite safe. So I think what's outstanding is effectiveness, and I think a new trial designed properly in the United States with adequate site selection that would represent the U.S. demographic better would be obviously strongly advised. But maybe we can ask -- have the FDA answer the question of is this all because of breakthrough technology in terms of Keith's question.

DR. LANGE: Dr. Zuckerman.

DR. ZUCKERMAN: Yes. Thank you, Drs. Batchelor and Allen for asking the key question which is, why are we here today? And to a large extent, it revolves around a disagreement between the Sponsor and FDA regarding what is implied currently for the breakthrough device designation for this particular device.

At the beginning of this Panel meeting today, in the Sponsor's Slides 12 and 13 and in subsequent FDA slides, we all recognize that this device has a breakthrough designation as granted by FDA and therefore has the potential to be an important treatment modality and it benefits from increased interaction between FDA and the Sponsor.

As a result of the breakthrough designation and other recent guidance documents regarding uncertainty, there are several other factors to consider. Most importantly, the standard for a reasonable assurance of safety and effectiveness for a PMA device is not altered. However, in our consideration of whether this particular device is safe and effective, we do do our usual due diligence and we look at the benefit variables and the risk variables.

Now, by virtue of the breakthrough designation, it allows FDA and the Sponsor to deal with the uncertainty in these particular variables in a very flexible manner when appropriate. For example, by virtue of the breakthrough designation and guidance documents that go with it, there may be certain instances where the uncertainty in the benefit with the remaining uncertainty in the benefit and risk variables could be appropriately handled in the postmarket arena, and that's where the Sponsor is right now.

On the other hand, the FDA believes that given the uncertainty here for the benefit and risk variables, and the context with which we're dealing, meaning the patient population, known features of the device, etc., that this type of uncertainty would be better cleared up with a premarket randomized trial that has been referred to as COSIRA-II.

Regardless of what the Sponsor and FDA believe at this point, it's very important

that we hear now, independently from this Advisory Panel, what the Advisory Panel would recommend given that we have a breakthrough device with the potential for treatment of a very important population, and we have the COSIRA-I study.

So I hope, Dr. Batchelor, that with that preface you can help us out here.

DR. LANGE: So I've got Dr. Mathew, Dr. Yuh, and Dr. Vetrovec and Dr. Yeh and Dr. Ohman.

DR. MATHEW: Verghese Mathew. Thank you, Dr. Lange.

I think we all agree that the pivotal trial hasn't been done, but that's what we'd like to see. Now, for whatever reason that couldn't be done the first time around in terms of sample size and the robustness of data collection and the difficulty in enrollment, so as I put on the hat of bringing therapies to patients that don't have good options, I guess my question is how likely is it going to succeed the second time around if that's the direction we're going, is that we really need that pivotal trial, whether it's premarket or postmarket.

And I would say that if it was postmarket, it would be virtually impossible, at least in my mind, to enroll in a trial where you approve a device and then ask people to randomize yet again. I think the path of least resistance is patients that would fit the bill for inclusion would probably just get this as a clinical device. So if there are other pathways to explore this in a registry-type fashion postmarket, I think that would be reasonable to discuss. But I think randomization after approval will be less successful than the first go-around.

Thank you.

DR. LANGE: I've got Dr. Yuh, Dr. Vetrovec, Dr. Yeh, and Dr. Ohman.

DR. YUH: Thanks, Dr. Lange. David Yuh.

You know, I understand the good intentions for this breakthrough device rubric, but I'm concerned in a general sense that this is kind of a slippery slope where you can do a suboptimal study and then in a way work closely with the FDA to try to smooth out the

edges in an effort to get it approved. I just worry that we might be setting a precedent that could get out of hand in terms of new devices.

Many devices can be, you know, depending on how you define them, considered a breakthrough device, but that's just an overall concern I have at looking at the litany of flaws in this particular study. Even though that they probably represent some sort of positive signal for efficacy, it's still the quality of the study that bothers me and setting a precedent for accepting something like that through this mechanism.

DR. ZUCKERMAN: Dr. Yuh, that's why the FDA guidance document on uncertainty is very carefully written with the breakthrough devices guidance document so that if the probability of success of accomplishing something in the post-approval setting is not high, then that is not a recommended strategy. So again, I believe the guidances are written very consistent with good clinical judgment and as you've noted, we're looking for good clinical input here to solve a difficult situation.

DR. LANGE: I've got Dr. Vetrovec, Dr. Yeh, Dr. Ohman, Dr. Gersh, and Dr. Hirshfeld, and then I'll close it after that.

DR. VETROVEC: The concern here, Dr. Zuckerman, I think this was very helpful for you to outline this, I'm not sure I've quite caught the nuances of this. I think we could say that this device seems to have a relative benefit, but the better approach, we might not have to randomize if we could come up with a really definitive mechanism of action so that we could measure that and show there was a difference with that, and it correlated with the symptom relief seen in a registry. So I don't know how flexible these decisions can be. So I think there's a small pathway to work our way through this. But the question then becomes if you do the postmarketing study and you do all I say and it turns out negative, are you going to take it off of the market?

DR. ZUCKERMAN: You're asking the FDA?

DR. VETROVEC: Yes.

DR. ZUCKERMAN: Again, I would first of all ask you to think about this from a clinical perspective. Do you have a high enough uncertainty right now that what would you recommend if that case actually occurred and how would it affect your decision making because that should be a factor, that benefit-risk paradigm that you just pointed out and was included in one of Dr. Raben's introductory slides this morning, so I must put it back to you as a Panel member.

DR. LANGE: In other words, it would come back to Panel at that point, George.

DR. VETROVEC: Okay. I guess my sense would be that I think there's a very narrow path that might --

(Audio feedback.)

DR. VETROVEC: -- despite all the limits, but I'm just not quite sure how that all plays out. But I think one could devise it but it would be very important to have some better understanding of how it affects ischemia or whether there's a gradient relationship or something else that you could correlate with the results.

DR. LANGE: Dr. Yeh.

DR. YEH: Thanks, Dr. Lange. Robert Yeh.

I was going to -- you know, when I put on my sort of clinical hat and I think about it, I think this is a really, really important patient population for which I am often sent patients and we struggle to treat these patients. So I understand the breakthrough designation, this is a really important patient population that has limited therapies, and when I think about some of the things that we do offer to these patients currently in clinical practice, I must say that many of the things that we offer these patients have -- are on equally thin evidence bases and I'm sure it would be riskier, I think. I direct our CTO and PCI program and I have to agree with one of the comments which is I think that we're on thinner evidence even

there and certainly those procedures are risky. So when I think about it and if this were to be approved, would I offer it to some of those patients? I think that I would, based on what's been presented.

At the same time, when I put my scientific hat on, I say do I feel confident in the effect size that's been demonstrated? I don't. Do I feel confident in a mechanism? I don't at all feel confident in the mechanism based on what's been presented. You know, do I feel good about safety? I do feel good about the safety and I don't think any additional premarket information is going to alleviate any further concerns about safety that were raised about intracoronary sinus dilation, that will all be -- need really long term follow-up and sort of registry types of data, also.

So at the end, I'm sort of mixed here because I think what the science has presented does not adequately convince me that this is a very efficacious device. At the same time, the patient population is a high-need population where we are grasping at different treatments. That's the sort of mixed feelings I have about this.

DR. LANGE: I'm going to ask Dr. Ohman, Dr. Gersh, Dr. Hirshfeld, and Dr. Connor.

Dr. Ohman.

DR. OHMAN: Yes, thank you.

I think this helps a lot, Dr. Zuckerman, that you sort of laid it out in this regard, and being one who sees these patients on a very regular basis, I can concur that they seek, they desperately seek, things that work for them. But we also know that treating angina, there's a fair bit of placebo effect and many of these patients are convinced that certain things work and other things don't work. I think what we have to safeguard is that we understand the science and that we can actually back it up with objective evidence that show that it does indeed reduce ischemia. Otherwise, it will be very hard. If there would be a multitude of devices available through mechanisms that are not entirely straightforward, we would

face much harder clinical decision making than we do right now.

Finally, I would say on the breakthrough aspect of this, while these patients are suffering and they're having terrible quality of life, they're actually, as Dr. Henry pointed out in one of his earlier slides on mortality, yearly mortality is actually quite low and it's comparable to other patients with angina. So in a way, I can understand where we'd want to care and take care of the quality of life of our patients, I think it becomes less urgent as patients live and while they have poor quality of life, I think it's important for us to establish what really works.

DR. LANGE: Thank you.

Dr. Gersh, Dr. Hirshfeld, and then Dr. Connor. And then I'll summarize.

DR. GERSH: Thank you, thank you.

Basically, I'm in agreement. I agree, that I don't think safety is a real concern. I feel fairly comfortable with the data that have already been presented, but it is very difficult to me to make a decision about efficacy on the basis of a hundred and two randomized patients and many of the other issues we've heard. So I think we need a carefully designed randomized trial performed in the United States, blinded with a sham, and the endpoints to be determined as has been discussed earlier today.

DR. LANGE: Great. Thank you, sir.

Dr. Hirshfeld.

DR. HIRSHFELD: Yeah, I just wanted to mention I'm having a déjà vu moment here because it's just about 2 years ago that this group was here with the Impulse Dynamics Optimizer PMA and that was the first breakthrough device that this Panel had to deal with. And I recall very well that we were really concerned about the fact that this device did not have any objective data in terms of physiologic data that supported it and yet, because of the breakthrough device categorization, the Panel ultimately voted to approve it and it's on

the market. I think we're in a similar situation here that we have, at best, a small effect size demonstrated clinically and we have inadequate functional data to support that. And so I think, in terms of the direction in which we go, are we going to relax criteria for breakthrough devices or are we going to stick with the more rigorous for efficacy?

DR. LANGE: Dr. Connor.

DR. HIRSHFELD: And I've got Bram's attention.

DR. LANGE: I'm sorry. Dr. Connor and then Dr. Zuckerman.

DR. CONNOR: Yeah, this may be a question for my clinical colleagues, I almost asked this earlier and didn't, but given what Dr. Yeh said, I wonder at times like these, for instance, this is supposed to mimic the Beck procedure noninvasively, you know, we can't -- FDA can't regulate the practice of medicine, it can only regulate what tools are on the market. So yeah, so I was wondering, given what Dr. Yeh said, kind of about what people do without this and is it -- you know, they do more risky things, they try anything because patients are willing to take risks to feel better and live their lives, like we've heard. So I was curious, like is the Beck procedure actually done these days? I guess that it can't be done for a lot of these patients, but I assume it can on some. So do people actually do that?

DR. LANGE: Not anymore, not anymore.

DR. CONNOR: Okay.

UNIDENTIFIED SPEAKER: No, that's not done.

DR. LANGE: Yeah. Dr. Starling.

DR. CONNOR: Good, thank you.

DR. LANGE: Dr. Starling and then I'll try to summarize so we can move on.

Dr. Starling. And then Dr. Zuckerman.

DR. STARLING: Thank you, Dr. Lange. Randall Starling.

And, you know, as a non-interventionalist, the point that I have to make is that as far

as breakthrough is concerned, I don't think if I can establish efficacy in my mind, I think safety, yes, but not efficacy. And what I worry about when we -- if we release something like this is that patients won't get proven therapies and it's very easy to default to something new versus pushing the envelope with what is already established. So this is what my concern is with respect to approval as breakthrough and then moving to a pivotal study. I'm in the camp that we need pivotal data now.

DR. LANGE: Okay. Dr. Zuckerman and then our patient rep would like to have a comment, as well.

So Dr. Zuckerman.

DR. ZUCKERMAN: Yes. I want to, first of all, thank Dr. Hirshfeld for his comments because, as he points out, we're trying to balance a multitude of factors. Number one, we would like, if at all possible, U.S. patients to have timely access to important new therapies. On the other hand, by virtue of our regulations, we do want to make sure that any approved devices have appropriate safety and effectiveness. This often can be a difficult situation and that's why we need an expert advisory panel, as we have assembled here today, to help us make this decision by giving us their best advice possible.

The best advice, though, that I would give to this Panel is found in a paragraph on page 16 of our uncertainty guidance, which is the paragraph right before the slide example that the Sponsor gave this morning. And let me read directly from the paragraph because I think it will help Dr. Hirshfeld and others.

"Finally, as noted above, the decision as to whether or not a device provides a reasonable assurance of safety and effectiveness is based on the totality of the valid scientific evidence, including clinical studies and nonclinical testing. The appropriate extent of uncertainty of benefits and risks in a given case will depend on considerations of the factors set forth in Section IV (e.g., the disease or condition at issue, the availability of

alternative products, and risk mitigations) and other relevant information concerning the device. We anticipate that the greatest extent of uncertainty discussed in the examples below would only be appropriate under rare circumstances and, in any case, the sponsor must show, among other things, that the totality of the valid scientific evidence provides a reasonable assurance of safety and effectiveness of the device."

So I would like to ask Dr. Hirshfeld and any other Panel member if this helps them put into appropriate context how to employ the fact that the device has been designated as a breakthrough device, but yet the regulatory bar still remains a reasonable assurance of safety and effectiveness.

Dr. Hirshfeld.

DR. HIRSHFELD: I agree. I think we should be very careful not to allow that designation to take our eye off the safety and effectiveness ball.

DR. LANGE: Thank you.

Jacqueline Alikhaani, you have some thoughts about this, and then I'll go to Dr. Batchelor. Jackie, you're on mute right now.

MS. ALIKHAANI: Right. I think that, as a consumer, as a patient, given the great discussion we've had here today, there's so much missing information and discrepancies related to that information that it just makes me feel uncomfortable, I mean, as a patient. Patients, when they get the consent form, they don't know about all this discussion we're having, you know, relative to breakthrough devices and whatnot. I still think we have to keep our eye on the ball. I think we need that new trial, we need it in the United States, we need to get it right so we can have all the evidence and there won't be any need for --

(Audio feedback.)

MS. ALIKHAANI: -- pressure from the doctors to make these decisions and trying to make the best safest decision for their patient with a need. Just let's just do the trial, that's

what I'd like to see.

DR. LANGE: Thank you.

MS. ALIKHAANI: And get the trial right this time.

DR. LANGE: Thank you, Jackie. Thanks for those comments.

Dr. Batchelor.

DR. BATCHELOR: I want to just start off by saying those are very sage comments, Jackie, and I'm actually going to really pound home kind of the same points. The way I look at this is what is the risk to society and our patients in not doing -- in letting this go through now and get approved and then having a real challenge doing a randomized trial, because I think to Dr. Mathew's point, it's going to very hard to do a randomized trial that's going to be really effective after this, after approval, and versus the risk of delay.

If we delay, I just don't think we're putting patients at risk in terms of death or serious complications other than just a lot of angina, but they've had angina for a long time prior to this and honestly, I look at this a little bit differently in terms of breakthrough technology. So if this was a breakthrough technology that was reducing myocardial infarction or death, it would be looked at, in my opinion, in a different light. But this is a breakthrough technology that's going to make people feel better but their annual mortality is still going to be somewhere between 2 and 4 to 5%, which is reasonable.

So if we delay, to me, it's not a huge jeopardy that we're exposing patients to and I think it's worthwhile because the science we'll get out of it will be much better and we'll be able to look Jacqueline in the eye and our patients in the eye and say we know this works and we're not going down a slippery slope where we're letting this creep in and then we're going to have a really hard time with a randomized trial later. So my advice is get it right and to hold off. I'm an interventional cardiologist, I'd love to do these devices, but those are my thoughts.

DR. WITTES: May I say something? This is Janet. Can you hear me?

DR. LANGE: Janet?

DR. WITTES: Yeah. Can I say something?

DR. LANGE: Who is Janet?

DR. HIRSHFELD: Janet Wittes.

DR. WITTES: Janet Wittes.

DR. LANGE: I'm sorry?

DR. WITTES: Never mind, okay.

DR. LANGE: I didn't see your voice.

(Crosstalk.)

DR. WITTES: That's all right, forget it.

DR. LANGE: Go ahead, Dr. Wittes, my apologies.

DR. WITTES: Okay. What I was going to say is if I believe if the data were convincing to me that this works for quality of life and symptoms, I would be very strongly favoring recommending approval of it. The fact that the mortality rate is low is not, to me, dispositive. What makes a difference to me is an inability, all the other things we've talked about that make it not clear that what we think we're seeing in the primary outcome is actually reproducible.

DR. LANGE: Great. All right, now I'm going to bring this to -- I'm going to bring this to a close, we have other questions.

Debra, I will ask for your opinion and Gary's at the very end before we vote, okay? But just because we've had a lot of discussion and we still have more to talk about, I think I can give you a show hands right now based upon the totality of information. The question is do we need additional premarket data from a randomized sham-controlled clinical study? And I'm just going to ask for a show of hands. Those that say yes, raise your hands.

(Show of hands.)

DR. LANGE: Those who say no, raise your hands.

(Show of hands.)

DR. LANGE: And there's one no and the rest are affirmative. Now, we can have additional discussion, we can talk about safety and efficacy, but Dr. Zuckerman, does this give you the direction and the opinion of the Panel right now?

DR. ZUCKERMAN: Yes, it does. Thank you.

DR. LANGE: Okay, all right. I appreciate that really robust discussion. Normally, right now I'd be looking around the room because you all are trying to get out to catch your flights, but I'm looking around, there's nobody in an airport, so I got you for a little bit longer, okay?

MS. ASEFA: I think Debra Dunn said she had a work commitment to keep and that's kind of -- that's why she wanted to speak --

DR. LANGE: I'm sorry. Debra, unmute yourself. At the very end of these questions I'll obviously call upon you and Jackie and Gary, but let's get your opinion right now based upon what you've heard.

MS. DUNN: Hear me?

DR. LANGE: Yes, ma'am.

MS. DUNN: Can you hear me? My name is Debra Dunn, I'm a patient advocate, and everything that we've been talking about here today really hits home. I'm a heart failure patient and during a simple device switch out, device number seven, my biventricular ICD, I got a staph infection in the pocket. So I had lead extraction and I had a cardiac tamponade. I was left with a septal opening of one inch and I received the Amplatzer device after the staph infection was taken care of, and I have been an expert witness for the FDA on the Amplatzer, which recycled back around, I'm not sure if we talked about that that was a

device that obviously came before a panel. I was not on that panel but I was an expert witness when it came back around because it was fragmenting and so I did have to present for that.

Everything here has been taken very seriously. I do live with angina, I'm a serious heart failure patient, and I respect the Panel, that they would like to take this back under advisement, get more clinical data to make a wise decision, but I can tell you living with angina every day as a patient, it's very unsettling and it's very scary.

But I guess when it all comes down to it, as a patient, we want to make sure that we're safe and whatever's being put in our body. My Amplatzer, who knows what will happen? But it was something that at the time it saved my life. So I'm 18 years out from my first heart attack and I'm doing great, I'm getting device number seven switched out and a new one put in real soon, so thank you for all your consideration.

DR. LANGE: Debra, thanks for that heartfelt comment, thanks for the perspective, we appreciate that. I appreciate you joining the Panel. And I can tell you, everybody on the Panel wishes you well with your next device and I hope you do, so thanks so much for sharing with us.

MS. DUNN: Thank you very much.

DR. LANGE: Sam.

DR. RABEN: So going to the next question, regarding patient demographics and other baseline characteristics, 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.

Question 5b is, 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.

DR. LANGE: I'm going to summarize that because we've talked about that, several individuals have, and Jackie, I'm going to give you credit, I don't think anybody could've said it any better than you. I think as difficult as it may be to get a more demographically diverse representative population, I think the feeling of the counsel of the Panel is that's absolutely necessary. If there's any disagreement -- John, how could you disagree with me? We've been working together for 15 years.

(Crosstalk.)

DR. SOMBERG: -- disagree. No, no, no.

DR. LANGE: Go ahead, John. Then I think --

DR. SOMBERG: I just want to say that it's advisable to have a heterogeneous population, but it's not been shown that Hispanics or people of African American descent have a more physiologic difference here. I mean, I think the important thing would be to include women and to have more people -- you know, not exclude microvascular disease. I think that is the clinically relevant discussion.

DR. LANGE: Okay. Dr. Borer and then Dr. Cigarroa and then Dr. Batchelor.

Jeff, you're on mute.

DR. BORER: I agree with John. I think the issue is we have other more important concerns than whether we have enough black or Hispanic patients or even enough women. The fact is that we have what we have. If the study were adequate otherwise, which it's not, then we could write a label that says these data apply to the population that was

studied, which was deficient in black or Hispanic patients and females. But if another trial is to be done, every effort has to be made to enhance the representation of black, Hispanic, and women patients. You can't be sure you're going to be able to find them. They couldn't in the first trial. So I think that this is very important, but it's not a drop-dead issue.

DR. LANGE: I'll go to Dr. Cigarroa and Dr. Batchelor. But Jeff, I'll remind you that the trial was done in Europe.

DR. BORER: Yeah, that's fine.

DR. LANGE: So Dr. Cigarroa, Dr. Batchelor, and Dr. Zuckerman.

DR. CIGARROA: I think this is a -- sorry, this is Joaquin Cigarroa for the record.

So I think the applicability of the study results to our refractory angina population is challenging to extrapolate. I do believe that there's need for additional clinical data for effectiveness in a demographically representative population.

If one looks at African Americans as an example and looks at LV mass and capillary density, which is really important in impacting, again, reversal of flow from the subendocardial to the epicardial, especially as left ventricular diastolic pressure increases, that difference in LV mass in a hypertensive population may be substantial and may adversely impact the efficacy of this, the purported mechanism the Sponsor has stated. So those differences are important.

We can say the same for women. Just because one has epicardial coronary artery disease does not decrease, per se, the commingling of microvascular disease and in fact, they often commingle. So I would state that this is an important issue that must be addressed prospectively.

DR. LANGE: Great. Dr. Batchelor.

Thank you, Dr. Cigarroa.

Dr. Batchelor.

DR. BATCHELOR: Thank you. Again, this is off of what was just said by Dr. Cigarroa very nicely. There are symptomatic differences in the way that patients present with angina and some African Americans are more likely to have shortness of breath and probably because of the superimposed hypertension and LV diastolic function issue, women obviously tend to present older and are more likely to present with atypical symptoms.

So I think Dr. Cigarroa also talked about some physiologic differences that might exist. I think we have to get really careful when you state there's never been a difference in the efficacy of a medication and/or an intervention across racial or ethnic groups because it really hasn't been studied. So to say that there's no difference doesn't mean that there's no difference, it's just that we don't know. We do know that there are -- we do tend to come to the table and to the clinician with slightly different characteristics depending on many factors including race, age, and gender so I would just caution us on that assumption, number one.

And then finally, remember, with the Food and Drug Administration Safety and Innovation Act from 2012 and what's come about from that, I think there's a responsibility now, I think we've got to start into a new phase of conversation where it's been signed into law and we have a responsibility to try to at least do our best to represent various ethnic and racial groups and women in clinical trials, otherwise we're just speaking into the air without really having anyone listen to us.

DR. LANGE: So Dr. Zuckerman, I think what you're hearing is we're not certain whether there are mechanistically different reasons, we're not sure whether different gender or different racial or ethnicities will respond differently, but we will never know unless they're studied and a study outside of the U.S. is a population that is different from us may not answer that question. So I think that the Panel overall would say -- I don't think anybody on the Panel would say we need less diversity in this study.

DR. ZUCKERMAN: So this has been an excellent discussion and I think it's also important, too, for the panelists to understand what the FDA regulations are. Number one, America is a heterogeneous country and our FDA regulations specifically state that if we're going to use outside U.S. data to make a decision about safety and effectiveness for a U.S. population, then that OUS population data really needs to be extrapolate-able to the U.S. situation and I think we've heard in this discussion some questions about that.

DR. LANGE: Great, thank you.

All right, Sam, may I have you move on?

DR. RABEN: Great. Question 5c. Acknowledging that an understanding of the Reducer's mechanism of action is not required 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 device, 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. LANGE: Dr. Allen.

DR. ALLEN: So I think, as Dr. Zuckerman and some of his esteemed colleagues at the FDA pointed out earlier, determining a mechanism doesn't -- it may enhance the benefit of getting an approved device, but it's not mandatory and I'm not as concerned about not having great data on mechanism as I am on the clinical trial design and how it was executed, that bothers me a lot more. If this had been a great trial, for example, this had been COSIRA-II, I probably wouldn't have minded not knowing what the mechanism is. I don't really how know aspirin works but I take it every day. So that would be my take on this.

DR. LANGE: Dr. Somberg.

DR. SOMBERG: If the Sponsor chose a feel-better primary endpoint, it would be important to have a secondary endpoint of ischemia measured either by treadmill, dobutamine echo or something else. The mechanism isn't critical. But to know that we're dealing with ischemia as an underlying improvement of symptoms is, I believe, very important.

DR. LANGE: Dr. Page and then Dr. Gersh.

DR. PAGE: Yeah, I agree with what was said about if it clearly works and it's clearly safe and we don't fully understand why, I can live with that. When we're on the cusp, I would like to have a better -- a fuller understanding of the scientific plausibility behind this and would hope that in the upcoming pivotal study, if that were to be conducted, we would have a better understanding of the anatomy, the shape of the human coronary sinus with this mature device in place, and a better understanding about truly the physiology underlying whatever response we're getting.

DR. LANGE: Great. Dr. Gersh.

Thank you, Dr. Page.

DR. GERSH: I think the pivotal study, if it's going to be done, should be in people with obstructive coronary disease and where I think mechanisms may be important is, I mean, in many ways the concept if this could work for microvascular angina is quite attractive. But in order to look at that, long before we do a randomized trial we have to identify the people with endothelial function studies and physiological hemodynamic studies at cath and then look at it in that group of patients completely where the benefits and the mechanisms may be different, but first of all we'll have to identify them and then think about mechanisms. But I think we mustn't lump together microvascular angina with microvascular dysfunction that is probably present in most people with obstructive disease.

I think of them as two very different entities and it may be that the mechanisms of benefit, if they're there, may vary between those who have non-obstructive and obstructive disease.

DR. LANGE: Dr. Brindis, do you have an opinion?

(Off microphone response.)

DR. LANGE: No. Dr. Mathew?

DR. MATHEW: I'd agree that mechanistic studies may be important if we're going to do a pivotal trial because I think we had the conversation earlier about subsets of patients that are going to be more likely to benefit and I think we still may have that issue to contend with if there's a second pivotal trial. So I think that the trouble of going through another well-designed and well-executed trial is going to go forward, I think mechanism should be some subset of that population.

DR. LANGE: Okay, thank you.

Dr. Starling.

DR. STARLING: Yeah, I think a mechanistic is an option that should be a secondary and it's going to get down to funding and resources. I think the hard endpoint that's described from the Sponsor for COSIRA-II of an exercise treadmill and an increase in 60 seconds in exercise time is an appropriate primary endpoint.

DR. LANGE: Okay. Dr. Yuh. You're muted, David. I'm sorry.

DR. YUH: I don't really have anything useful to add to the previous comments.

DR. LANGE: Okay. And so I'll ask -- I'll call the last person, Dr. Allen. And then I'll call on Dr. Batchelor.

Keith, you need to unmute yourself. Any comments?

DR. ALLEN: I really don't have anything to add.

DR. LANGE: Okay. Dr. Batchelor, any opinion on this?

DR. BATCHELOR: I think the previous speakers have really laid this out nicely.

Noting else.

DR. LANGE: So what I'm hearing, Bram, is it certainly needs to be a robust clinical study and the values of animal studies would be helping to identify subsets or providing mechanisms when the results of the pivotal clinical study are "on the bubble," as Dr. Page mentioned, in which case the mechanism study would kind of push them over the finish line.

DR. ZUCKERMAN: Thank you.

DR. LANGE: Great. Thanks for everybody's opinion on that. Sam.

DR. RABEN: Okay. Question Number 6 is regarding the benefit and risk. Given the totality of the evidence regarding the effectiveness and safety profile for the device, please comment on the benefit-risk profile for this device.

DR. LANGE: Do we want to do that or do we just want to go straight to safety and effectiveness at this point? I think we've talked a lot about this already previously or do you want to -- do you feel comfortable with that, Dr. Zuckerman, or do you want us to address this?

DR. ZUCKERMAN: If there are any brief Panel comments regarding the benefit-risk ratio that Panel members would like to make for the open public record, this is the time because subsequently they will need to vote on these questions. So if they'd like to bring up any points, comments, it's appropriate at this point.

DR. LANGE: Okay. And I see Dr. Page would like to, Dr. Mathew would like to.

DR. PAGE: Yeah, we talk about this being a relatively low-risk procedure and as invasive cardiac procedures go, it is. But it's not a zero risk. The embolization in real-world is reported. And the other thing I think we should keep in mind that, just as the very compelling statement from that patient who's been through various procedures including lead extractions and the like, some of these patients are going to need a biventricular

pacemaker and we don't have any data as to accessing the coronary sinus with a biventricular lead. We could do an intervention to open it up that undoes the effect of this device, perhaps.

So I think risk is low, risk would be acceptable for a device that was clearly showing effectiveness, but it's not zero risk. Any of the invasive people on the line know any time you get invasive something bad can happen.

DR. LANGE: Okay. Dr. Mathew.

DR. MATHEW: Yeah, I generally concur. I mean, I think this is relatively safe, it sounds like there's a learning curve from the data they presented but it's relatively safe, I presume, if you proctor people through this for a case or two. So I think the denominator's low, I think the benefit is modest at best and by that function, the ratio probably is favorable but I think we all agree that the benefit is modest at best based on the data we've seen so far.

DR. LANGE: Okay. Dr. Allen. And then Dr. Cigarroa.

DR. ALLEN: So I guess I agree with what mostly has been said, but I really think we focus more on the acute risk of the procedure and while it's an invasive procedure, I think the acute risk is low. I really don't know what the long-term risk of this implantable device is and 6 months seems to me a very short window for an implanted intravascular device to determine its safety even in the intermediate term.

DR. LANGE: Okay. Dr. Cigarroa and then Dr. Yuh and then Dr. Somberg.

DR. CIGARROA: This is Joaquin Cigarroa for the record.

So as I think about the totality of the evidence, effectiveness and safety profile, the benefit-risk profile to me is impacted by what is the endpoint, is it death, is it infarct or stroke? Or is it, in this case, a symptom which clearly is important but is not death or myocardial infarction?

And therefore when I think about safety, I also then say well, is this effective and as we have all been discussing, the degree of uncertainty regarding effectiveness, at least in my mind, is on a low, medium or high, is substantially high. And therefore even though the short-term safety appears reasonable, it's hard for me to believe that the benefit-risk profile with the data we know and the endpoint that has been chosen is favorable without additional insights and without additional high-quality data.

DR. LANGE: Dr. Yuh.

DR. YUH: Thank you, Dr. Lange. David Yuh.

Yeah, I think looking at the profile of the adverse events for this particular device, I'm pretty satisfied given certain factors and the patient population we're looking at in terms of characterizing the risk of the device, at least in the short term, and I think I feel that I would feel confident in giving informed consent to the patients with all the caveats, patients that are truly looking for a last-ditch alternative for a very debilitating condition, so that's my take on the safety profile. Under other circumstances I might be more -- have more stringent requirements, but I think I'm satisfied with the overall picture of safety for this device.

DR. LANGE: Dr. Somberg.

DR. SOMBERG: I just want to reiterate what I said earlier about the FDA should question the use of antiplatelet agents with this device, it sits on the venous side, the question is why not antithrombotic agents and also the possibility of late stent thrombosis. One of the problems with coronary sinus in this situation is if you had a coronary sinus thrombosis, it often presents as angina or myocardial infarction and that would be on the continuum of the natural progression of these patients' disease. So how do you differentiate that? I think some thought should be given, an appropriate therapy introduced early, maybe to anti-coagulate patients for a period of time while they

endothelialize the stent.

DR. LANGE: Our Consumer Rep, Jackie Alikhaani, has asked to speak. Jackie. And then I'll got to Dr. Yeh. You're muted, Jackie. Thank you.

MS. ALIKHAANI: Yes. Yes, like was already said, I think that every procedure has a risk, we all know that, and I think that patients -- I mean, I don't think it's possible to do a really good benefit-risk assessment without having all the information we need. We don't have all the evidence because we don't -- you know, it wasn't there in the trial, that's what we've been talking about for hours.

So patients, even the patients who are having a lot of quality of life issues and a lot of pain, I think people are depending on us to do really due diligence in terms of getting all that evidence, getting everything that we can and just lay that out for patients to know about and they really can make informed decisions based on the evidence that is given to them so people won't be making decisions in the dark and later on, when something goes wrong, then who's going to be liable for that? I think we should do everything we can to get all the information we can that -- it's just worth it.

DR. LANGE: Thank you, Ms. Alikhaani.

Dr. Yeh.

DR. YEH: Thank you, Robert Yeh for the record.

I think that, you know, there was a comment about the short-term safety of the device and 6 months being too short, I do think that the safety evaluation probably is the one thing that will be based on single-arm type of data and for those data, I do feel confident that those long-term data that were presented from -- the one thing that maybe the Reducer single-arm study might be good for is to show that weren't sort of a large number of late complications that were unanticipated at, say, the multi-year -- you know, 3 to 5-year period.

But when I think about, you know, if this were the only data that we were ever going to get, it feels to me that the device is safe and if I were betting on it from just a pure probability Bayesian standpoint, I would say that the evidence suggests that the device has probably a greater chance than not of being effective. And so based on just a point estimate, I think that effectiveness probably exceeds -- the benefit probably exceeds the risk, but I don't think we're choosing on the basis, I don't think we make this decision on the basis of point estimates especially when there are wide confidence intervals around all of these assessments.

And so even though I think that the benefit-risk profile does favor the device, I think there's enough uncertainty here and that we're probably making decisions not based on point estimates, but we probably should make the decision based on how confident we are in those point estimates. And I think there's not enough certainty here to say definitively that the benefit-risk profile is greater than zero.

DR. LANGE: Great. And I'll add one final comment because I'm not -- my comments have been consistent with what everybody else has said. I don't feel like we have adequate safety data, there's no secondary endpoints in a small group. We have, again, 2000 patients in long-term follow-up, we assess they don't have coronary sinus thrombosis because no patient reported it. We don't have really adequate long, good follow-up and it's not been very rigorous, so I can't really can't assess -- I can't say it's safe. I'm not saying it's harmful, I just can't -- I don't think there's enough data to suggest it's safe. That's just my opinion.

So we've addressed Question 6, I think. Bram, you've heard from the Committee, in toto they don't feel like the benefit-risk profile of the device is favorable primarily because of lack of confidence in the benefit. Most Committee members feel like the risk is low, I'm probably on the outside of that bubble.

DR. ZUCKERMAN: Thank you.

DR. LANGE: Great.

DR. RABEN: So next, to discuss the proposed post-approval study. In response to the concerns identified by FDA during the initial rounds of review, the Sponsor has proposed the following potential post-approval study: Neovasc has committed to do a post-approval randomized, double-blind, sham-controlled study in a country where the Reducer is not approved to allow the collection of data to reduce the amount of remaining uncertainty FDA may have.

Note: This requested discussion item related to the proposed post-approval study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA.

FDA may require a post-approval study (or studies) at the time of approval of a PMA to provide information on the continued safety and effectiveness of the approved device. These studies are not intended to provide a reasonable assurance of safety and effectiveness, as the determination must be established prior to device approval, and are typically not randomized. FDA is concerned that after making a determination that there is a reasonable assurance that the device is safe and effective in a limited option patient population, it may not be appropriate or feasible, due to the lack of clinical equipoise, to mandate a new trial as a condition of approval in which patients who lack alternative treatments would be randomized to a sham control.

So for 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.

DR. LANGE: So Bram, I think that the Panel addressed this previously and that is all except for one member thought that a premarket approval study was necessary to move

forward with approval. And so based upon that, I'll speak for the Panel, anybody's willing to disagree, there's no postmarket study approval, again, except with one member voting otherwise that would give the assurance of effectiveness and safety that would warrant us to recommend FDA approval.

DR. ZUCKERMAN: Thank you, Dr. Lange.

DR. LANGE: Dr. Brindis.

DR. BRINDIS: Yeah, so you know, I agree with everything that you just said, Richard, but if -- I'm still puzzled by the issue of a breakthrough technology and despite reading the definition just put up and also Bram's sage comments on how we should look at it. So I'm wondering if you could have a setup with the company, a preapproval study which allows this so-called breakthrough technology that allows at some point the patient being given the option to roll over to the active group, sort of I think how it was implied in the trial set up -- proposed by the company. And I would not -- in terms of this post-approval study, for all the reasons, particularly well articulated by Wayne, I would like to have that here, not in another country.

DR. ZUCKERMAN: Okay. Dr. Brindis, the question is really centered on there is uncertainty right now and the need for additional data and is it realistic to expect that these additional data to decrease uncertainty or, as Dr. Yeh pointed out, to decrease the width of the confidence interval, should it be -- could it be realistically done in the post-approval setting or in the premarket setting. And I think, as Dr. Lange has summarized, unless other panelists disagree, that realistically it needs to be done in the premarket setting.

DR. BRINDIS: Right.

DR. ZUCKERMAN: What you brought up is a different question that the Agency can discuss with the Sponsor at a different time, which is after a certain -- if a randomized, controlled trial is being conducted, are there certain criteria where patients who might be

randomized to the control group and are failing standard treatment be crossed over, and that's always an important consideration that can be discussed with the Sponsor, you pointed out some reasons to consider it, but it's really independent from this question.

DR. BRINDIS: I agree.

DR. ZUCKERMAN: Thank you.

DR. LANGE: I think that may be the last question prior to moving to safety and effectiveness, is that correct?

DR. RABEN: That is the last question, but then we will move to summations.

DR. LANGE: Absolutely. So at this time, the Panel will hear summations, comments or clarifications from the FDA. The FDA will have 10 minutes. Following that, the Panel will hear summaries, comments, and clarifications from the Sponsor and the Sponsor will also have 10 minutes. So with that, let me turn over to the FDA first.

DR. RABEN: Great, thank you.

Today's Panel meeting has focused on the clinical data and supplementary information provided by the Sponsor to support the Neovasc Reducer System. We discussed the regulatory history of the Reducer device and the regulatory considerations regarding FDA's Breakthrough Devices Program and uncertainty guidance. FDA explained that the breakthrough device program is intended to provide the American public with timely access to new beneficial devices with the potential for significant impact but does not modify or reduce the statutory requirements for device approval. That is, the Reducer device must demonstrate a reasonable assurance of safety and effectiveness.

We particularly appreciate the Panel's view on the strengths and limitations of the data including whether the COSIRA patients had refractory angina despite an optimal antianginal therapy, study blinding, the amount and imbalance of missing data, identification of patients most likely to benefit, the device's mechanism of action, the

importance of anginal symptoms and objective ischemia endpoints, treatment effect size, and lastly, enrolled study subjects' demographics distributions, compared to the U.S. We thank the Panel for their attention and discussion and for your careful consideration of this PMA.

DR. LANGE: Great. Thank you very much from the FDA both for your summary and for an excellent presentation at the beginning of the meeting.

And now for the Sponsor, 10 minutes as well for comments.

MS. BEBEAU: Thank you, Dr. Lange. I would like Dr. Stone to provide some commentary, as well as Dr. Henry.

DR. STONE: Well, thank you very much, this has been a long day and an excellent discussion. I think most of the points that have been made are actually points that we realize. You know, I've led over 120, maybe 130 randomized trials in my career and I was not involved in COSIRA, so I guess you might ask so why I am sitting here today helping the Sponsor with this data with my interpretation and analysis? And in that regard, I want to bring it back to the patient and this is really a desperate patient cohort. There's plenty of patients that, as you've heard from testimonials, including the patient advocate, are really leading unhappy lives at best and sometimes desperate lives at worst because of severe ongoing angina with minimal activities or no activities.

And so to have a therapy that may benefit these patients, I think myself as a cardiologist who's taken care of these patients for 30 years, is very important. When you look at, again, the options for patients who have exhausted coronary revascularization and antianginal medications, there are few. In fact, if you look at the randomized trial at EECP, it wasn't studied in Class IV patients and two-thirds of the patients had Class I or II. So then we're really left with surgical TMR or heart transplantation, which are really both therapies much more beyond that do have substantial safety concerns.

So for me, when I've got a patient in front of me that really needs something, the first thing I'm going to ask is okay, is it a safe therapy and I really do think that there's a lot of data to suggest that there's safety with this device. The procedure itself for an experienced interventional cardiologist is not that much more than putting in a stent in a normal vein. It's through a central line approach which residents do every single day, let alone cardiologists, and it really can be trained quite easily. And when you look at the bulk of the safety data, I mean, the SAEs in the COSIRA trial tended to favor the device arm, the MACE events and may (ph.) events tended to favor the device arm and you saw a training effect over time from experience to experience. So this really does, to me, seem like a safe device.

So it really does come down to effectiveness, and I understand the limitations of the dataset that you've seen, but I would say that angina is what matters most to these patients, I think it was Dr. Yeh that said it. It's not ischemia, it's not exercise duration of a few extra seconds, it's angina. And a two class or more reduction in CCS angina class is a robust reduction. I mean, there's really no misinterpreting that. And the Seattle Angina Questionnaire tracked along perfectly with that. In fact, there was a statistically significant improvement in Seattle angina quality.

The p-value, if you will, the alpha for the primary pre-specified endpoint was 0.2, so there's only a 2% chance that that's a false positive finding. It's not from 0.01, but it's pretty good for the pre-specified primary endpoint.

The number needed to treat was only about three to five which, for a relatively safe device, especially to get a two-class reduction in CCS angina is quite low and much better than antianginal drugs.

So then the last point I'll make is yes, the REDUCER-I data, of course, is open label and the five or six investigator-sponsor studies are open label and without concurrent

control arm. So yes, there's much more limited implications you can draw from that data. But the fact that they are consistent with the COSIRA study in terms of angina improvement and Seattle Angina Questionnaire improvement, I do think is some supportive data in terms of effectiveness.

So the question I guess I would ask is, if you have a patient in front of you, for the cardiologists here, or if you have a family member that really had disabling angina and you were to have this potentially relatively safe therapy available to them, would you want to offer it to them?

I do believe that we can do a post-approval trial. Not all patients in the United States will get reimbursed for this device, we will allow crossovers at 6 months, we will enroll patients outside the United States, we will ensure that there's diversity, which I do think is a very important issue and I take all those comments to heart. We will ensure that the blind is maintained. Although in that regard the one thing I'll say is you cannot see this device on a chest X-ray or an echo, you can't see it, okay, it's too small. You have to have a CT scan to be able to see it. So I do believe that the blinding, although we don't have a questionnaire to prove it, I do believe that the blinding in COSIRA was reasonable.

So bottom line, we don't have a perfect dataset by any means and as I said in my early comments, do I wish we had had a 500-patient sham-controlled trial, do I wish we were a hundred percent confident in mechanism and so in ischemia reduction? Yes, I do. But I just keep coming back to the unmet clinical need, the fact that this was recognized by the FDA by giving it a breakthrough designation, everyone on the Panel knows about these patients and while they don't deny if we were to start tomorrow a randomized trial, it would probably take 4 to 5 years before we would have that answer, especially in the COVID era. Again, not an excuse, but just the reality. Thank you very much.

MS. BEBEAU: Dr. Henry.

DR. HENRY: Thank you. I appreciate the opportunity to take a few moments and really, I'll tell you, I agree a hundred percent with what Gregg just summarized, including that we wish we had more data and I do believe that doing a postmarket trial will be doable. But I want to add a couple key points.

First of all, this is an incredibly challenging patient population to do clinical trials and in particular, they are miserable. And currently in the United States, they have no options, and currently what we're providing to those patients are riskier than what we saw today with the safety. So I do believe that the safety profiles are excellent based on the data that you saw with more than 2,000 patients and I do believe, taking care of these patients every day, that the risk-benefit profile is good. And I do believe that we need to do more data with -- and like COSIRA-II in terms of the postmarketing trial.

The last point I will make is that I would love to have us say that it's different in the United States, but the reality of this trial is the baseline characteristics and the medications are basically identical to the clinical trials that have been done in the United States including MUST-EECP, AGENT 3 and 4, RENEW --

(Audio cut out.)

DR. HENRY: -- I will end and I -- did I lose me?

DR. LANGE: We lost you for just in your last sentence, Tim, you're back on.

DR. HENRY: Yeah, so I think I'll stop with that but -- because I think Gregg's summary was outstanding and I want to thank the Panel because it really is an outstanding Panel with extensive experience taking care of these patients and so this discussion has been outstanding today.

MS. BEBEAU: Thank you, Dr. Henry.

From Neovasc, I want to thank the Panel for their time and for the careful considerations. And I would add again that the company is definitely committed to doing a

postmarket REDUCER-II study. Thank you for your time.

DR. LANGE: Great. I want to express my appreciation to the Sponsor, Dr. Stone, Dr. Henry, Chris Mullin, as well. Your presentations were excellent, you all were very responsive to the questions, very informative, and very respectful, as well. So to our colleagues, Dr. Stone, Dr. Henry, to Neovasc, I want to express my appreciation. Thank you.

We're now ready to move on to vote on the Panel's recommendations to the FDA. Prior to doing that, I'd like to ask Jacqueline Alikhaani, as our Consumer Rep, if she has any last comments. She'll have the last comment before we vote. Unfortunately, she's not a voting member. So Jackie.

MS. ALIKHAANI: Yes. Great discussion today, it was a really very informative and educational process and I appreciate the opportunity to be a part of this Panel. I think that we need to include the patient voice in more and more of these kind of discussions so patients can be able to make -- patients want to be empowered to make informed decisions and they have to do that in collaboration with the doctor and that includes the doctor having the best evidence from research.

And you can't get the best evidence without the best designed trials that show the best outcomes to inform everybody about what's the best decision. And I think when we do that, I think everybody feels good when they know you've done your best. And I know the best is not always easy to get to, I know the trials are complicated. But thank you so much for allowing me to be a part of this and speak out.

DR. LANGE: Ms. Alikhaani, thank you for participating and staying with us to the end. I really appreciate your perspectives and your opinions, thank you for sharing.

MS. ALIKHAANI: You're welcome.

DR. LANGE: We're now ready to vote on the Panel's recommendations to the FDA for Neovasc Reducer System. I'm happy to report I got no pre-election votes and we're not

mailing it into a ballot. So we will be conducting via e-mail which is a little unusual, we've not done that before. So Aden will give you some instructions for that. The Panel is expected to respond to three questions relating to safety, effectiveness, and benefit versus risk. And Aden Asefa will now read two definitions to assist in the voting process.

MS. ASEFA: Thank you, Dr. Lange.

Before we go into the vote, I just want to read a COI that I did not mention into the record. For the duration of the Circulatory System Devices Panel meeting on October 27th, 2020, Ms. Jacqueline Alikhaani has been appointed to serve as a temporary nonvoting Consumer Representative. For the record, Ms. Alikhaani serves as a consumer rep for the Cardiovascular and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. Ms. Alikhaani is a special Government employee who has undergone the customary conflict of interest review and has reviewed the materials to be considered at the meeting. The appointment was authorized by Russell Fortney, Director of the Advisory Committee Oversight and Management Staff, on September 22nd, 2020.

DR. LANGE: All right, Jackie, you're official now.

MS. ASEFA: Okay, Jim.

The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket applications that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. The definitions of safety and effectiveness are as follows:

Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the

probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Panel members, we will now begin the voting process. I will read the proposed indication for use and the three voting questions and send each of the voting members an e-mail to respond to. Once I read all the three questions, we will tally the votes and read them into the record.

The indications for use is as follows: The Reducer System is intended for patients suffering from refractory angina pectoris despite guideline directed medical therapy, who are unsuitable for revascularization by coronary artery bypass grafting (CABG) or by percutaneous coronary intervention (PCI).

Voting Question Number 1: Is there a reasonable assurance that the Neovasc Reducer System is safe for patients who meet the criteria specified in the proposed indication? Please vote now yes, no or abstain.

(Panel vote.)

MS. ASEFA: Voting Question Number 2 reads as follows: 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? Please vote now yes, no or abstain.

(Panel vote.)

MS. ASEFA: The third and final voting question reads as follows: Do the benefits of

the Neovasc Reducer System outweigh the risks for use in patients who meet the criteria specified in the proposed indication? Please vote now yes, no or abstain.

(Panel vote.)

DR. ALLEN: We have gotten an e-mail by now from you?

(Crosstalk.)

MS. ASEFA: -- tally and verify the official votes.

DR. LANGE: I'm sorry, if you've --

DR. ALLEN: I've not gotten any e-mails.

DR. LANGE: Yeah, I haven't gotten an e-mail, either.

MS. ASEFA: Oh, Dr. Lange, you wouldn't have gotten an e-mail. So I sent the e-mail at 6:20 p.m.

DR. PAGE: I received an e-mail and voted.

DR. SOMBERG: Is this an interactive e-mail or you just write (1) yes, no; (2) yes, no?

MS. ASEFA: Yes.

DR. ALLEN: If I just check it and go to the next thing, it doesn't hold.

MS. ASEFA: Oh, it's just an e-mail, it's just a reply e-mail.

DR. SOMBERG: So you just reply --

MS. ASEFA: Yeah.

DR. SOMBERG: -- and give your answers?

MS. ASEFA: Yeah.

DR. SOMBERG: Okay, it's not like a Google --

MS. ASEFA: Yeah, I know.

DR. SOMBERG: -- form or something? No, okay.

DR. ALLEN: I haven't gotten -- I haven't gotten an e-mail.

(Crosstalk.)

DR. LANGE: Okay.

UNIDENTIFIED SPEAKER: I voted.

DR. LANGE: If you've not gotten an email, would you raise your hand?

(Show of hands.)

DR. LANGE: Dr. Allen did not. Dr. Brindis did not. Dr. Vetrovec did not. Dr. Connor, Dr. Wittes, Dr. Bonde. I guess we knew how you guys were going to vote and we decided not to extend one.

DR. BRINDIS: I have your e-mail --

(Crosstalk.)

DR. BRINDIS: I can send it on to you, but I've not received --

DR. WITTES: Can we just tell you how we're going to vote?

DR. LANGE: No, we got to -- no, we have to do it anonymously first, Janet, and then we tally them. But thank you --

DR. WITTES: All right, well.

DR. LANGE: Thank you for asking.

DR. SOMBERG: Well, it's another example of social media blocking the election.

(Laughter.)

DR. LANGE: That's fake news, John.

DR. SOMBERG: Richard, that's my line usually.

DR. LANGE: Okay, again let me see -- if you've not gotten it, let me see hands again.

(Show of hands.)

DR. LANGE: All right. And so Jim Swink, let me -- keep them up for a second until I call and then put your hand out. So Keith Allen has not, Ralph Brindis has not, Randall Starling has not, George Vetrovec has not, Jason Connor has not, Janet Wittes has not, and Pramod Bonde has not.

DR. BRINDIS: You know, Richard, one option is we could vote privately, chat to her if that may not be working. I just got it, it looks like.

DR. LANGE: Yeah. We thought about that but sometimes it becomes less private than you'd like.

DR. STARLING: I have the e-mail, Rich.

DR. LANGE: Okay, great. I'm going to wait for 30 --

DR. CONNOR: No, I don't. But Aden, I have your e-mail. Aden, can I just send you an e-mail that's not in response to yours?

MS. ASEFA: I mean, that's fine. It's just basically saying yes, no or abstain to the three voting questions.

DR. LANGE: One, two, three, okay. Has anybody else not gotten the e-mail at this point?

(Audio feedback.)

DR. LANGE: I still got Dr. Vetrovec, Dr. Bonde, and Dr. Allen still.

DR. ALLEN: Yeah, I just got -- I just got the e-mail. I'm just going to write one, two, and three and put my vote.

DR. LANGE: That would be great.

DR. ALLEN: It's just a blank e-mail to respond to.

DR. LANGE: That sounds great.

Dr. Vetrovec.

DR. VETROVEC: I got mine.

DR. LANGE: Super, super.

Dr. Bonde, do you have yours yet? You're muted. So Dr. Bonde, do you have Aden's e-mail address?

DR. BONDE: Yeah.

DR. LANGE: If you'll just put one, two, and three and vote for each of those, safety, effectiveness, and benefit-risk. And then we'll make sure that Aden has all the votes.

I see, Bernie, you're trying to vote three times. Don't do that, Bernie. Jason asked what e-mail are you using, to Jim Swink.

DR. CONNOR: No, you can ignore that, I thought that was just to James.

DR. LANGE: Okay.

DR. CONNOR: I sent Aden my e-mail.

DR. LANGE: Got it, super.

(Tally of votes.)

DR. LANGE: All right.

DR. VETROVEC: How many times can we vote?

(Laughter.)

DR. BATCHELOR: As many times as you need to get it right, George.

(Laughter.)

DR. VETROVEC: I lived in Chicago as a boy, so I'm familiar with this.

DR. SOMBERG: Then there's no limit if you're from Chicago.

(Crosstalk.)

DR. ZUCKERMAN: Could we pause a moment?

Dr. Lange, do you know if Dr. Wittes is having a technical problem? I thought I heard her trying to speak again.

DR. LANGE: Janet, can you hear me?

(Audio feedback.)

DR. LANGE: So Aden, does Janet -- has Janet voted? Has Dr. Wittes voted?

MS. ASEFA: Yes, I can see her vote.

DR. LANGE: Okay. And Dr. Wittes, your audio -- your audio sounds like it's

somewhere between Mars and Jupiter. If it gets to that point where we can't hear you, I may have you type your response in terms of any no responses so we can enter it for the record.

But Aden, have you got everybody's vote?

MS. ASEFA: I think so. I'm still tallying them up.

DR. LANGE: While she's doing that, let me thank the Panel and Jim and Dino sitting in audiovisual at the end who has spent hours, countless hours, before the meeting making sure it works and with few exceptions, Dr. Wittes being one of them, it's worked pretty well. And I want to thank you, all the Panel members, this kind of a meeting goes a little bit longer because we're not sitting in the same room. But on the down -- or the upside is you don't have to fly back home or drive back home.

MS. ASEFA: Janet, did you vote? I did get an e-mail, but you didn't vote.

DR. WITTES: I'm trying to vote, I'm trying to.

MS. ASEFA: Okay.

DR. SOMBERG: Do we get paid by the hour for this or --

(Laughter.)

DR. LANGE: You do and you're on Mountain Time right now.

DR. SOMBERG: Illinois we have very strict rules about payment. Fifteen dollars an hour, even.

(Pause.)

DR. SOMBERG: Bram, you look so worried. The polls are in already.

(Pause.)

MS. ASEFA: Okay. Dr. Page, did I get your vote? Oh, yeah, I got it.

DR. PAGE: I sent one.

MS. ASEFA: Yes, I got it. Yeah. And then Dr. Wittes, Janet Wittes. Just waiting on

her --

DR. WITTES: No, but have you gotten -- I sent several -- several times I sent. You didn't get any of them?

MS. ASEFA: I didn't get the results, but I did get an e-mail from you. Hold on one second.

DR. LANGE: Okay, let me ask a question. Has everybody else voted?

MS. ASEFA: Yeah, everyone has voted.

DR. LANGE: Okay. So Janet, if you'd like to give your vote verbally right now, we'll take it. We'd ultimately reveal that anyway. Do you want --

DR. WITTES: No, no, no.

DR. LANGE: No? Okay.

DR. WITTES: Yeah, I voted no, no, no.

DR. LANGE: No, no, no. Okay. So let's enter those.

DR. WITTES: Sadly.

DR. LANGE: I thought that was your response to me when I said do you want to give a verbal thing and you said no, no, no, I thought --

DR. SOMBERG: And she said yes, yes, yes to that.

DR. WITTES: No, but with sadness I voted no, no, no.

DR. LANGE: Okay, we'll get the final tally here in just a moment.

(Pause.)

DR. LANGE: He's working on the hanging chads right now, we should have those resolved pretty quickly.

MS. ASEFA: Sorry about this.

DR. SOMBERG: Just imagine if the U.S. post office was involved. Three months.

(Pause.)

MS. ASEFA: Sorry, I have people double-checking my work.

DR. LANGE: Thank you, Aden. It's important to get it right, so thank you.

DR. VETROVEC: Does this go to the Supreme Court if there are any questions?

(Laughter.)

MS. ASEFA: Sure.

DR. ZUCKERMAN: Yes, it can, George. That's why it's really important just to give Aden a few minutes. I know that everyone wants to eat dinner and so forth, but it's really important.

DR. VETROVEC: No, I agree. I just thought it was funny.

DR. ZUCKERMAN: And as a preview, after Aden summates the votes, Dr. Lange will be asking Panel members to specify why they voted in a certain way. So right now, during this downtime, if you could, think about your responses so that that section can move along efficiently.

(Pause.)

MS. ASEFA: Okay. So the votes have been captured and I will now read the votes into the record.

On Question 1, the Panel voted 14 yes, 4 no, and 0 abstain the data shows reasonable assurance that the Neovasc Reducer System is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 1 yes, 17 no, and 0 abstain that there is a reasonable assurance that the Neovasc Reducer System is effective for use in patients who meet the criteria specified in the proposed indication.

And on Question 3, the Panel voted 3 yes, 13 no, and 2 abstain that the benefits of the Neovasc Reducer System outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

The three voting questions are now complete.

DR. LANGE: Aden, thank you for taking the time to get it right. I appreciate it, thanks.

MS. ASEFA: Thank you.

DR. LANGE: I will now ask the Panel members to discuss their votes and please feel free to opine about why you voted yes or no on Questions 1, 2, and 3. And I'll run down the list.

Dr. Vetrovec, you first.

DR. VETROVEC: I think the whole question really turns on how refractory patients or a patient is. I voted that there was safety, yes. I voted no to proving that it is effective. And I voted yes for risk-benefit, but I qualified that, which I can't do, I realize, but my verbal qualification is it depends on how symptomatic the patient is and where they are because it's not a terribly risky device. And so if the patient is symptomatic enough, I think I'd be willing to take it or anybody would be willing to take it, so I think that's the dilemma.

DR. LANGE: Thank you, Dr. Vetrovec.

Dr. Starling.

DR. STARLING: Yes, thank you. Randall Starling.

So I'm very sympathetic to this patient group and frequently see these patients at the request of my interventional colleagues. As far as safety, I voted yes, based on the totality of data I was comfortable. The second question as far as effectiveness, I voted no, being uncomfortable with the data presented from the randomized trial and the sample of just over a hundred patients and the lack of the Reducer information, pushing it over for the reasons that we discussed during the meeting. As far as risk-benefit, I again voted no and my no vote was based -- primarily based on lack of any convincing efficacy.

DR. LANGE: Dr. Connor.

DR. CONNOR: Yes, Jason Connor here.

So I voted yes to safety, no to efficacy, and abstain for the risk-benefit. I think safety, given what we've seen in this trial, what we've seen in the open label, and then just the experience in Europe has all been positive with no big safety concerns.

The efficacy, for all the reasons discussed, I won't reiterate, is weak. You know, the company got FDA feedback, chose not to accept it and ran the trial elsewhere, they have an open IDE with FDA feedback for a trial they chose not to initiate and I think, you know, they had plenty of chances to run and obtain the efficacy that we all would like to have seen.

When it comes down to risk-benefit, I really appreciate hearing from the patients we heard from after lunch, I understand how debilitating this can be. And so my abstain vote there was because not as a clinician seeing these patients, I don't exactly feel qualified to weigh the benefit and the risk given it seems the risk is very low.

DR. LANGE: Thank you, Dr. Connor.

Dr. Brindis.

DR. BRINDIS: I voted yes for safety, no for efficacy, and no for risk-benefit. Again, I want to thank you, Richard, for running this historic meeting and but most of all, I do feel a lot of concern for the -- empathy for the patients involved. I'm really sorry that the company opted not to take on this trial when the FDA offered it a couple years ago, we'd be further along in terms of potentially helping our patients with a device that potentially could be of value.

DR. LANGE: Thank you, Dr. Brindis.

Dr. Allen.

DR. ALLEN: Yes, I voted yes for safety. Although I do question the long-term safety, I think overall the totality pushed me to vote yes. I voted no on efficacy. There are just too many issues with the trial. And I also have great conflicts. The FDA is, I think, doing a great

job at working with companies proactively to get trials designed correctly and the company had a chance to do this the right way and chose not to and the data just isn't good enough for me to vote yes. And risk over benefit, we have a zero in the denominator and you can't have a doable number, so I voted no on risk-benefit.

DR. LANGE: Dr. Wittes, don't surprise me you changed your vote now.

(Audio feedback.)

DR. LANGE: And unfortunately we can't get the sound issues worked out. Janet, you might want to turn your video off and see if that helps.

DR. WITTES: No, I'll chat.

DR. LANGE: That's good.

DR. WITTES: Good that I'm chatting or good that you can hear me?

DR. LANGE: We can hear you well now, go ahead.

DR. WITTES: Okay.

(Audio feedback.)

DR. LANGE: And now we can't, Janet, I'm so sorry. My apologies. If you chat, I'll make sure I read it to get it into the record.

I'll move on to Dr. Page at this point.

DR. PAGE: Thank you. I voted yes in terms of safety from the perspective that if it were an effective device, the safety, while it's not perfect, it would be acceptable. In terms of reasonable assurance of effectiveness for the reasons that I and others have enumerated, it just does not clear the bar. And then the issue of overall, I had to vote no, as well. I must say, as others have said, I was moved by hearing the patients and their families. The concept of no option, the concept of feeling desperate, the people talked about the urgent need and the patients need hope, but we shouldn't give them false hope. We need to be providing -- even with this vulnerable population, we need to provide them

something that we truly believe is going to be effective, and that was not proven today.

DR. LANGE: Well said. Thank you, Dr. Page.

Dr. Bonde.

DR. BONDE: I feel very sympathetic and I truly feel empathy for this patient population. I voted yes for the safety, yes, it can be safely put into these patients. However, I voted no for the other two questions because I don't think there's enough data to support either effectiveness or to prove a risk versus benefit ratio for these patients. So though we would like to help these patients, we would not like to have a device that is not having a proven efficacy and benefit.

DR. LANGE: Thank you, Dr. Bonde.

For the record, I'll read Dr. Wittes' comments. She voted no for safety because there is not enough long-term safety and I think 52 patients is too small a sample size to assess safety even in the short term. No for efficacy for all the reasons we all discussed. It made me very sad to vote no because I wanted to be convinced. I have no for risk-benefit because of the no for efficacy.

Thank you, Dr. Wittes.

Dr. Yuh.

DR. YUH: Thank you, Dr. Lange.

I voted yes for safety. I think, as I mentioned before, the totality of the safety profile data gave me confidence in the safety of the device. I voted no on the efficacy. You know, I don't want to enumerate all the flaws, but none of them was a deal killer to me or a fatal flaw but in totality, I think -- I just didn't have the confidence to meet the standard. The standard is the standard for efficacy and I just wasn't confident, and therefore I voted abstain on the ratio only because I think there may very well be a positive signal there but just couldn't be convinced with this particular trial and that's why I had to abstain.

DR. LANGE: Thank you, Dr. Yuh.

Dr. Yeh.

DR. YEH: I voted a yes for safety for all the reasons that have been enumerated. I voted no for efficacy because I didn't feel confident enough in that assessment and maybe I should -- there was an unknown for risk-benefit or uncertain I would've voted for that one, but I just -- but I voted no for risk-benefit just on the basis of although I think there may be a benefit, very similar to what Dr. Yuh just said, I'm just not confident enough that that's truly there.

DR. LANGE: Thank you, Dr. Yeh.

Dr. Batchelor.

DR. BATCHELOR: Yeah, I was really, really torn and I thought the statements from the patients were quite compelling and some comments at the end I thought were actually quite helpful. I was looking at this through the lens of it being a breakthrough designation, as well, and as an interventionalist who treats a lot of these patients who are really desperate for therapy and who right now are getting things like EECP and chronic total occlusion interventions which are probably less efficacious than for EECP and more dangerous. So I think that this is a safe procedure, I was convinced by the over 2,000 patients treated, but I think we would see something come out if it was an unsafe procedure.

In terms of the effectiveness, I switched this last minute and I'm going to be an outlier because I thought about this. I initially voted no and I switched because I thought all the things that we discussed regarding the lack of -- the concerns about the placebo effect. If anything, that would bias toward the null and create less ability for us to actually distinguish the treatment effect between the two arms and that would, in fact, slightly disadvantage the device. I think the device is probably -- probably does work for angina, I

don't know that it works for ischemia, but as a patient-centered outcome for simply angina, I think that there's a good chance that this device does work, therefore I actually switched my vote last minute and said yes, and then because the risk-benefit profile is based on those two answers, I had to actually vote yes for the risk-benefit relationship. And this has all been in the context of absolutely requiring more data and that's where I think that's -- that's where I feel that -- you know, this would be completely switched around if this was an end decision, but linked to the requirement for a randomized trial with the structure that we described, I'm okay making these -- I'm standing firmly by these answers.

DR. LANGE: Thank you, Dr. Batchelor.

Dr. Ohman.

DR. OHMAN: Yes, thank you, Dr. Lange.

I'm going to thank the Sponsor, Neovasc, for actually bringing forward a great new technology, and I also want to thank the FDA for doing very careful analysis of the very limited database that was presented to them.

I voted no on safety mainly because I really don't know the safety long term beyond the 6 months. It was fairly good data up to about a year, but after that it drops off quite dramatically and a lot of the long-term issues such as the impact that this might have on diastolic heart failure or other things were not available in the dataset, which I think is very important because many of these patients do get that.

I voted no for efficacy for the reasons that I couldn't link ischemia, which is objective, with a device that I would put in permanently when over about nearly half the patients had very little treatment benefit, so that makes it very hard. And then the final aspect is, of course, if I voted no on both I couldn't actually say that there was any risk-benefit equation that would be favorable. Thank you.

DR. LANGE: Thank you, Dr. Ohman.

Dr. Cigarroa.

DR. CIGARROA: So I, too, would like to thank the FDA and the Sponsor for their thoughtful approach to presenting the data and analyzing it and framing critical discussions for us today. These patients are very challenging, having cared for them on a frequent basis for over 25 years now, and because of this unmet need that adversely impacts quality of life, I wanted to vote yes on each of them. However, the conversations from today and the data presented, to me, provided clarity even though I didn't like the answers I was provided as it relates to the vote because of the unmet need for patients.

As it relates to safety, although I have concerns about the long-term components, I think the overall data presented made me vote yes despite the limitations of that data. As it relates to efficacy, I would say that the primarily male Caucasian European and non-U.S. approach made it very difficult for me to extrapolate our heterogeneous population, and then the challenges of a small sample size with the flaws that we discussed further cemented my response for voting no, which led to a vote of no on the third.

DR. LANGE: Thank you, Dr. Cigarroa.

Dr. Hirshfeld.

DR. HIRSHFELD: I'd like to also really compliment FDA on an outstanding and rigorous presentation and keeping us at a very high level through this whole meeting.

I voted no, no, and no, and for many reasons that were already outlined. I thought that the 6-month safety data was too short for a permanently implanted device. For as far as efficacy was concerned, I thought that the subjective signal of efficacy was there, but weak, and the objective signal of anti-ischemia is lacking and I thought we needed some more strength in each of those in order to vote for efficacy and that led me to, obviously, no for risk-benefit.

I had two other thoughts that I'd like to share. The first is I believe we heard data

today that suggested that in the countries in which this device is approved there's been somewhere around 2,000 devices implanted and that's over 9 years since the CE mark was granted. So I wonder if the clinicians in the countries where it's approved for the CE mark are telling us something if this patient population is as large as it is and there's been only that many implanted.

The second thing is that I think that if FDA were to approve this device now on the premise that a randomized pivotal trial is going to be done subsequently, there's a certain hypocrisy in that course of action, and so I think that it would be inconsistent to say we're going to approve it but you haven't -- to go on and demonstrate efficacy, so those are all reasons why I was a no, no, no person.

DR. LANGE: Thank you, Dr. Hirshfeld.

Dr. Mathew.

DR. MATHEW: Yeah, Verg Mathew here, Verghese Mathew. Thank you, Dr. Lange. Thanks for the opportunity to be a part of this very comprehensive discussion, I respect the opinion and contribution of every single person on the call here, so thank you for that.

I voted yes for safety for the reasons that have been enumerated. I voted no for efficacy. I was willing to buy the primary endpoint was met and I think that's important to say. I would've been more compelled if a secondary endpoint that was objective would've been appropriately powered and met, and I was concerned about the missingness of data in that regard, as well.

In terms of benefit-risk, I voted yes for similar reasons that Dr. Batchelor outlined, I think there's probably a signal for effect here. I think the relative risk is low. I think more data is important and I think how one formulates that, whether it's a randomized trial preapproval, I think for reasons I mentioned before, I think a randomized trial post-approval is challenging but whether there would be a pathway forward for a meticulous agreement

on a mandatory registry-type thing post-approval would be another consideration that I mentioned earlier with David. Those are my thoughts and thanks again for the opportunity to participate.

DR. LANGE: Thank you for participating, Dr. Mathew, appreciate it.

Dr. Gersh.

DR. GERSH: Thank you, Dr. Lange.

Well, this is my first meeting, it's really been a great experience for me. I'm very pleased to be part of the Panel and thank the FDA for inviting me. I really, really enjoyed the day and I have been very impressed with what I've heard and the level of discussion.

I voted yes for safety, but I accept that longer-term data would be beneficial. In terms of efficacy, I voted no for all the reasons you've heard and I think it's just too few patients and the signal, there's a signal there but given the other limitations to the data, I could not -- I didn't feel I could vote for efficacy.

My third was no really based upon Number 2. Until we have some proof of efficacy, I'm not sure I feel comfortable assessing risk-benefit. If there's a randomized trial that shows even a mild to moderate but significant signal, then I think I would support the risk-benefit ratio. Thank you.

DR. LANGE: Thank you, Dr. Gersh. And welcome to the Committee, we're glad to have you for the first time.

Dr. Somberg, this is not your first ride.

DR. SOMBERG: You should've said rodeo.

DR. LANGE: Go, John.

DR. SOMBERG: Okay. Well, I voted no for safety because I felt the long-term data was really inadequate for a permanently implanted device. I do not think the risk of anticoagulation has been evaluated. Because it's on the venous side I think there's going to

be a need for an antithrombotic, warfarin, for instance, and that might increase the bleeds. And I also think there's -- I was disturbed by the discussion of stent thrombosis and whether there's a thrombosis or not, and I think that needs to be worked out pre-clinically so we know if there is an incidence of thrombosis because if you do have a coronary sinus thrombosis it may present with angina or MI and it's going to be a question if it's disease progression or not.

Okay, I also voted no for efficacy because I think the population was not defined and the data was very interesting in that those people with the mildest or the least drugs, which we will say the least resistant patients, benefitted the most. So I'm not sure this drug will be effective in a drug-resistant end-stage population. I think it may be an antianginal but then again it's going to be a risk-benefit ratio whether you want to take a medicine that can be easily stopped versus you want to have a permanent implant with the risk that that ensues. So not knowing the safety, not knowing the efficacy, obviously I voted no for the third question.

DR. LANGE: Thank you, Dr. Somberg.

DR. SOMBERG: Thank you.

DR. LANGE: And Dr. Borer. And again, Jeff, if you'll unmute. Thank you.

(No response.)

DR. LANGE: Can't hear you yet. Find that unmute button one more time. Should be in the top right, I think.

DR. CONNOR: And mine's lower left if you're on a Mac.

DR. SOMBERG: Yeah, lower left.

DR. LANGE: I'll just ask you to unmute. Yeah, so Jeff, are you able to see that mute button down on the lower left?

DR. CONNOR: Is your phone on mute?

(No response.)

DR. LANGE: I'm going to ask you to unmute. And I'm sorry, neither I nor the audiovisual host is able to unmute anybody. Wait for just a minute.

DR. SOMBERG: Maybe he can chat in.

DR. LANGE: Yeah. So Jeff, would you like to just type in on the chat and I can enter it into the record?

(No response.)

DR. LANGE: You don't see the chat, either. Okay.

MS. ALIKHAANI: Maybe he can just send an e-mail.

DR. LANGE: Yeah. Jeff, you're there. Yeah, you're there. Don't touch anything.

DR. BORER: Okay.

DR. LANGE: Just talk.

DR. BORER: With regard to safety, I voted yes.

DR. LANGE: Okay.

DR. BORER: With trepidation because I agree totally with John and others that the long-term data aren't there, that the issues about the need for antithrombotic therapy hasn't been worked out. I mean, there are a lot of problems with it, but from the data that exist, it seems to me unlikely that this device is going to cause an important safety problem, so I voted yes.

With regard to efficacy, I had to vote no, first because the data aren't there and second and perhaps more importantly, because the population was poorly defined. I have no idea who we would want to give this device to. It's people with refractory angina, but that was never defined, so I couldn't possibly vote yes for that. And if I couldn't vote yes for effectiveness, then how could I vote yes for the relationship between effectiveness and safety, so I voted no for that, also. So that's why I voted the way I did.

DR. LANGE: Great. And I don't vote unless there's a tie, but I always appreciated the fact and respected Dr. Page who always told us how he voted regardless, and I would've voted no on all three for the reasons that you all discussed already.

I would like to thank the Panel, it really is an august panel, very accomplished individuals on here. Thank you for those who I have served with before and those of you who are new serving on the Panel. I want to thank the FDA, excellent presentations, excellent analysis, excellent discussion, and excellent preparation. The same to the Sponsor, I think the presentations were outstanding and again, I appreciate you addressing the issues. I look forward to you working with the FDA, and I hope that instructions and observations that we provided will help you to work with the FDA to get this to a point where we can reevaluate it and assess its safety and efficacy and hopefully, approve it for this very needy population. And I want to thank our public hearing speakers for their contributions and Jackie Alikhaani, our Consumer Rep, as well.

Dr. Zuckerman, do you have any final comments?

DR. ZUCKERMAN: Yes. I especially want to thank Dr. Lange for running an extremely successful virtual advisory panel meeting. This is the first devices advisory panel meeting that has been run in the COVID era virtually and Dr. Lange has certainly set the standard. So thank you. Also, I'd like to thank all the Panel members for the extremely excellent work that was done this afternoon. The FDA and more importantly, the American people owe you a debt of gratitude. So thank you and Godspeed.

DR. LANGE: With those comments, this meeting of the Circulatory Devices Panel is now adjourned. Again, thank you to everybody. Have a good night.

(Whereupon, at 8:01 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY DEVICES PANEL

October 27, 2020

Via Zoom

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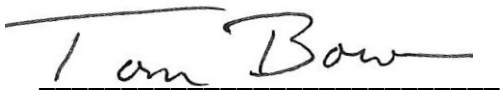

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