UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

CIRCULATORY DEVICES PANEL

+ + +

February 23, 2017
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

RICHARD PAGE, M.D.	Panel Chair
GEORGE W. VETROVEC, M.D., MACC, MScai	Voting Member
DAVID NAFTEL, Ph.D.	Voting Member
JOAQUIN E. CIGARROA, M.D.	Voting Member
DAVID D. YUH, M.D., FACS, FACC	Temporary Non-Voting Member
JEFFREY S. BORER, M.D.	Temporary Non-Voting Member
JOHN C. SOMBERG, M.D.	Temporary Non-Voting Member
JEFFREY BRINKER, M.D.	Temporary Non-Voting Member
DAVID C. GOOD, M.D.	Temporary Non-Voting Member
ERICK MAGNUS OHMAN, M.B., FRCPI, FACC	Temporary Non-Voting Member
GUERRY M. PEAVY, Ph.D.	Temporary Non-Voting Member
DONNA RAE ROBERTS, M.D.	Temporary Non-Voting Member
JOHN W. HAMMON, JR., M.D.	Temporary Non-Voting Member
LORI E. DODD, Ph.D.	Temporary Non-Voting Member
KEVIN M. DUFF, Ph.D., ABPP(CN)	Temporary Non-Voting Member
NAVEEN THURAMALLA, M.S., CCRP	Industry Representative
NAFTALI Z. FRANKEL, M.S.	Consumer Representative
PHILLIP POSNER, Ph.D.	Patient Representative
EVELLA WASHINGTON	Designated Federal Officer

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

RANDALL BROCKMAN, M.D.
Clinical Deputy Director
Office of Device Evaluation

STEPHANIE CACCOMO
Press Contact

FDA PRESENTERS:

CDR SADAF A. TOOR, M.S.
Biomedical Engineer
U.S. Public Health Service
Peripheral Interventional Devices Branch
Division of Cardiovascular Devices
Office of Device Evaluation

DONNA BUCKLEY, M.D., M.S.
Division of Cardiovascular Devices
Office of Device Evaluation

LI MING DONG, Ph.D.
Division of Biostatistics
Office of Surveillance and Biometrics

SPONSOR PRESENTERS:

THOMAS ENGELS
Vice President of Clinical Affairs
Claret Medical, Inc.

MARTIN B. LEON, M.D.
Professor of Medicine
Columbia University

RENU VIRMANI, M.D.
President, CVPath Institute, Inc.
Clinical Professor, George Washington University

WILLIAM A. GRAY, M.D.
System Chief of the Division of Cardiovascular Disease
Lankenau Medical Center
Main Line Health

AZIN PARHIZGAR, Ph.D.
President and CEO
Claret Medical, Inc.

SPONSOR ADVISORS:

ROBERT ZIVADINOV, M.D., Ph.D.
Professor of Neurology
Director, Buffalo Neuroimaging Analysis Center

MICHAEL DWYER, Ph.D.
Director of Technical Imaging
Buffalo Neuroimaging Analysis Center
Assistant Professor of Neurology
University of Buffalo

ROSEANN WHITE, M.A.
Director, Pragmatic Clinical Trial Statistics
Duke Clinical Research Institute

RONALD LAZAR, Ph.D.
Professor of Neuropsychology
Columbia University Medical Center

OPEN PUBLIC HEARING SPEAKERS:

JIM McCUTCHEON, M.D.
Private Citizen

NICOLAS M. VAN MIEGHEM, M.D., Ph.D., FESC
The Thoraxcenter, Erasmus MC
Rotterdam, the Netherlands

JOCHEN WÖHRLE, Prof. Dr.
Head, Interventional Cardiology
University of Ulm
Ulm, Germany

DAVID LANGE, M.D.
Cedars-Sinai Medical Center

ADNAN H. SIDDIQUI, M.D., Ph.D.
University of Buffalo
American Association of Neurological Surgeons
Congress of Neurological Surgeons
Society of NeuroInterventional Surgeons

SAIF ANWARUDDIN, M.D.
Perelman School of Medicine
University of Pennsylvania

LARRY RUVO
Keep Memory Alive
Cleveland Clinic Lou Ruvo Center for Brain Health

ROBERT E. ECKLEY
Patient

SUSAN ROCKENBACH
Daughter of Marie Bartman, Patient

INDEX

INDEX

INDEX

M E E T I N G

(8:09 a.m.)

DR. PAGE: Good morning, everyone. Sorry to be starting a little bit late. I'd like to call this meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee to order.

My name is Richard Page. I'm Chair of the Panel. I'm also chair of medicine at the University of Wisconsin in Madison, and I am a clinical cardiac electrophysiologist by training.

I note for the record that the Panel 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 and make recommendations on information regarding the de novo request for Claret Medical, Incorporated's SENTINEL Cerebral Protection System. FDA is seeking guidance from its expert panel to decide if the clinical performance of this device is safe and effective and supports the proposed intended use. If the performance is acceptable, FDA is seeking guidance on the types of information needed in the device labeling to support the safe and effective use of the device.

Before we begin, I will ask our distinguished Panel members and the FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'd first like to start with Dr. Randall Brockman, who is sitting in for Dr. Zuckerman today.

Dr. Brockman.

DR. BROCKMAN: Good morning. Thank you. I'm Randy Brockman. I'm the Clinical Deputy Director in the Office of Device Evaluation, and as Dr. Page mentioned, I'm sitting in for Bram Zuckerman, who wasn't able to join us this morning.

DR. VETROVEC: George Vetrovec, BCU Medical Center, Professor Emeritus, interventional cardiology.

DR. SOMBERG: John Somberg. I'm a Professor of Medicine, Cardiology, and Pharmacology at Rush University in Chicago.

DR. OHMAN: Magnus Ohman, cardiologist at Duke University Medical Center in North Carolina, and I'm vice chair of medicine at Duke.

DR. HAMMON: I'm John Hammon and I am a cardiothoracic surgeon, and I'm on the faculty of Wake Forest University Medical Center in Winston-Salem, North Carolina.

DR. DUFF: Kevin Duff. I'm at the University of Utah. I am a professor in the department of neurology and a clinical neuropsychologist.

DR. PEAVY: I'm Guerry Peavy, University of California, San Diego, in the department of neurosciences, and my area of expertise is neuropsychology.

DR. BRINKER: I'm Jeff Brinker, Professor of Medicine and Radiology and an interventional cardiologist at Johns Hopkins.

DR. YUH: Good morning. I'm David Yuh. I'm the chairman of the department of surgery at Stamford Hospital in Stamford, Connecticut, and my area of expertise is in valvular surgery and cardiac surgery.

MS. WASHINGTON: My name is Evella Washington. I am the DFO.

DR. NAFTEL: My name's David Naftel. I am a biostatistician in the division of cardiac surgery at the University of Alabama at Birmingham.

DR. CIGARROA: I'm Joaquin Cigarroa. I'm the clinical chief for the Knight Cardiovascular Institute at OHSU, Clinical Professor of Medicine and an interventional cardiologist.

DR. DODD: I'm Lori Dodd. I am a biostatistician at the National Institute of Allergy and Infectious Diseases.

DR. BORER: My name is Jeff Borer, and I am a cardiologist. I'm Professor of Medicine, Cell Biology, Radiology, and Public Health, and former chairman of medicine and the chief of cardiology at SUNY Downstate in New York City.

DR. GOOD: Good morning. I'm David Good, and I'm Professor of Neurology at Penn State College of Medicine at Hershey. My clinical interests are stroke and stroke rehabilitation.

DR. ROBERTS: I'm Donna Roberts. I am an Associate Professor of Radiology at the Medical University in South Carolina, and my specialty is Neuroradiology.

MR. THURAMALLA: Good morning. I'm Naveen Thuramalla, Vice President of Regulatory Affairs at ARKRAY. On this Panel, I serve as an Industry Representative. Thank you.

MR. FRANKEL: Good morning. My name is Z. Frankel, Consumer Representative.

DR. POSNER: Phil Posner. I am a Patient Representative and retired Professor of Electrophysiology, Cardiology, and Neuroscience at the University of Florida.

DR. PAGE: Thank you very much. As you can see, we have an outstanding Panel today with various areas of expertise that are going to be critical for our activities in this Panel meeting.

Members of the audience, if you've not done so already, please sign the attendance sheets that are on the tables by the doors.

Ms. Evella Washington, who is the Designated Federal Officer for the Circulatory System Devices Panel, will now make some introductory remarks.

MS. WASHINGTON: The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act 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 today's discussions, 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 and make recommendations on the de novo submission sponsored by Claret Medical, Incorporated, for their SENTINEL Cerebral Protection System, the first-of-its-kind embolic protection device to be used with transcatheter aortic valve replacement procedures. The system, a percutaneously delivered embolic protection catheter inserted into the right radial and brachial artery, is designed to capture and remove embolic material (thrombus debris) that may enter protected arteries during TAVR. At the completion of the TAVR procedure, the proximal and distal filters are resheathed and removed from the patient along with any captured embolic debris.

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.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry. He is employed by ARKRAY, Incorporated.

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 exclusion will be noted for the record.

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

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript. Thank you.

For the duration of the Circulatory System Devices meeting on February the 23rd, 2017, Drs. David Good and Donna Roberts have been appointed to serve as Temporary Non-Voting Members. And Dr. Phillip Posner has been appointed as a Temporary Non-Voting Patient Representative. For the record, Drs. Good and Posner serve as consultants to the Peripheral and Central Nervous System Drugs Advisory Committee at the Center for Drug Evaluation and Research, and Dr. Roberts serves as a consultant to the Medical Imaging Drugs Advisory Committee at CDER. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

Their appointment was authorized by Dr. Janice Soreth, the Associate Commissioner for Special Medical Programs, on January 31st of 2017.

Before I turn this meeting back over to Dr. Page, I would like to make a few general

announcements.

The transcript of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today's meeting is Stephanie Caccomo.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are planning to present during today's Open Public Hearing session, please sign in with Mr. Artair Mallett at the registration desk.

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

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Page.

DR. PAGE: Thank you, Ms. Washington.

I'd like to make a couple other comments in terms of process today. For the Panel members, please be sure you turn off your microphone when you're done speaking. If you need to get my attention, raise your hand, please, and I'll acknowledge you, but don't be pushing the button for priority in making comments. But likewise, it affects the acoustics for you and others if your microphone is on and you're not speaking.

Speaking of speaking, I do ask that the panelists keep any conversations, while we are called to order, just among ourselves on the microphone as opposed to any side conversations. Everything you think and say we want to know, and everything when we are

called to order really needs to be in the transcript. So I'll just remind you of that. And finally, when we are out of session, obviously, we will not discuss the matter at hand.

So with that, we'll proceed with the Sponsor's presentation. I'd like to invite Claret Medical to approach the lectern.

I will remind 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.

The Sponsor will have exactly 90 minutes or less, if you wish, to present. And we welcome you, and please begin your presentation.

MR. ENGELS: Good morning. I'm Thomas Engels, Vice President of Clinical Affairs at Claret Medical. On behalf of Claret I'd like to thank you, the Panel and FDA, for the time you've spent reviewing the information on the SENTINEL Cerebral Protection System and for inviting us to present at this meeting.

The SENTINEL system is a Class II, medium-risk device, temporary accessory placed prior to transcatheter aortic valve replacement, or TAVR, and then removed after the procedure. It's an important embolic protection accessory to TAVR because of ischemic cerebral or vascular events, including strokes caused by dislodged particles and other materials during the TAVR procedure.

Embolic protection devices, or EPDs, have been used to prevent cerebral embolization in carotid stenting for approximately 15 years. There are no EPDs available on the U.S. market intended for protection during TAVR procedures, and the SENTINEL system is the first to be evaluated for this indication.

The SENTINEL system was CE marked in 2013 and has been used in more than 3,000 TAVR procedures, to date, outside of the United States.

In the U.S., Claret proposes that the SENTINEL be indicated for use as a cerebral

protection device to capture and remove embolic material while performing TAVR procedures in order to reduce ischemic injury to the brain periprocedurally.

We also recommend that the indication give specific guidance on the diameters of arteries at the site of filter placement, as shown here. This indication is narrowly consistent with approvals in European countries.

Next, I'd like to show an animation of how the SENTINEL system is delivered.

The SENTINEL system is inserted into the patient's right arm via the radial or brachial artery. The device is advanced until the distal tip is in the ascending aorta. The proximal filter is deployed in the brachiocephalic artery, protecting the right common carotid and right vertebral arteries.

The distal tip is then cannulated into the left common carotid artery in order to deploy the second filter with minimal interference or footprint in the aorta. Both filters remain in place during TAVR, capturing debris that may be liberated by catheter manipulations, balloon dilatations, and valve deployment.

At the end of the TAVR procedure, the SENTINEL system and all captured debris are retrieved in reverse order of deployment. The SENTINEL system is then removed, taking away filters and embolic materials they collected.

As you'll hear in greater detail during our presentation, the study met the primary safety endpoint, 30-day MACCE. The primary effectiveness endpoint was based on median new lesion volume measured by diffusion-weighted MRI. We were successful in meeting the observed treatment effect threshold of 30%. However, the difference between test and control was not statistically significant.

The SENTINEL system performed as intended and was successfully delivered and retrieved in 94% of patients. There was one major access complication related to SENTINEL use, which was reported post-procedure and resolved without clinical sequelae.

Importantly, the SENTINEL system was effective in capturing embolic material in 99% of patients.

As I'm sure the Panel knows, there are three classes of medical devices ranging from low to high risk. SENTINEL is a medium-risk device, and in our case, the de novo pathway was required due to lack of a predicate device for embolic protection during TAVR procedures. De novo pathways are relatively new, and the SENTINEL is the first medium-risk device of its kind going through this process. Historically, the de novo pathway risk-benefit balance is based on the totality of premarket, including clinical and nonclinical evidence as well as postmarket measures.

With this background in mind, I'd like to review our presentation outline and introduce our speakers.

Dr. Marty Leon, Professor of Medicine at Columbia University Medical Center, will present background data on TAVR and its potential complications. He will describe the SENTINEL device and review an actual procedure. He will then provide an overview of the SENTINEL trial design and safety data.

Dr. Renu Virmani, President of the CVPath Institute and a clinical professor at George Washington University, will review the histopathology and morphology data generated from analysis of captured embolic debris.

After Dr. Virmani's presentation, Dr. Leon will return to present key effectiveness outcomes data.

And then Dr. Bill Gray, System Chief of the Division of Cardiovascular Disease at Main Line Health, will provide insights into the history of neuroprotection and carotid artery stenting and provide his perspective on the historical data compared to SENTINEL.

Finally, Dr. Azin Parhizgar will conclude our presentation.

In addition to our presenters, we've invited external experts to assist us in answering

your questions after the presentation. All of our external experts have been compensated for their time and expenses in preparation for our meeting today. Drs. Leon, Linke, Mehran, and Lazar are members of the company's clinical steering committee and have been compensated for their services in part in the form of stock options and aggregate options granted represent less than 1% ownership in the company.

I would now like to invite Dr. Leon to the lectern.

DR. LEON: Thank you. My name is Martin Leon. I'd like to thank the Sponsor for their determined efforts to bring forward a complete and meaningful dataset to discuss this morning.

For the past 35 years I've been a clinical interventional cardiologist, and for the past decade I focused much of my interest and research on the development of transcatheter aortic valve replacement. From the outset, we've been concerned about the random and unpredictable occurrence of strokes associated with this new procedure. From a clinician's perspective, any procedural change or accessory device which could potentially reduce ischemic brain injury would be highly valued.

Our concerns about strokes associated with TAVR was amply demonstrated in this early randomized clinical trial published in the *New England Journal of Medicine* in 2011, comparing TAVR to surgery. The incidence of strokes and TIAs was twofold higher in TAVR-treated patients versus surgery.

Neurologic events after TAVR are largely due to embolic material liberated during the procedure from the diseased aortic valvar complex. In this slide are typical examples of heavily calcified stenotic aortic valves. First, a radiograph of a surgical specimen is shown on the left and an autopsy specimen on the right. These severely diseased aortic valves and aortas are prone to the release of embolic debris with mechanical manipulation by guide wires, catheters, balloons, and especially large, stiff TAVR devices.

In fact, the last paragraph from the editorial of this *New England Journal of Medicine* manuscript concluded by saying, "Technical refinement of transcatheter valves and adjunctive procedures, such as the use of embolic protection devices, will facilitate transcatheter replacement and may improve outcomes, but these new devices should be evaluated in controlled trials with randomization against current standard techniques."

This morning we will present the first rigorously conducted, multicenter, controlled clinical trial randomizing cerebral embolic protection versus standard therapy during TAVR procedures. We believe that in the future, cerebral embolic protection will be even more relevant in an era of continued growth in TAVR procedures, extending to younger and lower surgical risk patients.

In 2015 TAVR accounted for 32% of all Medicare aortic valve replacements in the United States. And if we project globally, TAVR is expected to grow approximately fourfold in the next 10 years.

A careful examination of the literature indicates that strokes occur after TAVR in approximately 3 to 7% of patients in the first 30 days after the procedure. Up to as many as 85% of these strokes occurred during the acute phase after TAVR in patients who could potentially benefit from cerebral embolic protection. From multiple studies, we know that strokes after TAVR are associated with increased 1-year all-cause mortality and significantly reduced quality of life.

It's also important to note that the reported frequency of strokes is highly dependent on the specific definitions applied and the ascertainment methods used. An especially important ascertainment factor is whether or not there is systematic neurology examinations after the procedure.

This is a recent analysis involving the PARTNER I data offered by Samir Kapadia, one of the principal investigators of the SENTINEL trial, including more than 2600 patients with

CEC adjudication of neurologic events. There is a marked acute-phase increase in stroke risk which peaked at 2 days after TAVR, with a low constant hazard risk of about 0.8% per year thereafter.

This figure from the manuscript graphically depicts the acute-phase stroke risk, which constitutes the vast majority of strokes occurring after TAVR procedures.

Clearly, there is a broad spectrum of brain injury caused by the embolic material which may be released during cardiovascular procedures. Most dramatic are clinical neurologic events that could be classified as either disabling or non-disabling strokes or transient ischemic attacks.

In addition, there could be brain injury and infarction detected by diffusion-weighted MRI studies that are not represented as clinical events.

Finally, there may be neurologic damage, also without overt symptoms, which may result in either acute or chronic changes in neurocognitive function.

Due to the relatively low frequency of overt neurologic events during TAVR, we selected brain injury detected by DW-MRI studies as a surrogate effectiveness endpoint in the SENTINEL trial. We chose neuroimaging as a surrogate endpoint for several reasons.

First, multiple prior studies have demonstrated frequent DW-MRI abnormalities after TAVR, occurring in 68 to 100% of patients. In most of these patients there are multiple infarcts, which results in some level of permanent ischemic brain damage.

Second, utilizing advanced quantitative MRI techniques, we can reliably measure the number and size or total volume of these new lesions.

Finally, the design of the SENTINEL trial was largely based on results from the CLEAN-TAVI study published in *JAMA* last year. CLEAN-TAVI was a randomized controlled study of 100 TAVR patients, performed at a single center in Germany with a single TAVR device. In the test arm, an earlier version of the SENTINEL device was employed. Importantly, the

exact same MRI methodology and core laboratory were used in both CLEAN-TAVI and the SENTINEL trial.

Next, I'd like to describe the SENTINEL device, show you a case example and discuss the concept of the cerebral protection. During many of the presentations today, the distinction between protected territories versus all territories will be discussed.

When the SENTINEL device is placed, the proximal filter in the brachiocephalic artery and the distal filter in the left common carotid artery protect approximately 90% of the blood flow to the brain. The left vertebral artery is unprotected, representing the remaining 10% of the blood flow to the brain. Nonetheless, the intracerebral vasculature is complex and variable from patient to patient depending on many things, including the intactness of the circle of Willis.

These volume-rendered, color-coded images are based upon quantitative, high-resolution, T1-weighted images from patients analyzed by the newer imaging core laboratory at the University of Buffalo, and take into account vascular territories protected and unprotected by the SENTINEL filter device. The protected zones in green represent an average of 74% of the total brain volume and include the anterior and middle cerebral arteries and the right posterior inferior cerebella artery.

The unprotected zone in red represents approximately 2% of the overall brain volume and reflects flow from the left posterior inferior cerebella artery, which only receives blood flow from the left vertebral artery without admixture from other vessels.

The partially protected zones in yellow, representing approximately 24% of the brain volume, are dependent upon the intactness of the circle of Willis and includes territories in which there is admixture of blood flow from the unprotected left vertebral artery.

The SENTINEL dual-filter system is shown on the insert of this slide. There are two independent filters which capture and remove embolic material. These polyurethane filters

are very similar to filters used during carotid stent procedures and have a pore size of 140 µ. Standard right transradial sheath access techniques are used to introduce the system in patients through a 6 French guiding catheter. A one-size SENTINEL system accommodates a range of vessel diameters and can be used in most vessels. There is a deflectable compound-curve catheter that facilitates cannulation of the left common carotid artery. It's significant to point out that the entire catheter system assumes a minimal profile in the aortic arch, so there is little interaction of the SENTINEL device with other devices used during the TAVR procedure.

This is an edited case from the SENTINEL trial. You can see the device handle which actuates the filters and catheters. It's introduced in the right radial artery. The SENTINEL device is inserted prior to introduction of any other catheters. Over a coronary guide wire the device is placed in the ascending aorta. Deployment of the proximal filter in the proximal brachiocephalic artery is achieved by retracting the catheter. The catheter tip is then deflected and directed with a probing guide wire to cannulate the left common carotid artery. The catheter is then withdrawn slightly, following the guide wire to the roof of the aortic arch. And you can see, relative to the pigtail catheter, that it truly does sit at the roof of the aortic arch without interfering with other introduced devices. The distal filter is deployed, achieving cerebral protection.

After achieving protection, balloon catheters and TAVR devices are advanced to complete the valve implantation procedure. In this case you're seeing a Sapien XT valve, which now crosses the native aortic valve. With rapid ventricular pacing and balloon expansion the valve is deployed. The balloon is then deflated and then the delivery system is removed.

Finally, the SENTINEL device is removed in reverse order, collapsing the nitinol hoop filters to capture and retrieve the embolic debris liberated during the procedure. The

insertion time of the SENTINEL device takes approximately 3 to 5 minutes, and the total dwell time during the procedure is approximately 15 to 30 minutes.

I'd like to now focus on the Sentinel trial design. All patients in the SENTINEL trial had severe symptomatic aortic stenosis and were appropriate candidates for TAVR, representing high surgical risk patients. A total of 363 TAVR patients were randomized 1:1:1 into three arms: a safety arm, a test arm, and a control arm. The 123 patients in the safety arm were to be treated with the SENTINEL device. Another 121 patients in the test arm were also to be treated with the SENTINEL device, and the remaining 119 patients in the control arm were treated without the SENTINEL device.

In test arm patients, the filters were removed at the end of the case and were analyzed for histopathology and morphometry. These embolic material analyses will be presented by Dr. Renu Virmani.

All patients in safety, test, and control arms had careful clinical evaluations, including systematic neurology assessments at baseline and at follow-up time points. The test and control arms were randomized in a neuroimaging MRI study with serial scans performed at baseline and post-TAVR at 2 to 7 days and at 30 days. Those same groups were also randomized in a serial neurocognitive assessment study at baseline and post-TAVR at 30 days and at 90 days.

The key inclusion criteria for the SENTINEL trial is shown on this slide. All patients had symptomatic severe aortic stenosis based upon echo criteria and were eligible for treatment in the United States or Germany with a commercially approved TAVR system. Four different TAVR devices were used during the course of this clinical trial without stratification during randomization. All patient candidates had acceptable aortic arch anatomy and target vessel diameters without significant stenoses.

Key exclusion criteria are shown on this slide. Anatomic exclusions were either

unsuitable right upper extremity arteries for placement of a 6 French catheter or unsuitable brachiocephalic, left common carotid or aortic arch vessels from a standpoint of size, calcification, or tortuosity.

Clinical exclusions were patients with recent CVAs or TIAs, prior neurologic events with persistent deficits, carotid disease requiring treatment within 6 weeks, strict or relative contraindications to MRI studies, renal insufficiency, severe LV dysfunction, and recent balloon aortic valvuloplasty.

Three hundred and sixty-three patients were enrolled and randomized at 19 centers, including 17 in the United States and 2 in Germany. All of the centers are shown on this slide with the number of patients enrolled at each site. At 5 of the centers, more than 20 patients were enrolled in the SENTINEL trial, including Cedars-Sinai Medical Center, the Leipzig Heart Center, Columbia University Medical Center, the Cleveland Clinic, and the University of Pennsylvania.

This slide describes the study administration of the SENTINEL trial. This was a complex study that required multiple rigorous analyses and several core laboratories with special expertise. There were three co-PIs, two from the United States and one from Germany. The key individuals representing the clinical trial management and the various core laboratories are here today and are available to respond to questions.

There were four different valve types that were used during the course of this study, based upon FDA approval times and other factors. This slide provides an understanding of the valve type distribution, which changed over time. By the end of 2015, the dominant TAVR systems were Evolut R and Sapien 3. Importantly, the choice of a TAVR system for any given case was solely determined by the operators at the site and the decision was made after randomization.

Despite the fact that there was no stratification during randomization, overall, there

were no significant differences in valve type distribution across the three study arms. Approximately 52% of patients received Sapien 3 valves, 18% Sapien XT, 26% Evolut R, and only 4% CoreValve.

Now, I'd like to present the SENTINEL trial results pertaining to safety and device performance.

This slide details the various safety populations: all patients who were randomized, the analyzed ITT population, which excluded patients who did not receive TAVR or lost to follow-up or withdrew from the study before the 30-day safety endpoint, and the as-treated population, which excluded the nine patients in whom the SENTINEL device wasn't inserted.

The device cohort included safety and test arms in which the SENTINEL device was intended for use. The primary safety endpoint was the randomized patients in the device cohort with imputation for missing data.

It's important to mention that none of the 18 patients in the randomized population who were excluded from the analyzed ITT population were known to have had MACCE events.

The primary safety endpoint was a non-inferiority analysis compared with an agreed-upon performance goal. The endpoint is non-hierarchical, major adverse cardiac and cerebrovascular events at 30 days, consisting of all-cause mortality, all strokes, and Stage 3 acute kidney injury within 72 hours of the procedure.

The observed MACCE rate was compared to a historical MACCE performance goal based upon a weighted average of all previous FDA pivotal TAVR studies. The weighted average MACCE performance goal was 13.3%. The upper bound of the one-sided 95% confidence interval for MACCE from the device safety cohort, including the safety and test arm subjects, must be less than 18.3%, including a 5% adjustment or non-inferiority margin.

In addition, the device cohort, all of whom were intended to receive a SENTINEL

device, was also compared to the randomized non-SENTINEL control arm.

The patient demographics for all three arms are displayed in this table. Demographic characteristics are well balanced without important differences between the three arms. To briefly summarize, these are elderly patients, on average more than 80 years old, with an equal distribution of men and women. The average STS scores were between 6.2 and 7.5%. Less than 10% of patients had either previous strokes or previous TIAs. Approximately one-third had diabetes, and one-third had a history of atrial fibrillation. There was a high frequency of significant comorbidities, including coronary artery disease and peripheral vascular disease. These were very symptomatic patients with more than 80% having New York Heart Association Class III or IV symptoms. The valve areas were approximately 0.7 cm^2, and the mean aortic valve gradients were above 40 mm.

Thirteen patients or 5.6% of the device arm did not receive a SENTINEL device: three who were never treated with TAVR, six where there was inadequate right upper extremity vascular access, three others where later review of the CT scans and angiograms indicated that the SENTINEL insertion should not be attempted, and one patient who was incorrectly placed in the control arm.

The SENTINEL access site was the radial artery in 94.4% of patients and the brachial artery in 5.6%. Both filters were deployed in 94.4% of patients, and at least one filter was successfully deployed in 99.6% of patients.

Relevant procedural factors are outlined in this table. Compared to control patients, the procedure time was extended an average of 13 minutes in the device cohort. Fluoroscopy time was also slightly longer by 2 minutes in the device cohort.

As mentioned, the performance goal, including the non-inferiority margin, was 18.3%. The primary safety MACCE endpoint in the randomized population with imputation for missing data was 7.4%. MACCE outcomes in the analyzed ITT population and the

as-treated population were 7.3 and 7.6%, respectively, as seen on this slide. The p-values compared with the performance goal were all less than 0.001.

This slide shows the same safety MACCE data for the three populations now compared to the 13.3% performance goal without the non-inferiority margin adjustment. Again, the p-values were highly significant for all populations.

Comparing the SENTINEL-treated patients, both the safety and test arms versus the control arm in the analyzed ITT population, MACCE was 7.3% in SENTINEL arms and 9.9% in the control arm. This difference was not statistically significant.

Thirty-day clinical safety results for the ITT population are shown on this table. Post-TAVR strokes were diagnosed in 5.6% of patients in the SENTINEL device arm versus 9.1% in the control arm, representing a 38% reduction that was not statistically significant. There was only SENTINEL-related vascular complication, a late post-discharge pseudoaneurysm at a brachial artery that was treated with thrombin injection without consequences.

The pre-specified endpoint was 30-day MACCE. However, since this is an accessory temporary device which is only in place during the procedure itself, it is also informative to look at differences in periprocedural stroke frequency. In this slide, all strokes in the SENTINEL versus control arms are displayed on Days 1, 2, and 3 as well as the total for the first 3 days. During this periprocedural observation period, there was a 63% reduction in stroke frequency in SENTINEL-treated patients, from 8.2 to 3%. The p-value was 0.052.

To summarize the safety data, the primary safety endpoint was achieved as the 30-day SENTINEL MACCE outcomes were below the pre-specified performance goal, and this difference was highly significant.

The 30-day SENTINEL MACCE of 7.3% was numerically lower than the randomized controlled MACCE of 9.9%.

The 30-day SENTINEL stroke frequency, which was 5.6%, was also numerically lower

than the 9.1% stroke frequency in controls.

A post hoc analysis of periprocedural strokes in the first 72 hours after TAVR indicated a greater reduction in strokes with SENTINEL, from 8.2% to 3%.

And there was only one SENTINEL-related access site complication.

I'd like to now introduce Dr. Renu Virmani, who will discuss the histopathology analyses.

DR. VIRMANI: Thank you, Marty.

And good morning. Thank you for the opportunity to present the results of the histopathology analysis from the SENTINEL trial.

The SENTINEL trial included a pre-specified histopathology and morphometric analysis plan for the captured debris in the filters. CVPath forwarded prepackaged kits to each site for the standardized collection and fixation of the debris; from the 105 patients in the test arm, received 210 filters. The material captured from these filters were processed and embedded in paraffin and sectioned. The contents of the slides were then classified by the type of tissue captured. The type of tissue identified consisted of acute and organizing thrombus, arterial wall with and without thrombus, foreign material, valve tissue, calcified nodules, and thrombus with or without myocardium.

In addition to analyzing the debris for the type of material, a morphometric analysis was performed to determine the size of the captured material. An automated analysis for the particle size was performed. The maximum and minimum dimensions of the five larger tissue pieces from each patient were measured. The morphology of the tissue was also characterized.

Materials were seen in 99% of the patients. Ninety-eight percent showed thrombus associated with other tissue, including foreign material. When you look at the type of material per patient, the most frequent captured tissue type was arterial wall in 94% of

patients. Valve tissue and calcified nodules were each found in 15% of patients. Foreign material was found in 35% of patients, myocardium 15%, and organizing thrombus in 7%. It is important to note that acute thrombus alone was only seen in 1%. Overall, 98% of subjects had the presence of tissue and/or foreign material, which are triggers for thrombus formation.

Our automated morphometric analysis of the debris showed virtually every patient had equal or greater than 0.15 mm debris. Ninety-one percent had debris equal or larger than 0.5 mm. Over half (55%) had a piece equal or greater than 1 mm, and 14% of patients had a piece of debris equal or greater than 2 mm in size.

We also looked at the number of particles collected that were greater than or equal to 0.5 mm. One in four patients, on average, had 25 particles in their filters that were greater than or equal to 0.5 mm in size. When the size of the captured tissue was manually measured, excluding thrombus only, we see that the relatively large debris was collected regardless of valve type.

Next, I'd like to show you images of the filter and debris from collected patients. First, I'll explain how we collected debris from the filter.

The first step is to take the debris from the SENTINEL filter, seen on the left, and filter through 40 µ mesh. The material is then processed, embedded in paraffin, and sectioned at 4 to 6 µ. Then the sections are stained with hematoxylin and eosin and Movat pentachrome stain for a total of five sections examined per filter. The tissue samples are then assessed by light microscopy.

The top two photographs of the filters are examples of both the distal and the proximal filter. The bottom two photographs show the material captured when processed through the 40 µ mesh. The histologic images, which are next to the photographs, are examples of the arterial wall and valve tissue. The proximal filter had larger amounts of

debris as compared to the distal. Both filters contained a combination of arterial wall and valve tissue and acute thrombus, which is magenta in color. The valve tissue can be recognized by the presence of elastin fibers stained black by the Movat pentachrome stain. The following four slides are organized in a similar manner as this slide.

Here I'd like to show you an example of a case where the filter captured predominantly valve tissue and calcium. There were more than 20 individual pieces of calcium in the proximal filter alone. Given that the calcium was observed in the form of nodules, the source most likely is from the aortic valve.

In this case, the filter captured primarily myocardium. Seven of the pieces consisted of myocardium with or without thrombus.

Foreign material was captured in 35% of the samples. In this patient, foreign material was found in both the filters, along with thrombus. The material is basophilic in character and non-cellular in nature. This material is nonresorbable and is likely to reside in the cerebrovascular tissues permanently.

Finally, I'd like to share the findings from this distal filter which contained the largest individual piece of debris captured in the study. The largest dimension of this sample was 5.4 mm in length, highlighted in red circle, and represents valve tissue with a piece of calcium. An obvious question to ask is whether the arterial wall material that is captured in the SENTINEL filters was generated by TAVR or by the SENTINEL.

As you can see here, TAVR devices are larger, stiffer, and have potentially more traumatic features than the SENTINEL device and are thus much more likely to be the source of arterial wall debris captured in the filters. In addition, the SENTINEL has an atraumatic flexible tip and contact with the aortic wall is minimal. Therefore, most of the arterial debris, I believe, comes from the aorta because TAVR traverses through the iliac artery, abdominothoracic arch, and ascending aorta.

In summary, tissue or foreign material combined with aortic thrombus was found in 98% of patients. Debris was captured from all valve types. Acute thrombus alone was observed in only 1% of the patients, valve tissue and calcium nodules captured in 50% of the patients, foreign material captured in roughly 35% of the patients, and one in four patients had 25 particles greater than 0.5 mm in size.

Thank you. Next, Dr. Leon will present the efficacy results of the SENTINEL trial.

DR. LEON: Thank you, Dr. Virmani.

I'd like to now present the SENTINEL trial effectiveness data from the neuroimaging substudy.

Serial 3 T scan acquisitions were obtained at baseline, at 2 to 7 days, and at 30 days on the same scanner. At all sites, the imaging core lab was certified according to the MRI technologist manual and approved by the MRI physicist. The MRI sequence is acquired or diffusion-weighted to detect acute changes, T2/FLAIR images to detect chronic changes, a B0 field map and high-resolution 3D T1-weighted anatomical images. The scans were transferred, queried, and accepted in real time.

The MRI analysis of new lesions included a blinded core lab analysis of all scans, serial co-registration and subtraction, artifact and distortion correction, and per-lesion quantification and longitudinal tracking.

In this example of serial DW-MRI scans, baseline and early post-TAVR images are juxtaposed next to the subtraction image which is used for lesion identification and quantification. The actual volumes of specific new lesions are shown to provide some perspective with regard to lesion size.

In this series of FLAIR images at baseline in three different patients, the spectrum of baseline pretreatment brain injury is shown, from almost none on the left to severe on the right image. Importantly, 99% of patients had abnormal baseline FLAIR images.

In this slide, the randomized population of the imaging cohort comprising the test and control arms is shown first. In 21% of these patients, serial MR studies at baseline and early after TAVR weren't performed due to various reasons, including clinical factors associated with high-risk TAVR patients, the need for new pacemakers precluding MRIs, and either the absence of a SENTINEL device implanted or a TAVR procedure performed. Paired serial DW-MRI images were obtained in 91 tests in 98 control patients, which was the analyzed ITT population.

The primary effectiveness endpoint was a surrogate endpoint based upon all imaging data that had been previously available at the time of trial design formulation in 2014. The surrogate endpoint, which was agreed to in consultation with the FDA, was median total new lesion volume in protected territories assessed by DW-MRI paired scans with subtraction performed at baseline and between 2 to 7 days after TAVR.

There were two study success criteria for this endpoint. Criterion No. 1 was statistical superiority of the test arm compared with the control arm in median new lesion volume, and Criterion No. 2 was an observed treatment effect of at least 30% reduction in median new lesion volume between the test and control arms.

The primary effectiveness analysis was performed in the analyzed ITT population and also was imputed for the total randomized imaging population to account for missing data. The randomized population with imputation was the primary effectiveness endpoint.

This slide shows the primary effectiveness results in protected territories for the randomized patients with imputation and the analyzed ITT population. Imputation for missing data was based on a predictive mean-matching method, and factors used in the imputation algorithm included the severity of valve calcification, BMI, TAVR type, the presence of procedural strokes, pre- or post-dilation, and mean aortic valve gradients. In the randomized patients with imputation, the median new lesion volume was 174 mm^3 in

control patients and 109 mm^3 in test patients, a 37% reduction which was not statistically significant. The p-value was 0.24.

In the analyzed ITT population, all of whom had paired serial DW-MRI scans, the median new lesion volume for control patients was 178 mm^3 compared to 103 mm^3 in the test arm, a 42% reduction which was also not statistically significant. The p-value was 0.33.

In this table, median new lesion volume in the analysis ITT population is presented for test and control arms in protected, partially protected, unprotected, and all territories. As you can see, in the unprotected territories there were no differences. Nor were there statistically significant differences in the partially protected territories. In fact, there were no significant p-values for any of the territory analyses.

This slide shows individual patient data in the five test and nine control arm patients with diagnosed clinical strokes after TAVR. Total new lesion volume and total new lesion number are represented on the y-axis. In this patient-based analysis in individuals with strokes, both the size and number of new lesions appeared to be diminished after SENTINEL compared with control.

The accuracy of predicting clinical strokes based upon the patterns of DW-MRI brain injury are problematic. These are 3D renderings of 2- to 7-day DW-MRI scans from three control arm patients with strokes after a TAVR. In the case on the left, it was a very large-volume lesion. In the center case, there were many smaller-volume lesions. And in the case on the right, there was only a solitary small lesion, perhaps in a critical location. Clearly, new lesion size or volume, which was selected as the surrogate primary effectiveness endpoint for this study, although important, is not the sole determinant of clinical neurologic events.

A potential additional source of effectiveness data derives from other randomized controlled trials using the SENTINEL Cerebral Protection System. Therefore, we are

presenting an individual patient-level meta-analysis of effectiveness, including all available randomized clinical trial results. The justification for considering this meta-analysis of all available data is the thesis that in retrospect the SENTINEL trial was underpowered to achieve its primary effectiveness endpoint.

This slide shows data from the CLEAN-TAVI randomized trial from which the SENTINEL study hypotheses were developed. The test arm results are consistent in both studies. But in the control arm of the SENTINEL trial, the observed new lesion volumes were much lower, and there was higher variability compared with design assumptions, contributing to a reduced power to discern significant differences between the groups.

There were two other randomized controlled studies with the SENTINEL cerebral protection device. We mentioned the CLEAN-TAVI study, which was a 100-patient, blinded, randomized trial at a single center in Germany and included 94 patients with serial 3 T DW-MRI scans. All patients in this study were treated with CoreValve TAVR. There is also the MISTRAL-C study, which was a 65-patient, blinded, randomized, multicenter trial conducted in Europe. Thirty-seven patients had serial 3 T MRI studies. These patients were treated with Sapien 3, Sapien XT, and CoreValve TAVR. And, of course, the third trial was the pivotal SENTINEL trial that we've just reviewed at length.

Each of these studies used the same primary effectiveness endpoint of serial DW-MRI imaging. All had similar study designs including inclusion and exclusion criteria and use of the SENTINEL versus control treatment. The first two studies were conducted solely in Europe and thus may represent a somewhat different patient population than the largely U.S.-enrolled SENTINEL trial.

A post hoc, single-stage meta-analysis was performed using a mixed linear model with the treatment group as a fixed effect and the study as a random effect. These forest plots for protected territories show the treatment effect for each of the studies and overall

for all studies. There is consistency in the effects. And combining the three studies involving 319 randomized patients, there is a statistically significant 38% reduction in mean new lesion volume with SENTINEL cerebral protection. The p-value was 0.017.

In this similar meta-analysis of all territories, there was a 24% reduction in mean new lesion volume. This was not statistically significant, but the p-value was 0.18.

We also performed an exploratory neurocognitive function substudy in the SENTINEL trial. A panel of neurocognitive function studies was carefully selected and customized to discern changes which would most likely be associated with diffuse cerebral embolic events. Five domains were assigned, including attention, verbal and visual memory, executive function, and processing speed. These were corrected for covariates of mental status and depression state. These examinations took approximately 1 hour to complete on each patient.

The trial design for the serial neurocognitive function substudy is shown on this slide. Of the 240 randomized patients, an eligible group of analyzed ITT patients had serial neurocognitive function studies at baseline and at 30 days. Ninety-three patients were in the test arm and 92 in the control arm.

The composite Z-score represents the sum changes from baseline for the five domains. There were no differences between test and control in the composite Z-scores. Similarly, there were also no differences in any of the individual domains between test and control.

The SENTINEL trial effectiveness results can be summarized as follows: With regard to the primary effectiveness endpoint, median new lesion volume in protected territories, there was an observed treatment effect of 42%, achieving and exceeding the pre-specified criterion. But the difference in new median lesion volume between test and control arms was not statistically significant. This criterion was not achieved.

Integrating the data from the post hoc meta-analysis of all three randomized trials, there was a significant reduction in total new lesion volume, providing additional evidence of effectiveness.

I'd now like to introduce Dr. William Gray, who will provide some important perspectives on the history of neuroprotection during cardiovascular procedures.

DR. GRAY: Thank you, Marty.

Good morning. My name is Dr. Bill Gray. I am an interventional cardiologist and assistant chief of cardiovascular services at Main Line Health in Philadelphia. I have served as national principal investigator for more than 15 clinical trials of coronary, endovascular, and structural heart interventions, with a special emphasis on carotid interventions. I have been asked to take a look at the results of the SENTINEL trial in the context of the nearly 15-year neuroprotection history that came before it.

When we look at the catheter-based filters used in carotid artery stenting, they are quite similar to the SENTINEL device. I have put several representative samples of carotid artery stent filter embolic protection devices on this slide as a comparator to the Claret SENTINEL, which is located on the right side of the slide. As you can see, they have several common features. Most importantly, they're all deployed on a 1/14,000th wire system from a collapsed state using a constraining sheath. Because there is such similarity between the filters used for embolic protection with carotid artery stenting and the Claret device, it is reasonable to compare these experiences. Perhaps the greatest difference between these devices is in how they were studied.

Although there are almost a dozen carotid approval or clearance studies involving filter embolic protection, the SENTINEL device nevertheless represents the first randomized controlled trial in filter embolic protection ever performed to assess the efficacy of the filter protection separately from the main procedure. As such, it's an admirable undertaking.

Because the SENTINEL device had no predicates, the metrics for measuring effectiveness were not well established. And because the incidence of important clinical events, such as stroke, are relatively infrequent, it would have taken a few thousand patients to power such a study, much more than is practical for a Class II accessory device. Therefore, surrogate endpoints like DW-MRI are used. Unfortunately, DW-MRI testing is still being refined as an endpoint, and issues surrounding the timing of the acquisition of the scans post-procedure, the effect of preexisting abnormalities on outcomes, the requisite Tesla strength of the magnets, and so on, have not been standardized.

Moreover, the metrics used for comparison and the expected treatment effect of filter embolic protection on this DW-MRI surrogate were not well established. As a result, the SENTINEL study power analysis was based on a very limited dataset, the only one that was available, the 100 prior patient outcome study using a similar device, not an ideal basis on which to predicate a pivotal clinical trial.

Moving from efficacy endpoints to safety, it is evident that these devices are safe. Vascular trauma from the use of filter embolic protection during carotid artery stenting is exceedingly rare and was not seen at all in the SENTINEL trial. This is not surprising given the parallels of filter construction already detailed. Further, adding to the device safety for both carotid and SENTINEL EPDs are the short filter dwell times.

The third observation about the carotid artery stenting and TAVR EPD is that both of them appear to capture significant amounts of liberated debris during the procedure. The ARCHeR study of approximately 400 patients is probably the most carefully run study of debris collected in carotid artery stenting embolic protection devices. This is the study that ultimately led to the first device approval in the United States.

In that ARCHeR trial, 57% of all filters collected had debris. The types of embolic material collected included a broad sampling of foam cells, smooth muscle cells,

cholesterol, collagen/elastin, and platelet/fibrin and were representative of the upstream lesion which was being intervened on.

In addition, 24% of the filters from ARCHeR had more than 20 particles. By comparison, in the SENTINEL study we saw approximately twice the debris capture and twice the number of filters with more than 20 particles as was observed in the ARCHeR study.

A fourth similarity between SENTINEL and carotid filters is the observed reduction in stroke. As mentioned at the beginning of my section, there are no randomized trials looking at carotid artery stenting with or without embolic protection, since all trials employed embolic protection in combination with a stent. However, there were several meta-analyses, the most prominent one which is listed here on the left-hand graph. In this meta-analysis from Garg et al., there was a 42% reduction in the overall rates of stroke after the introduction of a filter embolic protection device into the carotid artery stenting environment. In the SENTINEL study, a similar 39% proportion of reduction in the rate of stroke was observed.

Beyond these direct comparisons of filter protection, there are a couple other important perspectives to bring. Carotid artery stent device approval in the United States actually took place in 2004. This approval led to a significant increase in the use of filter-protected carotid artery stenting, with procedural volumes increasing nearly 15-fold from approximately 5,000 before approval to about 75,000 in the same span of years of approval. This marked increase in carotid artery stenting volume was associated with a demonstrable 50% reduction in overall complication rates after device approval. It is felt that these significant improvements in patient outcomes are likely secondary to the widespread adoption and availability of embolic protection and refinements in patient selection and operator technique. The point here is that the SENTINEL filter embolic protection device

and trial are really just the beginning of embolic protection experience in TAVR and that, if approved, it appears that improvements in patient outcomes could be expected for very similar reasons.

In summary, the prior history and experience with filter embolic protection in carotid stenting brings five perspectives to the SENTINEL data:

First, SENTINEL is the first and only FDA IDE trial to isolate and separate embolic protection and assess its neuroprotective effects when linked to a specific procedure, in this case, TAVR.

Second, the SENTINEL safety profile is good and consistent with prior carotid artery stenting embolic protection studies.

Third, like carotid embolic protection, SENTINEL filter collection resulted in a higher percentage of debris capture.

Fourth, the incorporation of SENTINEL into TAVR resulted in stroke reduction proportionate and similar to that seen in the adoption of carotid artery stenting embolic protection.

And lastly, further patient outcome improvements, specifically stroke, can be anticipated once TAVR EPD is more broadly available, based on prior similar filter embolic protection experience in carotid stenting.

Thank you for your time. And I'd like to now to invite Dr. Azin Parhizgar to the lectern to conclude this presentation.

DR. PARHIZGAR: Thank you, Dr. Gray.

Good morning. My name is Azin Parhizgar. I am the president and CEO of Claret Medical. I would also like to thank the FDA and the Panel members for the time you've spent in reviewing the SENTINEL data and preparing for this meeting. Claret Medical is a start-up company whose sole focus for the last 8 years has been to develop the best

cerebral protection device in order to address the unmet clinical need of protecting a patient's brain from acute embolic ischemic injury or stroke.

The SENTINEL is an accessory device with a 4-year history of use outside of the United States. SENTINEL is the first U.S./European, multicenter, randomized controlled embolic protection device trial, and it provides confirmation of safety and benefit of embolic protection in a dynamically and rapidly evolving main therapy, and that is TAVR.

For the primary effectiveness analysis of MRI-based new lesion volume, one statistical criterion was not met, as the treatment group was not statistically superior to the control. The second criterion was met with an observed treatment difference between test and control arm of greater than 30%. While we failed to show a statistically significant difference in reducing MRI lesion volume, the clinical relevance of amount of debris collection is clear.

Here are examples of debris from the use of SENTINEL in some TAVR patients. I would like to underscore that we collected debris in 99% of all SENTINEL samples analyzed, and debris was variable in size and nature. And as we mentioned earlier, one in four patients had, on average, 25 particles in their filters that were greater than or equal to 0.5 mm in size.

The importance of debris collection can be extended to the results seen in the composite endpoint of MACCE and observed stroke rates. The use of the SENTINEL device resulted in a 30-day rate of MACCE that met the performance goal of 18.3%. This result was consistently seen in all three analysis populations and remains statistically significant even against the calculative MACCE rate of 13.3%.

If we look at the stroke within the first 3 days of TAVR, which is the time frame where SENTINEL as an accessory device during the procedure will provide the greatest benefit, we will see that stroke rates are 3% versus 8.2%, and this is a 63% relative observed

difference.

In summary, the SENTINEL trial demonstrated that SENTINEL is safe and it performs as intended, with minimal adverse effects and without disrupting the TAVR workflow. This study also demonstrated reduction of periprocedural stroke rate when SENTINEL was used, and it yielded a 42% observed treatment effect in median lesion volume. Importantly, SENTINEL captured a wide spectrum of embolic debris in practically all patients.

If the de novo is granted, Claret is committed to a significant training program. Our commercial training program will mirror the program that was proven to be highly effective as a part of our IDE training module. It will include the following: a comprehensive didactic training segment, hands-on learning with an appropriate anatomical model, as well as up to a five proctored case training with a Claret clinical specialist. This training program was well received as we prepared each IDE site in the SENTINEL trial, and the paucity of the SENTINEL-related adverse events is a testimony to the effectiveness of the training and close monitoring.

We're also fully committed to working closely with the FDA in developing a robust postmarket surveillance program that is reasonable and appropriate for this class and type of technology. We will commit to collecting more device performance data to ensure the safety results seen in the SENTINEL trial translated to a successful commercial roll-out. The collection of data can be standalone registry or a TVT module with limited number of sites consecutively enrolling patients.

In conclusion, the company believes that the SENTINEL device can be a valuable tool for the interventional cardiologist as well as the cardiac surgeons in order to safeguard their patients when they assess benefit-risk of the TAVR procedure for their individual patients.

I'd like to thank you for your time and attention. With the permission of the Chair, we look forward to answering all your questions.

DR. PAGE: Thank you. I'd like to thank the Sponsor and the speakers for very clear and concise presentations.

Now I'll open the meeting to the Panel, looking for brief clarifying questions for the Sponsor. Please remember that the Panel may also ask the Sponsor questions during the Panel deliberation. And I've seen Dr. Somberg and Dr. Borer.

Dr. Somberg.

DR. SOMBERG: I have two areas of questions. One is I think there's going to be a lot of importance, at least in my mind, to the meta-analysis and I was asking for a little bit more detail. When I was reading the panel pack, it said that a mixed effects model was used. I noticed your forest plot is not the traditional one with the point -- the effect size, magnitude of the point correlating the contribution to the forest plot.

Can you present later on, after maybe lunch, the fixed effects model, a random effects model? And if you chose the random effects or if there was a difference, was there a covariate analysis done? So some of this detail would help me in understanding that.

DR. PAGE: So Dr. Borer, you've asked for some work to be accomplished over lunch.

DR. SOMBERG: I'm Somberg.

DR. PAGE: I'm going to ask FDA as to helping me keep track of any homework assignments over lunch. Who's going to help with that? Okay, I see someone raising their hand.

DR. BROCKMAN: We'll take care of that.

DR. PAGE: What I'll do is look to you to make sure you have captured the question asked so I'm not having to repeat the question.

And likewise, was the question clear to the Sponsor in terms of what you can answer now and what you might be asked to accomplish over the lunch break?

DR. LEON: I think, to have those data, particularly to have them represented in

graphic form, would take a few moments. So I think after the lunch break we'll be prepared to fully answer that question and provide the necessary details, which are entirely reasonable, with respect to the meta-analysis.

DR. PAGE: And FDA, are you clear on what the question is? Okay, good. Thank you.

And Dr. Borer, I'll ask you to go ahead and ask one more question, and then after that, we're going to go around the table.

DR. SOMBERG: It's Dr. Somberg.

DR. PAGE: Did you have another question?

DR. SOMBERG: Yeah. My other confusion, I think, is more likely to be characterized, is on page -- oh, let's see now. This is the volume on page 34, Slide 68.

DR. PAGE: Could we put up that slide, please?

DR. SOMBERG: Could you go through this a little bit more, because it seems to me that when you go from the protected area to the unprotected area, the median new lesion volume vitiates, and why is that? Do you have any comments? Is there a potential for differential effects to the unprotected area because why would that go away?

DR. LEON: It's a very good question. Again, the study was powered to show differences in the protected zones, and the first column in this table represents the data that we previously showed in the ITT, the analyzed ITT population. The difference between the protected zones and all territories, which is the bottom column, represents either those partially protected or unprotected. Certainly, there is the potential that there could be shunting or actually worsening in the unprotected zones. We did not see that looking at the median new lesion volume, as shown on this slide. In fact, there was very little material in the true unprotected zones. We used median rather than mean because that had been the standard for previous trials, and based upon the skewedness of the data, the partially protected zone, there were slight differences that were obviously not significant, suggesting

that there was no benefit and no detriment in those zones. So it's an effort to show all of the data, the major differences clearly being in the protected zone.

DR. PAGE: Thank you. I've seen Dr. Borer, then Dr. Cigarroa, then Dr. Yuh.

Dr. Borer.

DR. BORER: Thank you. First, thank you very much. I thought that was a lovely presentation that the Sponsor presented.

I have a question for Dr. Virmani and anyone else who wants to answer. The filters appear to me to be delicate structures, and they have to be resheathed at the end of the procedure, which would seem to me to lead to the potential for shearing and damage to the filter with release of maybe pieces of the filter. Now, you wouldn't see that because they wouldn't be captured by the filter, but you did put these filters in paraffin. I wonder if there was any evidence of damage to the filters, any holes in them, anything that would suggest that when this procedure is performed, often in tortuous vessels, that the filter might be damaged and might add to the injury.

DR. LEON: I think that's a great question. Let me begin to answer, and then I'll have Dr. Virmani come up and deal with the histopathology or the paraffin-embedding light microscopy.

These are the same filters we've been using in carotid stenting for 15 years. They're a 140 µ pore size, they're polyurethane, and there is a nitinol hoop which tends to pivot depending upon vessel size. When the filters are retracted, the actual filter itself is pleated, and it's designed in such a way that there is no loss of embolic material. This has been tested in animals, and it's been tested on the bench, so the likelihood that retractional retrieval of the filter would actually lose material would seem to be extremely low. Whether or not there was actually damage to the filters, I'll ask Dr. Virmani to address.

DR. VIRMANI: The filters actually are not put in paraffin. It is really the debris; we

take it out and then put it in paraffin. The filters were really intact. We have done in animals scanning electron microscopy. We've never seen damaged filter.

DR. PAGE: Thank you, Dr. Borer.

Dr. Cigarroa.

DR. CIGARROA: I have two types of questions. One is a simple one. For Slide 74, which was the meta-analysis of effectiveness, change in mean new lesion volumes, could that be presented in the afternoon as median so that I have a comparison relative to how the randomized trial was done?

DR. LEON: We certainly can respond to that. It's a little bit more difficult to normalize the data. So these data were normalized to be able to represent the mean lesion volume, but we'll do our best to give you a sense as to what the median new lesion volumes would look like in a meta-analysis as well.

DR. CIGARROA: Thank you.

DR. PAGE: So is that clear in terms of the question? You're going to be able to do that over lunch?

(Off microphone response.)

DR. PAGE: Thank you.

DR. CIGARROA: The second is a periprocedural issue. There are known factors during the procedure that are associated with an increased risk for embolic material, and I was wondering whether or not this afternoon three bits of data could be shared with us regarding the periprocedural. Number one would be the pre- and/or post-dilatation between the test and control arms. The second would be the use of general anesthesia versus conscious sedation. And the final is in the carotid -- correction, in the carotid stenting trials, we learned that it's not only the issue of embolic material resulting in the appearance of DWI changes, but also the degree of hypotension. And so hypotension

coupled with or without embolic material can be associated with changes on MRI finding by DWI. Do we have any information between test and control regarding the degree and persistence of hypotension?

DR. LEON: Those are all very relevant. A little bit difficult to answer all of those questions. Certainly, the pre- and post-dilatation numbers we can easily provide. I can tell you straightaway that there were no differences between test and control. There were differences among sites because there's an operator preference issue and also valve types with respect to pre- and post-dilatation. But overall test and control, there were no differences.

Certainly, the issue of hypotension is something we struggle with because we do rapid ventricular pacing to induce hypotension to even deploy some of these devices. However, we did not see any systematic differences. We did look at intraprocedural blood pressure. Nor did we see evidences of persistent hypotension that we felt might have been associated with a neurologic event. But we'll review the data again just to be certain that we give you a complete answer.

DR. CIGARROA: Thank you so much.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Yuh.

DR. YUH: Thank you very much.

One thing that's been kind of bothering me throughout this, or just causing questions with respect to the control or test arms or both, did you see differences in the volume of embolic load to the brain or insult to the brain amongst the different devices, the Sapien XT versus the Sapien 3? I know you had said that there were no formal stratifications between the different devices, but what I'm trying to get at was is, is the challenge to the device, to the protection device. Is it different between the different

devices? Between the different TAVR devices, rather? And that goes to relevance of the data going forward. You have two rapidly developing technologies evolving in parallel essentially, and for statistical analysis it seems more complicated. So basically, did you see differences in the challenge, the embolic challenge between the different TAVR devices, with respect to this protection device?

DR. LEON: It's a great question. This study was burdened by the fact that four different devices were made available during the course of what was an 18-month enrollment period, certainly making it very difficult to isolate the effects of specific valve types. The study was not designed intended, and it would be inappropriate to infer specific valve type inferences based upon the small sample size and the lack of stratification during randomization for valve type, and the fact that the use of the valve or the decision about the valve was made after randomization and was highly operator and site dependent.

With respect to embolic debris, as Dr. Virmani showed, there was embolic debris that was collected -- and I'll show you the slide once more -- from every one of the devices, and significant amounts of embolic debris from the standpoint of number and size. So we did not see any material differences in the embolic debris in the test arm of the randomized portion where we collected the filters relative to valve types. But I want to again hasten to add, we struggle with this analysis because it was neither powered nor intended.

DR. YUH: But you didn't see -- or did you compare the MRI findings between the different TAVR devices in terms of total volume of embolic load to the brain?

DR. LEON: So you're asking for the MR data, not the embolic debris data?

DR. YUH: The MR data, right. An MRI --

The mean embolic volume in MRs in the control arm, in patients in the control arm versus the mean embolic volume in patients with -- between the different devices, rather. Did you see, in other words, a higher volume of MRI insult in the Sapien 3 versus the Sapien

XT patients?

DR. LEON: It's a very difficult question to answer because, as we look at these data, it is so confounded by so many things that I can't isolate valve type as being the only descriptor. When you use a valve that is a procedure, the frequency of pre- and post-dilatation is different. The baseline lesion burden was different with some of the valve types. The bias of the operator, in terms of what valves we used and what kinds of patients, factors into this. So we can certainly share the data, but we strongly advise against trying to interpret that as meaning that there really is a difference among valve types, because these confounders are irresolvable.

DR. PAGE: If I may follow up for just a moment, Dr. Leon. Did I hear you correctly, that the decision of which valve was used was left to the operator after the randomization to protection or not?

DR. LEON: Correct.

DR. PAGE: And is it possible that that would introduce any bias in terms of the operator, in terms of knowing that there was protection available, or did the operators just use whatever they thought was best or have their own protocol?

DR. LEON: I'm sure, theoretically, that that could have introduced bias. But I will tell you, knowing these sites and these investigators, the decisions were based upon clinical and anatomic factors, not whether or not protection was or was not available.

DR. PAGE: Great. Thank you.

Dr. Good.

DR. GOOD: Thank you very much. I'd also like to compliment the Sponsors on what I think was a very clear and a fairly well-balanced presentation. Thank you very much. I did have a couple -- one comment and then two questions. First of all, I appreciate the fact that neurologists were involved throughout this study. We know from prior studies that the

involvement of neurologists certainly changes the frequency of stroke. This has been well shown, and so I compliment you on that. I also compliment you on the fact that you did neuropsychological testing, and I'll be interested in what my neuropsychology colleagues have to say about that because obviously we're concerned about a possible burden of cognitive problems that could be long term even in these patients.

Now my two questions: First of all, and you may have to speculate on this, do you have any thoughts about the reason for the strokes that did occur, the DWI abnormalities that did occur in the protected territories? Now, it seems to me there are a couple possibilities. One might be the apposition of the valve against a vessel wall, if it's incomplete. Another might be that although most of the strokes were Day 1, that these could be after the protective device was removed. And probably you can't really say this, but perhaps you might want to speculate on that because obviously the protection was not complete.

The final question I had was really related to the pathology. On the material that we got from the Sponsor, on page 49, 7.5.1, this is a summary of the histopathological outcomes, and bullet point 3 says foreign material was speculated to be catheter coating and was captured in 35% of patients. But that's not what we heard from our neuropathologist, and I'm wondering if that's true, if this is catheter coating, whether that could somehow be improved and perhaps decrease the number of embolic events.

DR. LEON: Well, they're both interesting and speculative questions. Let me show you the slide again, looking at what we think. Even though the primary endpoint really relates to 30-day clinical outcomes, when you're dealing with a temporary accessory device, it at least is our opinion that looking at what we believe to be a more periprocedural time domain is more relevant, and obviously there appears to be a greater stroke reduction in that more relevant time domain. It turns out that 70% of the strokes in this study were in

the first 72 hours, and all of the strokes were in the first 7 days.

The issue about what happened in protected zones and how could you -- even with protection, how could you have a stroke -- actually within 72 hours there was one stroke in protected zones, and that one stroke was someone who had transient ataxia with a modified Rankin score at 30 days of zero. So there were not very many strokes in protected zones during that 72-hour period.

With respect to the particulate, this is something that we've seen before, and Dr. Virmani certainly can discuss this. Whenever you put guide wires, balloon catheters, large devices, and you transit them through a complex arterial tree and across valves, there is an effect of liberation of material. And so we don't believe this material is coming from the filter. We believe it's coming from all of the other accessory devices that are used during the course of the actual therapy itself, and it's not particularly uncommon to see that. It's important that this material does not resorb so it is permanently resident in the brain. We were surprised that 35% of patients did have catheter-related or based foreign material.

DR. PAGE: Thank you.

I have Dr. Peavy, Dr. Brinker, Dr. Roberts, and Dr. Naftel. And before the close, I will call on our Industry, Consumer, and Patient Representatives. But next, Dr. Peavy.

DR. PEAVY: Yes. It appears that the neuropsychological statistical outcomes were influenced by the power and by floor effects. So a question that I had that would help to understand the data better would be how impaired neuropsychologically the subjects were prior to the procedure. So if you have means even on the more global scales like the Mini-Mental and the MoCA for the two groups prior to the procedure, that would be helpful.

DR. LEON: We do have Mini-Mental status exam data. We don't have MoCA data, but I'm showing a slide which is representative of the neurocognitive function data. This is

looking at executive function, which we think is one of the more important domains. One of the reasons why we were concerned about the outcome and tried to explain why we didn't see any cognitive improvement at least, we feel, was this was an elderly, comorbid, frail population with more than 40% of patients having greater than one and a half of a standard deviation reduction in baseline neurocognitive function compared to average for age. And we felt that those very severely impaired individuals, which was very common in this study, may have influenced our ability to discern a difference.

DR. PEAVY: So at baseline they were -1.5?

DR. LEON: More than 40% had greater than one and a half standard deviations below the average for age.

DR. PEAVY: More than 40%. That includes both groups?

DR. LEON: Yes. Yes.

DR. PEAVY: Because you wouldn't necessarily assume that they are cognitively impaired.

DR. PAGE: Dr. Duff, do you have a comment about this specific issue?

DR. DUFF: Yeah.

DR. PAGE: Yes. Go ahead, please.

DR. DUFF: In the Executive Summary, in Table 44 they do list baseline scores on the neurocognitive tests, and from my read of it, executive functioning is the only one that shows significantly lower scores at baseline. The Z-scores for most of the other cognitive domains sort of hover around zero. So I think the figure that you showed, executive functioning is one domain that's affected. But when we look at the other ones, they don't seem to be nearly as impaired at baseline. In fact, the Mini-Mental status exam score at baseline for the test and control groups are both about 26.

DR. PAGE: This is a very valuable area for us to be discussing after the break.

DR. DUFF: Yeah, sure. I just wanted to bring out that --

DR. PAGE: So thank you for pointing that out.

DR. DUFF: -- data is available.

DR. PAGE: Thank you for pointing that out.

DR. LEON: Yeah, we do have additional data, and what I'd like to do is to have Dr. Lazar, who really supervised all of these data, perhaps explain it more articulately than I could.

DR. PAGE: Why don't we --

DR. LEON: But we do have more data that we're glad to share with you.

DR. PAGE: That would be great. We'll do that after the lunch break.

I still have on deck Drs. Brinker, Roberts, Naftel, and Dodd. We have 12 more minutes, and I also want to hear from our other representatives. So I will ask for just single, brief clarifying questions specifically that we need to address now. We will have more time to ask questions of the Sponsor and discuss.

Dr. Brinker.

DR. BRINKER: Marty, just to put things in perspective, do you have 6-month stroke and death data?

DR. LEON: I don't have 6-month data to present, but we can see what we have in our datasets. The endpoint was a 30-day endpoint.

DR. BRINKER: Right. But when you present the 72-hour endpoint, there's a significant or trending significant difference between the two groups, but by 30 days it's no longer significant. And I wonder what the reasonable impact of the procedure is at 6 months.

DR. LEON: Yeah. Well, 6 months was certainly not a clinical time point for follow-up. I'm sure these patients were followed at a year, but certainly not the entire group has been

followed at a year, yet. So our feeling is that if we're looking for a device that's going to have a periprocedural effect, that we need to look at the earlier time points. There is a lot of confounding when you start looking at strokes at a year, 2 years. You'd have to take into account all the other variables that affect stroke.

DR. LEON: I'm looking to see if we have any 1-year data.

DR. BRINKER: Okay, thank you.

DR. PAGE: Thank you.

Dr. Roberts.

DR. ROBERTS: Yes, thank you for a wonderful presentation. My question is about the, to me, black box of the imaging processing and if someone could give maybe a short discussion or presentation on how the images were processed, giving the importance of the image processing to the endpoint.

Several specific questions, such as were ADC values used for increasing the specificity of the DWI images? I think I understood that angiograms were performed. Pre-procedural, was there any use of the patient's variant vascular anatomy to help with determining protected and unprotected territories? Was FLAIR imaging done? Could you give specifics on the 2- to 7-day window when the imaging was performed during that time period and also how lesions were actually measured? That registration process is very difficult. I've done several studies with that. And so if someone could explain how that was done.

DR. LEON: Sure. I'm definitely not the someone who could explain all of those things. I can tell you, you know, we specifically used 3 T scans. It was the same scanner in each patient. We had baseline scans which were very informative to us, and there was, we believe, highly sensitive subtraction technology that was applied to be able to identify and quantify lesion size. We did do FLAIR imaging and FLAIR imaging at 30 days. But we'd be

glad to address a lot of these specific methodologic issues, and we'll have our directors of the neuroimaging core lab address that. Thank you.

DR. PAGE: That would be valuable after the lunch break. Thank you.

Dr. Naftel.

DR. NAFTEL: In looking at your -- first of all, nice presentation. I appreciate it. In looking at your new lesion volumes, you chose to compare the median, and you'd specified that before, and I actually totally agree. However, I sure would like to see the distributions of a box plot or something I really want to see, because the median is just one aspect of that. So I'd like to see the entire distribution for all the comparisons. That's one thing.

And you said just one question, but a second one. Forgive me --

DR. PAGE: You get a second one here, Dr. Naftel.

DR. NAFTEL: Forgive me for being a naive statistician, because I really am. But a question I don't know: Do these filters impede blood flow, and as they're capturing debris, do they even more impede blood flow, or is that a nonissue?

DR. LEON: Well, I think it's not naïve, and it's a great question, your second question. They're 140 µ in size. So unless you completely clog the filter, we don't anticipate -- and in multiple, both animal and in vitro models, there's no significant reduction of blood flow to the brain. We did not have any filters that were so filled with material that it would have impeded blood flow from any of the analyzed filters in the test arm that we saw. But that's a very good question.

With respect to showing the full distribution of data, we did show in this slide the interquartile ranges, but we'd be glad to show you the medians and the box plots that would go along with this, to be able to show you the distribution of data for the median new lesion volume.

DR. PAGE: That would be valuable. Thank you very much. And we'll look for that

after the lunch break.

Dr. Dodd.

DR. DODD: Yeah, I have several questions, but I will focus on just one which relates to surrogacy. A surrogate endpoint is an endpoint that gives the same result as a clinical benefit endpoint, and a clinical benefit endpoint is something that measures how a patient feels, functions, or behaves. So I would like to know, after lunch, what data existed prior to the start of the study or exists now that convinced us that this lesion volume in the protected territory only is, indeed, a surrogate in this sense.

DR. LEON: I think that's an important question and certainly one that we struggle with. In retrospect, we think this was an imperfect surrogate endpoint, and we can give you all the reasons for that when we come back and try to outline. At the time, we had to use the data that was available in 2014, which was a single randomized trial with what we thought was rigorous methodology upon which to base what we felt was the best surrogate endpoint that was available to allow us to do a randomized study with a quantitative efficacy endpoint. In retrospect, there are many things we learned during this study which speaks to the fact that this was an imperfect surrogate endpoint. And, in fact, we were both underpowered, and I don't think that this particular endpoint, by itself, reflects the clinical events that we're trying to prevent or reduce.

DR. PAGE: Thank you.

Dr. Hammon, did you have a question?

DR. HAMMON: Yeah, just one question. It's unusual to do a big study like this without having a true control group, and I realize it's unethical to put the catheter in a normal human, but I noticed that you've done extensive dog studies or pigs or whatever the animal. Did you find any vessel material or any other foreign material in the baskets at the end of those studies, and were there any problems related to the neurologic function in the

animals?

DR. LEON: That's a great question. I'm not quite sure how to analyze neurologic function in the animals, but --

DR. HAMMON: How about imaging?

DR. LEON: We did not do any neuroimaging in the animals, no. What we did do is -- and we used porcine rather than canine models, and we did do extensive animal work with dwell times that were as long as 3 hours to see if there was anything associated with the filter itself that could be deleterious. We didn't find any acute thrombus, we didn't find any particulate, we didn't find any injury to the arterial wall in those animal studies. So we believe and, based upon a 3,000-patient experience outside the United States and a 15-year history with carotid filters, we felt that there was nothing that we could identify that would suggest that this was anything other than a safe device. But we did not do neuroimaging in the animals, no.

DR. PAGE: Thank you. This has been very valuable. I'd like to now call on our Consumer, our Patient, and our Industry Representatives, if they had any specific question, a brief clarifying question for the Sponsor.

Mr. Frankel?

MR. FRANKEL: Yes, just a couple of quick clarifications. One is a follow-up to Dr. Yuh, if it would be possible to provide per TAVR device data of the outcomes of stroke and neurocognitive testing per TAVR device used.

DR. LEON: It's possible to show anything, but again we're going down a road where we feel very strongly, and the FDA certainly agrees in their analysis, and you know, they can express their own opinions. But to try to attribute device-specific effects would be problematic and confounded by the marked differences, all of which influence outcomes beyond just the device used.

MR. FRANKEL: Okay. And a quick follow-up to Dr. Good. Would you be able to provide any additional information -- in your paper you mention that the placement of the device may have been a cause of some of the lesions seen in the protected area. Do you have any additional data that supports that possibility?

DR. LEON: We don't have any direct data that the device placement has been responsible for any neurologic clinical events, no.

MR. FRANKEL: And two other quick --

DR. LEON: It's theoretically possible.

MR. FRANKEL: I just saw that it was noted in the paper, that possibility.

DR. LEON: I think we can speculate. We didn't see any dissections, we didn't see any perforations, we didn't see an in situ thrombus that we were able to identify angiographically that might have suggested that there was something associated with the filter placement that might have caused sufficient injury to result in a neurologic event.

MR. FRANKEL: Okay. In Dr. Naber's 2012 paper there was an antiplatelet pretreatment protocol in place.

DR. LEON: Yes.

MR. FRANKEL: Was there one in here as well?

DR. LEON: Absolutely, yes.

MR. FRANKEL: And was it the same?

DR. LEON: I don't recall that specific reference, but I can tell you what we usually do and what we have recommended, which is dual antiplatelet therapy, which is aspirin and thienopyridine for at least 1 month and the recommendation is up to 6 months. Obviously, a third of these patients had atrial fibrillation. Many of them are on warfarin. They're elderly patients. So this is left to the operator discretion with respect to what's safe for a given patient, but those were the recommendations.

MR. FRANKEL: And finally, in the MISTRAL-C paper --

DR. PAGE: We've got to move on here.

MR. FRANKEL: -- was there --

DR. PAGE: Mr. Frankel, we've got to move on here.

Dr. Posner.

DR. POSNER: Well, most of the questions have been asked. Just very simply, pre- and post-valve replacement, there's going to be an increase in cerebral blood flow, and I wonder if you have change in the various areas that were measured pre- and post-valve replacement.

And to get to the thing that other people have asked, the different valves that go in have different effects in inducing arrhythmias, septal changes, and possibly pulmonary outflow changes. And I know you can't put them together, but can you use that as some way of analyzing cofactors in the ones that you did see some problems with? Not to say it was the valve versus the filter, but there's a lot going on with the valves, and just to know that if the problems that you saw afterwards happened to occur in one and induced arrhythmias that induced pulmonary outflow changes, etc., etc.

DR. LEON: We didn't see any instances of left ventricular outflow tract obstruction associated with these aortic valves, at least in this study, and the frequency of either arrhythmias or conduction abnormalities is different among the different valves. The self-expanding devices have a higher frequency of conduction disturbances that necessitate the use of new pacemakers. There's no important difference in the frequency of post-procedure atrial fibrillation, which occurs in between 10 and 15% of patients irrespective of which valve is used.

DR. PAGE: Thank you.

And Mr. Thuramalla, did you have any brief clarifying question for the Sponsor?

MR. THURAMALLA: Yes. So, firstly, thank you for the excellent presentation. I have a very brief question. On Slide No. 37, the SENTINEL access site, radial was 94% approximately and brachial is about 6%. Do you anticipate any difference in the device success or complications associated with the different SENTINEL access sites?

DR. LEON: The one important access site complication did occur in a brachial artery. So when we use the brachial artery, it's usually because the radial artery is diseased and it may be a marker for more disease. So there certainly potentially could be more access site-related complications when the brachial artery is used. In this study it was 6%. Since there's only one complication, it's a little bit hard to generalize. Certainly, in the real-world setting in Europe, the brachial artery is used, but used infrequently. Even the ulna artery has been used, and access site complications have been exceedingly rare.

DR. PAGE: Okay, thank you very much to the Sponsor.

With that, we will move on and take a 15-minute break or a 14-minute break. We'll resume promptly at 10:15. I'll remind the Panel members not to discuss the meeting topic during the break amongst yourselves or with any member of the audience. We'll see you back at 10:15. Thank you.

(Off the record at 10:01 a.m.)

(On the record at 10:17 a.m.)

DR. PAGE: I'd like to call the meeting back to order. The FDA will now give their presentation.

I'd like to remind 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.

The FDA will have 90 minutes to present. Please begin. And welcome.

CDR TOOR: Good morning. My name is Sadaf Toor, and I am the lead reviewer for

the Claret Medical submission being discussed today.

The FDA review team for this submission is comprised of the following individuals: From the Office of Device Evaluation, myself; medical officers Donna Buckley and John Laschinger from the Division of Cardiovascular Devices; Peter Como and Claudette Brooks from the Division of Neurological and Physical Medicine Devices; and Lawrence Rodichok from FDA's Center for Drug Evaluation and Research, Division of Neurology Products; as well as biomedical engineers Victoria Rodriquez and Ryan Randall.

DR. PAGE: Could I ask you to speak a little closer to the microphone?

CDR TOOR: Oh, sorry.

DR. PAGE: And if we can increase the volume, that would be helpful. Thank you.

CDR TOOR: Sorry. I'll start with the review team again, in case anybody missed that. So from the Office of Device Evaluation, myself; medical officers Donna Buckley and John Laschinger from the Division of Cardiovascular Devices; Peter Como and Claudette Brooks from the Division of Neurological and Physical Medicine Devices; and Lawrence Rodichok from FDA's Center for Drug Evaluation and Research, Division of Neurology Products; as well as biomedical engineers Victoria Rodriquez and Ryan Randall, both from the Division of Cardiovascular Devices. From the Office of Surveillance and Biometrics, mathematical statisticians Li Ming Dong, Nelson Lu, Jianxiong Chu, and Terri Johnson.

The FDA presentation will be broken up as follows: I'll begin with an introduction and brief summary of the SENTINEL study design. This will be followed by presentations on the clinical and statistical results and considerations. I will then provide concluding remarks.

My introduction will cover a description of the SENTINEL device, the proposed indications for use for the device, an overview of the key regulatory milestones related to

the submission, an overview of the SENTINEL study design, and the primary discussion points FDA would like you to keep in mind for the afternoon session.

The SENTINEL is a 6 French, 95 cm working length, single-use, temporary, percutaneously delivered embolic protection catheter inserted into the right radial or brachial artery. The SENTINEL system employs two embolic filters consisting of nitinol frames and polyurethane film. The film is laser drilled with 140 µ holes.

The device is designed to protect three of the four cerebral vessels. Protected vessels include the right carotid and right vertebral arteries with proximal filter placement in the brachiocephalic artery, as well as the left carotid artery with distal filter placement in the left common carotid artery. The device does not protect the cerebral circulation supplied by the left vertebral artery. The proximal filter measures 15 mm in diameter, while the distal filter measures 10 mm in diameter. Following the percutaneously valve placement procedure, the system is removed.

The indication proposed by the Sponsor is "The SENTINEL Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain periprocedurally. The diameters of the arteries at the site of filter placement should be between 9 and 15 mm for the brachiocephalic and 6.5 to 10 mm in the left common carotid."

I'll now provide some background on the regulatory history of the de novo submission being discussed today.

In February of 2014 FDA conditionally approved the IDE for the SENTINEL study, allowing initiation of enrollment of U.S. subjects to the study. At the time, only the Sapien XT valve was commercially available in the U.S. The first patient was enrolled in the study the following October.

In May 2015 FDA approved modifications to the SENTINEL protocol, allowing the use of the newly available Medtronic CoreValve System. Approximately 10% of subjects had been enrolled at the time of this request.

Similarly, in July 2015 FDA approved modifications to the SENTINEL protocol, allowing the use of any FDA-approved TAVR device in order to accommodate use of newly available TAVR devices in the SENTINEL study as they became commercially available. Approximately 15% of subjects had been enrolled at the time of this request. The last patient was enrolled in the study in March 2016.

In May 2016 FDA approved a continued access portion of the study, but it was ultimately not pursued by the Sponsor.

On September 20 of 2016 FDA received de novo request DEN160043, the subject of this Advisory Panel meeting. The submission included the SENTINEL study clinical study report.

FDA would like to remind the Panel that the purpose of this meeting is to obtain input on critical aspects of the supporting clinical data. The Advisory Panel will not be asked to provide input on other regulatory aspects of the de novo pathway.

The objective of the SENTINEL study was to assess the safety and effectiveness of the Claret Medical SENTINEL Cerebral Protection System used for cerebral protection during TAVR compared to TAVR without cerebral protection.

The study is a prospective, single-blind, multicenter, randomized study using the SENTINEL system in patients with severe symptomatic calcified native aortic valve stenosis indicated for TAVR.

After successful CT angiography screening evaluation, baseline study assessments and patient selection criteria eligibility, patients were randomized in a 1:1:1 fashion, as depicted here. Patients in the safety arm received the SENTINEL system, but MRI and

neurocognitive test battery were not conducted for this group of patients.

Patients in the test arm received the SENTINEL system and MRI at baseline, 2 to 7 days, and 30 days. Neurocognitive testing was also performed at baseline, 2 to 7 days, 30 and 90 days.

Control arm patients underwent the TAVR procedure without the SENTINEL system. MRI and neurocognitive assessments were conducted with the same schedule as that for the test arm.

The primary safety endpoint was major adverse cardiac and cerebrovascular events at 30 days. MACCE was defined as all death, all stroke, and acute kidney injury, Class III at discharge or 72 hours post-procedure. MACCE events were adjudicated by a clinical events committee using VARC-2 definitions. The CEC was blinded to treatment arm and composed of two cardiologists, a vascular neurologist, a stroke neurologist, and a nephrologist.

Note that additional details regarding safety definitions are provided in Appendix V of the FDA Executive Summary.

The primary effectiveness endpoint was total new lesion volume in protected territories as assessed by DW-MRI at Day 2 to 7 post-procedure.

Study success required that all three of the following criteria be met. The first two success criteria included statistical hypothesis testing. The device needed to meet a performance goal for safety and needed to demonstrate superior effectiveness. The third success criteria was a requirement on the magnitude of the observed treatment difference. The device needed to demonstrate at least a 30% reduction in median total new lesion volume in protected territories when comparing the test arm to the control arm.

I would like to point out that FDA's presentation will not cover all the SENTINEL results which have been provided in your panel pack. Instead, FDA will focus our presentation on what we consider the most significant findings. As the next speakers

present, we would like you to keep in mind the following items for our afternoon discussion:

- The appropriateness of using DW-MRI as a surrogate effectiveness endpoint;
- The clinical significance of the primary and secondary effectiveness results;
- The clinical significance of debris capture;
- The clinical significance of the neurocognitive outcomes;
- The appropriateness of the proposed indications for use and labeling;
- Benefit-risk considerations; and finally,
- Considerations for postmarket data collection if the de novo request were to be granted by FDA.

This concludes my introduction. I will now hand over the presentation to other members of the FDA review team, beginning with Dr. Buckley, who will provide a detailed overview of the SENTINEL study clinical results and considerations.

DR. BUCKLEY: Good morning. I'm Donna Buckley, a medical officer and interventional radiologist in CDRH's Division of Cardiovascular Devices.

In discussion of the clinical results for the SENTINEL study, I'd like to first discuss the patient enrollment and accountability as well as the baseline and procedural characteristics. Then I'll discuss the safety results followed by the effectiveness results.

Starting with patient accountability and procedural characteristics in the SENTINEL study, there were 428 patients enrolled, and 363 of those patients were randomized in a 1:1:1 fashion to three arms: safety, test, or control. Recall that the safety and test arms received the SENTINEL device. The test arm also underwent MR and neurocognitive evaluation, as did the control arm. The combined safety and test arms were analyzed for primary safety compared to a performance goal and are referred to as the safety cohort. This generally includes those patients randomized to receive the SENTINEL device. The

primary safety analysis included comparison of 30-day MACCE events compared to a performance goal of 18.3%.

Additional secondary safety analyses compared 30-day MACCE events between the test and control arms as well as a combination of the safety and test arms versus the control arm. These additional secondary analyses were performed to provide insight with regard to potential safety trends between groups, that is, between those patients who received the SENTINEL device and those who did not. However, they were not performed with planned statistical hypothesis testing.

For all safety analyses, the Sponsor primarily reported ITT results. The ITT population differed slightly from the as-randomized group of patients. For safety, the ITT population excluded those patients who did not undergo TAVR, had no follow-up, or withdrew from the study. Since only 18 patients were excluded for these reasons, over 95% of randomized patients were analyzed for safety.

It's also important to note that the ITT-with-imputation population was considered by FDA as the primary pre-specified analysis in the statistical analysis plan. In their summary, the Sponsor primarily reported the results for the ITT population, that is, without imputation. For the sake of consistency with the Sponsor's presentation, I will primarily discuss the results of the ITT population since the fundamental clinical conclusions do not differ between the two analysis populations.

The primary effectiveness analysis included comparison of diffusion-weighted MR lesions between the test and control arms. Specifically, comparisons were made between new lesions as detected by DW-MR at 2 to 7 days post-TAVR compared to baseline.

The device was assessed for effectiveness using two criteria. Primary Effectiveness Criterion No. 1 was the statistical superiority criteria that the patients treated with the SENTINEL device had a lower median lesion volume compared to those who did not receive

the device. Because there was a concern that a slight statistical difference may not have clinical significance, an additional criterion was added. Primary Effectiveness Criterion No. 2 required that there be an observed reduction of at least 30% in lesion volume for patients who received the SENTINEL device versus those who did not have protection.

It's important to note that there is no robust clinical basis that a 30% reduction correlates to clinical benefit. However, this threshold was chosen with the Sponsor as their reasonable goal given the limited data in the field. Here, the Sponsor specified that the primary analysis be conducted for protected territories only. Therefore, new lesions in unprotected territories were not considered in the primary analysis.

Secondary analyses were also performed to include assessment of these endpoints when all territories or the patient's entire brain was included.

For effectiveness, because it's an imaging endpoint, the ITT population excluded those patients who did not have paired baseline and 2- to 7-day DW-MR data. There were additional reasons for exclusion, but overall, greater than 20% of randomized patients were excluded from the effectiveness analysis, primarily on the basis of missing MR data.

For baseline and procedural characteristics, there were statistical differences in diastolic blood pressure, STS score, stroke severity, procedure time and fluoroscopy time between the three study arms, but these differences were not believed to be clinically significant. Comparisons were also made between patients who had missing DW-MR data and those who did not. Differences were assessed and not believed to clearly impact fundamental conclusions from the primary analysis datasets. Overall, there were no concerning trends in baseline or procedural characteristics, and characteristics between groups were generally balanced.

Next, I'll go to safety outcomes.

The ITT primary safety analysis demonstrated that the 30-day MACCE rate for the

safety cohort, that is, the combined safety and test arms, was 7.3%. The 95% confidence upper limit of this value is 10.7%, which is below the performance goal of 18.3%. Therefore, overall, the primary safety endpoint was met.

Looking at the particular events that drove the safety endpoint, they included 3 deaths, 13 strokes, and 1 acute kidney injury. In this study, stroke was the primary contributor to the 17 safety endpoint events.

In addition to the primary performance goal safety assessment, additional comparisons were made between study arms. Here, patients who received the SENTINEL device, that is, patients in the safety and test arms, were compared to those who did not receive the device, or the control arm. Events are generally balanced with the largest comparative difference in non-disabling stroke. Nonetheless, there were no significant differences between the groups, and the small event numbers preclude rigorous comparison. It's also important to note that the study was not designed to demonstrate differences in clinical stroke.

A similar analysis was conducted for patients in the imaging cohort, since they had identical patient selection criterion follow-up. There were 7 events in the test arm and 11 events in the control arm. When comparing the test and control arms, similar conclusions are drawn in that there were no statistical differences or rigorous clinical trends in differences in event rates.

The incidence of major vascular complications was also assessed. Because separate radial or brachial access was used to place the SENTINEL device, access site complications were noted in this regard. Here, only one brachial artery pseudoaneurysm was noted following the procedure. The remainder of the vascular complications were primarily believed to be related to TAVR placement. In general, the study did not show major concerns regarding vascular complications specifically attributable to the SENTINEL device.

The serious adverse event rate included all serious adverse events and is believed to have been driven primarily by the TAVR procedure. The SAE rate was approximately 43% in both groups, and there were no concerning trends regarding the type and relative frequency of events.

Overall, there were no notable trends in device safety with regard to major or serious adverse events. Also, the vascular complications related to separate access and increase in both fluoroscopic and procedure time were not considered to be major safety issues that would substantively influence a regulatory decision. So, overall, there were no major concerns noted regarding the safety of the SENTINEL device.

Transitioning from the safety results to the effectiveness results, Primary Effectiveness Criterion No. 1 demonstrated that the median new lesion volume change as measured by the difference between the 2- to 7-day diffusion-weighted MR and the baseline diffusion-weighted MR was 75.1 mm^3. So for the imaging cohort, there was a reduction of 75 mm^3 in median new lesion volume in protected territories for patients who received the SENTINEL device compared to those who did not. The difference was not statistically significant, p of 0.33. Therefore, the Primary Effectiveness Study Success Criterion No. 1, the hypothesis test for statistical superiority, was not met.

Related to Success Criterion No. 2 for the imaging cohort, there was a reduction of 42.2% in median new lesion volume in protected territories for patients who received the SENTINEL device. This is above the pre-specified threshold of 30%. Therefore, the Primary Effectiveness Study Success Criterion No. 2 was met.

Looking at the primary endpoints and comparing results for analyses that included protected territories to those that included all cerebral territories, we see that there is a 75.1 mm^3 median lower lesion volume for protected territories for the SENTINEL device, which is reduced to a smaller difference of 15.8 mm^3 when all territories are considered.

If we were to further consider only those patients whose DW-MR data were obtained within the 2- to 7-day imaging window, that is, the results for the per-protocol population, the outcome shifts from a comparative decrease to a comparative increase in median lesion volume for SENTINEL patients.

In an opposite direction, the ITT with imputation analysis cohort shows a larger difference for lesion reduction in all territories of 63.9 mm^3 compared to the ITT population without imputation. Note that the ITT with imputation population accounts for the missing MR data by using estimates from the existing data.

Similarly, when reviewing the results for protected territories versus all territories for percent median lesion volume reduction, we see that there is a 42.2% reduction in median lesion volume for protected territories for the SENTINEL device, which is reduced to 5.1% reduction when all territories are considered. Percent reduction was not tested for statistical significance.

Again, when considering MR data from only those patients imaged in the 2- to 7-day window, the median new MR lesion volume for all territories shifts from a reduction to a slight increase of 3.4%.

Shifting to other secondary analyses, the neurocognitive assessments were made to evaluate whether the nonclinical strokes, that is, those detected by diffusion-weighted MR only, had a more subtle clinical impact detectable by neurocognitive testing. Here, five domains were combined (attention, executive function, processing speed, verbal memory, and visual memory) to create a composite Z-score. The change in Z-score at 30 days and 90 days was then assessed such that a positive change indicated an improvement in performance and a negative change indicated a decrement in performance. These Z-scores were then compared between groups. The changes were small, and there were no meaningful clinical trends between test and control arms with respect to the changes in

overall Z-scores at both 30 days and 90 days follow-up.

Here, the neurocognitive battery Z-score for both the test and control patients decreased at the 30-day follow-up and then increased at the 90-day follow-up. From these data, it is unclear whether the small change represents any clinically meaningful change in neurocognitive function, random variation, or confounding related to serial neurocognitive testing such as practice effects.

Review of the individual domains at 30 days also does not reveal any specific trends. Here, the change in Z-score at 30 days is graphed for each domain, with a positive score indicating improvement after TAVR and a negative score indicating a decrement after TAVR. Again, no meaningful clinical changes or trends regarding comparisons between groups were noted.

Additional effectiveness analyses were performed to further assess the potential impact of the device. In the SENTINEL study, the quality of life assessment did not reveal statistical or clinical differences between groups. In addition, a subanalysis by valve type was performed. Because the study was not designed or stratified by valve type to assess differences between groups, the data are inadequate to support inferences regarding performance of one valve type over another.

With regard to debris capture, in 99% of cases debris was captured with acute thrombus, and tissue and foreign material being the most commonly removed debris. The distinction of embolic capture versus possible filter-generated debris is unclear in some cases.

Overall, the SENTINEL study met one of the pre-specified effectiveness study success criteria but did not meet the other. Primary effectiveness analyses did not demonstrate a statistical significance, and a clinically meaningful reduction in cerebral ischemia is difficult to interpret.

Dr. Dong will now present the statistical results and considerations.

DR. DONG: Thank you, Dr. Buckley.

My name is Li Ming Dong, and I'm from the Division of Biostatistics, and I'm the statistical reviewer of this de novo submission. I will present SENTINEL statistical results and the considerations.

My presentation will be focused on the following: First, the analysis population used in presenting the findings of the SENTINEL study. Next, I will discuss some details on the analyses of the primary safety endpoint and the primary effectiveness endpoint. And last, I will present some data which are related to the question of lesion volume as the measure of cerebral ischemia.

Three sets of analysis populations were defined for the primary safety and effectiveness endpoints, respectively. These analysis populations were defined for different purposes. Since the safety cohort and imaging cohort included different study arms, ITT refers to different patient populations for the analysis of the primary safety endpoint and the analysis of the primary effectiveness endpoint.

ITT typically consists of all randomized subjects. Here, the Sponsor-defined ITT consists of subjects with observed endpoint data, that is, in the analysis of the primary safety endpoint, ITT refers to completers of the safety cohort. In the analysis of the primary effectiveness endpoint, ITT refers to the completers of the imaging cohort.

Analysis based on the full cohort with missing endpoint data imputed were also conducted and are considered as the primary analysis.

The as-treated population consists of patients who actually received the SENTINEL device. It is defined only for safety analysis and is appropriate for these purposes.

The per-protocol population was defined only for effectiveness analysis. It excluded the subjects with out-of-window MRI scans.

Next, I will comment on the analysis of the primary safety endpoint.

The analysis of the safety endpoint is based on the safety cohort consisting of 244 patients randomized to the safety arm and the test arm. Overall, 10 subjects have missing MACCE data at 30 days for reasons of TAVR not done or lost to follow-up. In addition, the SENTINEL device did not enter the vasculature or was removed prior to TAVR for nine patients.

This table presents the results of the primary safety endpoint based on three analysis populations. It can be seen that the 30-day MACCE rates based on all three analysis populations are very close, from 7.3% to 7.6%, and all met the safety success criteria.

Sensitivity analysis was conducted to evaluate the robustness of the safety outcome missing data. The worst-case scenario analysis showed that under the extreme assumption that all 10 subjects with missing 30-day MACCE data were assumed to have a MACCE event, the MACCE rate would be 11.1%, its upper 95% confidence limit 14.9%, still below the performance goal of 18.3% and meeting the safety criteria. Therefore, the primary safety endpoint is met, and missing data is unlikely to alter the conclusion.

Now I'd like to look at the analysis of the primary effectiveness endpoint. The analysis of the primary effectiveness endpoint is based on the imaging cohort and compares the test arm and the control arm with respect to new lesion volume in protected territories. In contrast to the safety analysis, there is a large number of subjects that have missing data in both arms, with 30 subjects with missing MRI data in the test arm and 21 in the control arm. When looking at the reasons for missing data, it appears that they are roughly balanced between the two arms, except that six subjects in the test arm had no MRI because the test device was not received. The per-protocol population further excluded 18 subjects, primarily due to out-of-window MRI scans.

The Wilcoxon rank-sum test was pre-specified as the analysis method for analyzing the primary effectiveness endpoint due to expected skewness of the lesion volume distribution. Based on rank, the statistical test compares medians of the test arm and the control arm and is not sensitive to outlying values. It is noted that the missing data rate (21%) is high, with 25% and 18% for the test arm and the control arm, respectively.

The Sponsor employed multiple imputations to impute the missing data using baseline variables. The analysis based on ITT with imputation was the pre-specified primary analysis. Here we noted that the results based on ITT with imputation and ITT for protected territory are similar. As Dr. Buckley previously mentioned, baseline demographics and the procedural characteristics were assessed for patients with and without missing data. Although some differences were noted, they are not believed to substantially impact the outcome.

The primary effectiveness endpoint included only assessment of diffusion-weighted MRI infarcts in protected territories, and infarcts in the left vertebral distribution were excluded. FDA believes it is important to consider effects in all territories when considering the totality of the data to support a marketing decision. Some additional analyses have been provided to also assess DW-MRI effects in all territories.

Here, the primary effectiveness results are presented for both protected territories and all territories. You have seen this table of the effectiveness outcome earlier. It is noted that for all territories, the observed differences are somewhat different for the three analysis populations. Comparisons in this table are between the medians.

Let's look at the distributions now. FDA plotted the frequency distribution of the observed total new lesion volume in both protected territories and all territories. These plots use equal width intervals in an increment of 200 mm^3. The first two bars represents rates of missing data, which is 25% for the test arm and 18% for the control arm. As

expected, the distributions are highly skewed with a long tail, and it's hard to see any trend.

The same data can be plotted using unequal-width intervals but equal-width intervals on the log scale. In log scale, the distribution of the observed total new lesion volume in protected territories for the test arm shows a small shift to the left, meaning that high percentages of the test arm patients had a lower lesion volume. This suggests a slightly lower total volume in the test arm. This observation is consistent with the results based on the medians. However, the total new lesion volumes in all territories are similar for the test arm and the control arm, suggesting no difference between the two.

To summarize the findings on the primary effectiveness endpoint, lesion volume distributions shows a small non-statistically significant shift towards the lower lesion volumes in the protected territories for the patients in the test arm compared with patients in the control arm. When all territories are analyzed, there is no clear trend of lesion volume reduction.

One of the questions we will ask the Panel is the appropriateness of using DW-MRI measurements of new lesion volume as a clinically meaningful measure of cerebral ischemia. In the next few slides I will present some observations related to this question.

DW-MRI measures post-procedure new lesion volume and was used to represent cerebral ischemia. This box plot displays the distribution of new lesion volume in protected territories for patients who had no clinical stroke within 30 days of procedure and for patients who experienced clinical stroke within 30 days.

Here, the test and the control arms are combined. Lesion volume was measured by DW-MRI at Day 2 to 7 post-procedure, and a natural log transformation was taken because the lesion volume distribution is highly skewed. The middle bar in the box represents the median. The bottom and the top of the box are 25th and 75th percentiles, respectively. Therefore, half of the data points are within the range of the box. The two ends of the

whiskers here are the maximum and the minimal values.

It is observed that patients with clinical stroke did tend to have high values of new lesion volume than those who didn't have stroke. However, the distribution of lesion volume for the two groups overlapped. This suggests that DW-MRI is a limited surrogate for stroke, and it is acknowledged that the same volume of cerebral ischemia may have substantially different clinical presentation depending on the location of the infarction.

This is a box plot for lesion volume in all territories. A similar trend of high lesion volume among patients with clinical stroke is observed. Although patients with lesion volume below 81 mm^3 would not have stroke, still, many patients with high lesion volume also had no stroke. I want to make a note that the group with stroke is a small group, only 14 patients.

Now, let's look at the correlation between the new lesion volume measured at Day 2 to 7 post-procedure with change in neurocognitive battery composite Z-score. Negative correlations are observed for both arms, suggesting that high lesion volume at Day 2 to 7 was associated with declining neurocognitive function at 30 days. However, with the correlation coefficients around -0.2, the correlation is weak.

This table shows the correlation of Day 30 T2/FLAIR MRI lesion volume with 30-day and the 90-day change in neurocognitive battery composite Z-score. As can be seen, there's no correlation between them for two arms.

In summary, it is observed that patients with clinical stroke tend to have somewhat higher new lesion volume in protected territories measured by DW-MRI 2 to 7 days post-procedure. A similar trend is also observed in all territories.

There's a weak correlation between Day 2 to 7 lesion volume and the 30-day change in neurocognitive composite Z-score.

This concludes my presentation. Next, Commander Toor will summarize the study

conclusions.

CDR TOOR: I'd like to conclude FDA's presentation with a brief summary of our primary observations about the data used to support this de novo request which we believe will be most relevant to your subsequent deliberations.

First, the study met the pre-specified safety success criterion, and there were no apparent safety concerns with use of the device.

Second, in terms of effectiveness, the trial was not designed to show that the device reduces clinical stroke, as this would require a very large sample size. Rather, it was designed to provide imaging and corroborating clinical evidence that the device reduces ischemic events in the brain as detected by DW-MRI.

The study demonstrated an observed reduction in median total new lesion volume in protected territories when comparing those with protection using the SENTINEL system to those without protection. However, it did not show that patients with protection using the SENTINEL system had a statistically significant reduction in new DW-MRI lesions in protected territories after TAVR.

Although observed trends favor the SENTINEL system, the clinical significance of the observed lesion volume reduction remains uncertain.

Next, the SENTINEL system is designed to protect territories of the cerebral vasculature supplied by the carotid and right vertebral arteries in patients undergoing TAVR. The left vertebral artery distribution is unprotected.

Although the study showed that the device captured debris in almost all cases, correlation of debris capture with DW-MRI findings remains unclear.

Additionally, FDA believes it's important to consider defects in all cerebral territories when considering the totality of the data to support a marketing decision, since the goal of embolic protection in TAVR is to protect the whole brain.

And lastly, there were no clear clinical trends in the aggregate neurocognitive test battery or its component Z-scores.

I'd like to thank all members of the FDA review team for their very valuable input. This concludes our presentation.

DR. PAGE: Thank you very much for a clear and concise presentation.

I'm looking for any brief clarifying questions from the Panel, and let's do one question at a time. I'll see Dr. Somberg.

DR. SOMBERG: Well, I have two questions, but I'll do one now and one if you call on me again. I'll play by your rules.

Okay. With that said, thank you for that very insightful review by the FDA. I think if we stipulate that the study, looking retrospectively, of course, is grossly underpowered, the importance of the meta-analysis comes to the fore. In the FDA's analysis, there was my impression of considerable hesitation to use that. In fact, you didn't refer to it at all, and you said the studies were not comparable, they're not compile-able, etc.

Can you explain that in a little bit more detail and why you think, in this situation, where the least burdensome approach is what the regulations require, that that is not an important consideration? And finally, that is, if you're willing to do that, all your box plots, etc., were presented on that small dataset. What about looking at the compiled dataset with a systematic analysis? And do you have that data?

CDR TOOR: So I'm going to let Dr. Buckley take this on, but I'd first like to ask if we can pull up FDA Backup Slide No. 6.

DR. BUCKLEY: The meta-analysis that was performed by the Sponsor did include data from the three studies, the CLEAN-TAVI, the MISTRAL-C, and what FDA considers to be the primary pivotal trial. We do not have the patient-level data and did not perform independent analyses with regard to the meta-analysis. We do consider this to be more of

a post hoc analysis. It does have some differences. Dr. Leon pointed out there are a lot of similarities with regard to some of these trials, but there are some differences as well. Each study did have a different combination of valves involved. The CLEAN-TAVI trial only had the CoreValve. They were relatively small OUS trials where, I think, there were only 37 patients that were contributed by the MISTRAL-C.

When we look at consistency of the data across the three different trials at a very high level, we see that with regard to new lesion volume in all territories in those areas that are boxed in blue, there's a large variability in the control median volumes, which gives us a little bit of reticence in just blankly putting together these studies. There are also some unclear differences because we did not consider this as, you know, pivotal information necessarily, but in terms of eligibility criteria being a little bit different. I understand the imaging was the same. But there are some limitations with the combination of this data, and there was some suggestion that the forest plots were based on mean data where we know that these are skewed datasets, and some other looks at that might be valuable.

DR. PAGE: Thank you.

Do either of our statisticians wish to comment on these data at this time?

(Off microphone response.)

DR. PAGE: I was looking to the Panel first.

DR. NAFTEL: Just one thing that we're seeing again and again. We've used medians for most of the comparisons, and when you look at this table and look at the means plus or minus the standard deviation, the standard deviation puts you way below zero, and it just reminds us that this is very skewed data. Your plots on a log scale shows me pretty clearly that all these data are normally distributed on a log scale, and you just as easily could have gone to parametric analyses, except it doesn't matter a hill of beans.

DR. PAGE: Thank you, Dr. Naftel.

Dr. Dong, did you want to further add to this discussion?

DR. DONG: Yes, I agree with Dr. Naftel. Another thing I want to make a comment is about the post hoc analysis nature of this meta-analysis because there's different ways of combining data from different studies. Here, the CLEAN-TAVI study is the randomized trial, but as the Sponsor pointed out, the SENTINEL study was designed based on the findings from CLEAN-TAVI. I mean, from our experience, it is not uncommon that in the early stage of the development, like typically Phase I and Phase II clinical trial, you see a large variable treatment effect, but once you conduct a well-controlled randomized control trial, you don't see those effects anymore. I mean, this was just my additional comment. Thank you.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: So they are talking about the meta-analysis, and I understand you didn't have the opportunity to use the patient-level data. There are sites that are similar in the SENTINEL trial as in the meta-analysis side, I believe, so there are some similarities. And the findings in the two European studies are much more in favor. I'm not saying that it's really positive, but it's in favor.

Is there any evidence of a learning curve or some other anatomical issues that play into this, while some centers may see some benefit and other centers see no benefit? Because if you look at all territories, there is no benefit.

DR. BUCKLEY: I'm not sure we have specific data on that. I would probably ask the Sponsor to see if they have any independent analyses looking at the individual sites OUS.

DR. PAGE: And one thing I'll point out is, at this point, giving homework to the FDA is more difficult. They don't have quite the statistical backup for this. Would you want to rephrase that? Is that a question that you'd like the Sponsor to potentially address over lunch, Dr. Ohman?

DR. OHMAN: Well, I could rephrase it to the Sponsor, then, and asking the very same question. There seems to be a variation in the performance across the Atlantic based on the three studies we have. Yet, there are some overlap in sites in the SENTINEL trial. So I'm curious as to how much of this plays into what we are actually observing.

DR. PAGE: Thank you.

Is that clear to the Sponsor? We're not asking you to address it now. Thank you.

DR. BROCKMAN: Dr. Page?

DR. PAGE: Other questions now for the FDA?

Dr. Somberg. Excuse me for a moment. Randy -- Dr. Brockman, I should say.

DR. BROCKMAN: Randy Brockman, FDA.

DR. PAGE: You have a comment. Please.

DR. BROCKMAN: Well, I just wanted to clarify. Dr. Ohman, were you specifically asking for information about a learning curve as well? And was that clear to the Sponsor?

DR. OHMAN: Well, I assumed they understood that to be --

DR. BROCKMAN: Was that clear? The learning curve? Thank you.

CDR TOOR: Can I add one comment in relation to that question?

DR. PAGE: Yes, Commander Toor.

CDR TOOR: So in terms of learning curve not specifically related to previous OUS experience with the device, the Sponsor did conduct an analysis to look at the highest enrolling sites versus the remaining, and it didn't show a difference. If you have a backup slide or information available on that, if I could ask Claret, maybe that would help to answer your question.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: This issue of total territory burden versus the protected territory is

confusing to me. I asked that to Dr. Leon. He made the point that there was no difference between the non-protected territories in the two groups, and when you look, it was all based on the protected territory difference. On Slide 42, the implication seems to be that whatever non-significant benefit in terms of lesion benefit you're seeing, burden, it tends to go away or it's markedly diminished when you look at total territory. Can you give me insight on that? I'm still confused on that point.

CDR TOOR: We can pull up Slide 42. We also have a backup slide on the different territories, if you want to show that. Just give me a minute, and I'll find the slide number.

(Pause.)

CDR TOOR: So I will just say that, in the protocol, the protocol defined protected territories. The definitions are in Appendix V.

DR. PAGE: Could you speak up a little bit, please?

CDR TOOR: Sorry. So the protocol defined protected territories, and the protocol definitions are provided in Appendix V. This idea of partially protected was not pre-specified in the protocol, so --

DR. BUCKLEY: This is Donna Buckley.

All of the work in preparation for the Panel was protected versus all, and there was a secondary distinction with regard to partial protection, and that's absent from our information because it wasn't part of the initial intent in terms of the statistical analysis plan. Are you asking for clarification with regard to the differences in the territories?

DR. SOMBERG: Not really. What I'm wrestling with is that the implication from, I think, Slide 42, in my mind -- and I just want to say, parenthetically, you got to make the slides larger for people who wear glasses, both the handouts and the projections. I can't really see Slide 42 up there either, so I can't tell you the data. But when you were presenting it and discussing it earlier, it seems that when you look at protected versus

non-protected and you count it all, the non-significant difference gets even less.

DR. BUCKLEY: Yes.

DR. SOMBERG: And what I'm wrestling with is, is that because of just diluting it down with a lot of noise, or is it because there's, I guess, to use Dr. Leon's term, shunting? Things go to the left of vertebral artery when they can't get into the right vertebral or the right carotid circulation. What is your analysis of the data you've looked at? And you can see it a lot better probably than I can.

DR. BUCKLEY: Well, you know, we don't know, and I'm not sure I have particular insight into exactly what's happening. But if you want to pull up Slide 8, Backup Slide 8 for FDA, and we look at the location of stroke with -- yeah. So if we look at stroke location and looking at Dr. Leon's slides for the delineation of protected, partially protected, versus unprotected, and on the left side we see, in the safety and test arms, that the SENTINEL device had 13 strokes, and when we look at where those strokes are located, we see that 46% are in protected territories, 23% unprotected, and 31% in partially protected. So stroke does occur at a greater extent in both the partially and unprotected territories compared to the protected. When we look at the control, the ratios are a little bit different. Now, I caution that these are quite small numbers, but it's hard to discern whether or not, based on the clinical data alone, there is an issue of shunting.

DR. PAGE: For our neurologists here, is there anybody who wants to make a comment about the possibility of shunting to the unprotected left vertebral as being an explanation for this difference that we see, albeit not statistically significant, the difference we see between in the protected that goes away when we looked at the entire brain?

Dr. Good.

DR. GOOD: Yeah. So I think you'd need a little more information. First of all, the Sponsor said that there was no impairment of cerebral blood flow based on these filters. So

I'm assuming that the flow is normal in the arteries that are involved with the filter. If that's the case, it would seem odd that you would get enough shunting up the left vertebral artery to cause all of this, but I don't have enough information to say more than that. I don't know if any of the other people want to comment on that.

DR. PAGE: I'm seeing shaking heads. Does that mean -- I'd love Dr. Peavy perhaps or Dr. Duff, if you want to make any comment regarding this conceptually. Shaking heads don't make the transcript very well.

DR. DUFF: No comment.

(Laughter.)

DR. PAGE: There you go.

Yes, Dr. Roberts.

DR. ROBERTS: It would be interesting to understand, you know, what the actual vascular anatomy is in these particular patients, and is this driven by some kind of vascular variant that we're not seeing?

DR. PAGE: Yes, Dr. Good.

DR. GOOD: One other thing. I think maybe the Sponsor has presented this earlier, but we're here talking in this slide only about strokes, and it would be interesting again to look at the DWI lesions in protected versus unprotected versus partially protected, since that's one of the surrogate outcomes here, and that might be of some value. I think they did present something, but I don't recall what it was. It might be nice to see that again.

DR. PAGE: And did the Sponsor have a similar slide to this in terms of the actual not stroke but embolic findings? Now, Dr. Leon, I am asking you if you might have that available or be able to make it available to us after the break.

DR. LEON: Yeah, we certainly can. Now, this distinction in this slide on protected, unprotected, and partially protected is the CEC adjudication of what they thought was

protected, partially protected, or unprotected. It has nothing to do with the DW-MRI imaging. But we gladly will show you the data that we have.

DR. PAGE: Great. Thank you.

Are there any other -- oh, yes, Dr. Dodd.

DR. DODD: Hi. I have a couple of questions related to the determination of the objective criteria, and maybe the FDA can help me understand the criteria of the 18.3% and what other variables I should be thinking about, because I'm always skeptical of sort of historical control data or set criteria because we know patient populations shift over time. So could you just lead me through the thinking behind why this would be an acceptable criteria? And then I have an additional follow-up question about the 30% for the second efficacy endpoint.

CDR TOOR: Sure. So for the performance goal, can we please pull up FDA Backup --

DR. DODD: Can you speak up just a little bit, please?

CDR TOOR: Sorry. Can we please pull up FDA Backup Slide No. 5? And Dr. Dong will help us through this explanation of the derivation of the performance goal.

DR. DONG: No. 5. This table shows how the performance goal was determined before the study in the IDE stage. Basically, it's a weighted average from a few past studies, namely, the PARTNER study and the CoreValve. And it's based on different observed MACCE rates, 30-day MACCE rates, and also they're weighted according to estimated patient population, I mean distribution among those different groups. So in the end, the weighted MACCE rate is 13.3%. Then a 5% margin was added. So that's how 18.3% is determined.

DR. DODD: So I guess I don't quite understand how the different weights were determined. And then as a follow-up to that, were the weights that you assumed, do you still agree that the weighting scheme was appropriate for the sample population in the

study?

DR. DONG: The weight was used -- I think it's coming from 1:2 ratio of the PARTNER to PARTNER II, and the 82.8% was the 17.9% for iliofemoral versus non-iliofemoral in CoreValve trial. And also, in the end, it is expected that the patient distribution, if you see the weight, the line above performance goal, it's estimated like two-thirds will be coming from patients similar to the PARTNER, and the one-third patient population would be similar to CoreValve. We didn't do same calculation after the data already had been collected.

DR. PAGE: Yes, Dr. Good and then Dr. Yuh.

DR. GOOD: I thought Dr. Dodd was asking another question about effectiveness criteria, too, but I might be wrong, and how the 30% difference between protected territories in the control arm and the treatment arm is determined. I thought that was part of your question.

DR. DODD: Well, I was asking -- that was my second question. You read my mind.

DR. PAGE: Then why don't you continue, Dr. Dodd? Go ahead.

DR. DODD: And maybe we can have this during the discussion because understanding this set efficacy or set safety level is pretty critical to me. I don't understand what the differences in baseline risk were between these two different studies or the four different studies that went into that. So maybe during the discussion you can educate me, unless the FDA wants to provide additional comment now.

DR. PAGE: I think we can discuss that as a panel when we get to that point. Thank you.

Dr. Yuh.

DR. YUH: Thank you.

Do you see a problem in the weighted analysis establishing your primary safety

endpoint was derived from studies that did not use a device that was predominantly used in this current trial? In other words, over 50% of the devices were apparently the Sapien 3 device, but none of these studies, as far as I can tell, incorporated that device. So how relevant is this established primary safety endpoint in terms of this current study's analysis?

DR. BUCKLEY: Yeah. I mean, I think some of that just speaks to the difficulty and the dynamic changes in introducing valves to the market and introducing them into the study over time and how that changes. To the best of our ability at the time when we were designing this trial 4 years ago, this is what we had, and we did what we could with it to try to come up with a reasonable estimate. But your point is well taken.

DR. YUH: I totally understand your limitation. I just wanted to bring that up just for, you know, future discussion to see if there might be a conflict or a discrepancy.

DR. PAGE: Thank you, Dr. Yuh.

Dr. Dodd.

DR. DODD: Yeah. So I want to come back to my second question, which relates to the second effectiveness criteria and how the 30% criteria was selected. I would like some input from the FDA on that. And furthermore, the 30%, as I understand it, doesn't incorporate any uncertainty in the estimate, which seems highly unusual to me. So why was it agreed that a fixed point estimate of 30%, being greater than that in the point estimate, would be an acceptable efficacy criteria?

DR. BUCKLEY: Again, I think you're pointing out the particular challenges with using an imaging endpoint when we have very limited information with regard to robust correlates with the imaging and robust clinical outcomes and the limitations when we use this for a measure of cerebral ischemia. In general, the CLEAN-TAVI trial, I think, used a threshold of about 50% in terms of the evidence that's related to lesion volume, showing a definitive clinical outcome. There really isn't a whole lot of data out there that would really

support a 30% threshold, and I tried to emphasize that in my remarks. The overall goal was to, in general, show that there is some type of margin of benefit beyond just a statistical difference.

Because we were uncertain, because there were so many uncertainties in designing this trial, we didn't want to end up in a situation where we had a statistical difference in median lesion volume that had absolutely no margin associated with it. With regard to that, there was some discussion about having a super-superiority trial where we would basically build in a margin in the superiority test. We ended up not going in that direction and having two different success criteria for multiple practical reasons in terms of sample size, etc.

DR. DODD: And so does the statistician want to comment on not accounting for the uncertainty in that 30% or in the 42% point estimate? Typically, I would think you would want to put a lower bound on that, which you did, and that does not include zero, which would, you know, suggest that it's likely that the point estimate for that difference in percent benefit includes no benefit.

DR. DONG: I totally agree with your point. But at the design stage, this is decided based on the clinical opinion, and also we didn't feel ready, at that time, to design a super-superiority trial to specify a margin at that time. So that's how we -- it's kind of like a compromise.

DR. BUCKLEY: Just to add to that, I think there was a little bit of reticence as well because there is no robust basis for the 30% margin. We did request hypothesis testing separately on that 30%, but because it lacks some clinical rigor in and of itself, there was not concurrence as far as that goes.

DR. PAGE: Dr. Cigarroa, did you have a question?

DR. CIGARROA: Yes, thank you.

I'd like FDA to comment on the Slide No. 5, on the performance goal for the primary safety endpoint and what thoughts one has in the weighted average accounting for 20% transapical. Patients who undergo transapical transcatheter aortic valve replacement often have different comorbidities, and what impact a lower transapical event rate might have on your primary safety endpoint in comparison to your weighted average versus what actually happened in the trial.

DR. PAGE: And boy, to think about to build on that, my recollection was there weren't that many transapical. Looking around the room, I'm looking for nods this time, as to whether we think transapical procedures should be included in evaluating what the risk is of a transfemoral TAVR, because it seems to me a completely different procedure, as shown here, and to my mind, a greater risk profile.

DR. SOMBERG: Wouldn't that be a good question for the Sponsor to address?

DR. PAGE: I'm sorry, Dr. Somberg?

DR. SOMBERG: Wouldn't that be a good question to ask the Sponsor to address in the afternoon session?

DR. PAGE: I'm looking at the Sponsor, and I'm seeing a nod over there, so I think that's a great idea.

Were there any other brief clarifying -- not right now, though. Thank you, Dr. Leon.

(Laughter.)

DR. PAGE: Were there any other brief clarifying questions for the FDA?

Again, Dr. Cigarroa.

DR. CIGARROA: Was the FDA going to comment on the --

DR. PAGE: I believe so.

DR. CIGARROA: -- question that I asked?

DR. BUCKLEY: Yeah. I mean, I don't think we have the details of that data to answer

your question in the granular form that you asked it, but I think it definitely does point to yet another limitation of the performance goal.

DR. PAGE: Thank you.

Mr. Frankel.

MR. FRANKEL: Just a quick follow-up to Dr. Ohman's question in terms of the procedural learning curve. I noticed that in the CLEAN-TAVI, in the literature available from that trial, they specifically noted in the context of their limitations that all the procedures were performed by the same team to eliminate the potential bias of a procedural learning curve, and they wrote that in the context that the results can't be necessarily generalized for the patient population and other transcatheter valves. So I was wondering, the FDA's assessment, whether that's an issue in terms of the meta-analysis performed over here.

DR. BUCKLEY: Yeah. I mean, when you have a single site experienced investigator, you might have different results, and that might affect the poolability of the information. Sure.

DR. PAGE: Thank you.

And Dr. Posner or Mr. Thuramalla, do you have any other questions for the FDA at this time?

DR. POSNER: No, thank you.

MR. THURAMALLA: No, from myself also.

DR. PAGE: Great. Thank you.

We're actually running ahead, but I want to have the open public comment sharply at 1:00. So Dr. Frankel -- I mean Dr. Leon, you've been very good about going back and forth from your seat. I will now ask you -- thank you to the FDA for this portion. I'm now going to open our discussion in advance of lunch and see if there's any opportunity at this time, whether the Sponsor has any other responses. If you don't, we've told you you'd have

lunch available to work on these, but if you had any of the responses to the Panel's questions, we might be able to address these a little bit early. Dr. Leon, is that possible?

DR. LEON: I'm sure we could address some of the questions, but we'd have to go over specifically which ones you'd like me to address. There were so many that were just discussed.

DR. PAGE: Just now you were going to come up to the lectern, and you had a comment. I'm giving you the opportunity to address that now.

DR. LEON: Sure. I'm trying to get a slide up for you. Certainly we agree that it's difficult to create a performance goal when you're dealing with historic data and that the ratio of transapical to transfemoral was different in those studies compared to the SENTINEL trial. It was one of the reasons why we did a weighted average. The weighted average assumption was that there'd be 80% transfemoral versus 20% transapical. Actually, in the trial itself, there were many more transfemoral cases.

When we redid the weighted average based upon the actual frequency of transfemoral to transapical, then the performance MACCE goal was not 13.3 but was 12.4%. But even at 12.4%, this was still statistically significantly different than the actual MACCE rates for any of the analysis populations, as shown on this slide, and that's both the actual performance goal and if you add an adjustment non-inferiority margin. So I agree that there was an imbalance of transapical to transfemoral. I agree that the comorbidities with transapical may be greater, but we attempted to account for that by a re-post hoc analysis to adjust for those differences.

DR. PAGE: And I think, Dr. Cigarroa, you had raised a concern about this. Does this satisfy your concern? I'm seeing Dr. Cigarroa --

DR. CIGARROA: It does. Thank you so much.

DR. PAGE: Yes, Dr. Somberg.

DR. SOMBERG: Just following up on that, I guess Dr. Cigarroa's suggestion was that maybe what -- since there's an overwhelming preponderance of femoral approach, maybe the database would not be suitable for determination and recommendation for the apical, and I wondered what your opinion is. You said there are different comorbidities, there are different potential risks, but I would think that once you -- you know, there's a good possibility of debris released from the valve itself. So do you think this would not be applicable to the apical approach? I'm sort of asking a leading question.

DR. LEON: We think it absolutely is. We think that there may in fact be more embolic material. In fact, as Dr. Virmani showed, some of the myocardial samples were associated with the transapical approach, which are clearly unrelated to the device and potentially could be captured.

I would make one other comment, that the historical performance goal was based upon MACCE data in which the stroke rates were not defined with systematic neurologic assessment. So the stroke rates, we believe, in retrospect for the historical performance goal, were in fact spuriously low, negatively biasing against the current study design where we did have neurologic assessment in all patients. So I believe that we certainly accounted for as much as we could. Some of the differences in looking at a performance goal -- and I think that the results do indicate appropriate safety.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: Yeah, I want to follow up on that question, Dr. Leon. I think it's fascinating that we use the approval studies for setting the bar when we know that practice changes quite a bit. And, in fact, the majority of the SENTINEL device trial was carried out at least 2 or 3 years after the approval studies. So can you comment on where you think the sort of natural MACCE rate might be when the SENTINEL trial was carried out? In other

words, is it a little bit less than the pivotal trials or about the same?

DR. LEON: Well, I think we did have a concurrent control arm, and that concurrent control arm, which reflected standard of practice at that time, understanding that there was an influence of shifting valve types -- but it's an admixture in both arms with a similar frequency of different valves, demonstrating that the MACCE rate was not statistically lower but was numerically lower than the control arm. So what we're trying to establish is safety, not superiority of MACCE versus control, but safety. Numerically, it clearly is less. So our feeling is that's the best we could do under the circumstances with a dynamic technology with multiple valve types, multiple sites, multiple experiences. It's a difficult analysis to do, but every way we look, it's safety. We don't see any evidence that there's a safety consideration here.

DR. OHMAN: Well, I would agree, but this actually shows that if this was the rate, you would have set the bar a little bit differently had you used this 9.9. Now, obviously, that was part of the study. So it raises the issue of how stable that control experience is.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Thank you.

You know, the determination of OPCs always involves some arbitrary decisions, but I'm still a little unclear. How did you come up with 5% as an additional factor in determining your performance goal?

DR. PAGE: You're asking the presentations --

DR. BORER: The Sponsor.

DR. PAGE: -- from the FDA or the Sponsor or just --

DR. BORER: No, no. I'm asking the Sponsor. They're the ones who did it, I guess.

DR. LEON: Well, this was an active discussion amongst the biostatistical expertise

within the Sponsor group and with the FDA, to agree on what would be a performance goal with an appropriate adjustment. Considering that the margin was 13.3, 5% was reasonable and reasonably consistent with other performance goals looking at safety done in other interventional trials during this time period.

DR. PAGE: And Dr. Leon, I appreciate your response and recognize that indeed these performance goals are established in discussions with the FDA.

Dr. Dong, do you want to come back and respond to how that 5% was established or negotiated?

DR. LEON: But you know, we did show -- take away the 5%. Let's have no non-inferiority margin. There still was a highly statistically significant difference with any of the analysis populations with the observed MACCE rates. So I don't know that the performance goal adds or subtracts very much because it was well below that performance goal.

DR. PAGE: I understand your perspective.

Dr. Dong, would you at least give the Panel comfort in terms of the way in which that number was established?

DR. DONG: I would say that the 5%, I mean, it's not based on -- there's no statistics analysis involved in determining the 5% margin. Basically, usually that's how it's normally done. I mean, the Sponsor proposed something, and then we discussed it. I mean, clinically if people agree, then we take it. I mean, it's not based on statistics.

DR. PAGE: Thank you. And I must say the number appears consistent with others that I've seen in similar protocols that have been negotiated between the FDA and the sponsor.

Dr. Naftel and then Dr. Dodd.

DR. NAFTEL: So I just want to agree with the whole discussion, that it is a discussion, and there is no primary statistical way to do this. It's arbitrary. I think the point that if

you'd stuck at the original bar without adding the 5%, it still looks good, and that gives me great comfort. You know, statistically, you could have a rate above the OPC that was still below the plus 5%, if you could have an observed rate greater, but you'd claim non-inferiority if you had a big enough sample size. So it's almost not a statistical discussion. It is a discussion between FDA and the Sponsor.

DR. PAGE: Dr. Dodd.

DR. DODD: Yeah, I'd just like a comment from the FDA. Typically, when I review non-inferiority studies, a non-inferiority margin is set with regard to efficacy. So we're willing to, you know, assume some detriment in efficacy, assuming the safety profile is good. In this case we're actually -- and this is more for future thinking about non-inferiority because I think the non-inferiority margin here is probably not an issue. But setting a non-inferiority margin for a safety endpoint seems a little unusual to me. Is this something just because I don't review a lot of studies from the FDA and devices, or is this unusual for you as well?

DR. BUCKLEY: It is not standard fare, nor is anything with this trial in general. Just to give a little bit more regulatory context in terms of the evolution of the design of this trial, we were in a regulatory context where we had embolic protection approved for carotid protection, and that carries an indication of basically debris capture, but no clinically meaningful endpoints were required for the approval of those devices for various reasons. Those are approved under sort of a 510(k) kind of process. Then we have this new device that's an adjunctive device to a valve procedure, intended to help mitigate a complication that occurs with that procedure. To have a trial that is reduction in stroke, which is the trial that I think everybody would like to have, just let's do a hypothesis where we just show stroke reduction was going to be a very difficult trial to run from practical reasons and for reasons because valve technology is evolving so quickly that getting a randomized trial that

big was going to be too onerous from a regulatory perspective.

And so that's where we ended up, in sort of an in-between meeting of the minds in looking at something that might represent something clinically meaningful beyond "captures debris." For example, some measure of cerebral ischemia as measured by perhaps diffusion-weighted MR and some type of clinical trends or correlates with regard to more sensitive tests like neurocognitive testing, etc. So that was how this trial, as imperfect as it may be -- but it was, I believe, a very rigorously run imaging trial for its kind. It's a very difficult study to do.

So I mean, I think there's a lot of imperfection in the development of the performance goal, for example, and no, we don't typically just let safety add a margin for it. But I think in the overall context of what we were trying to design in terms of a clinical trial, I don't think we anticipated that we were going to have significant safety events, and it turned out it worked out that the statistics ended up working out well, even with the sensitivity analysis. But from a trial design perspective, that's not standard fare.

DR. PAGE: Thank you.

Dr. Vetrovec. And then I see Dr. Borer, Dr. Somberg, and Dr. Roberts.

DR. VETROVEC: I'd like the Sponsor to back up to Slide 68 and sort of explain that to me. Maybe I'm missing it, but it appears that the unprotected zones had no volume of territory affected.

DR. LEON: Again, this is median new lesion volume. If it were a mean analysis, it would be different. It would be different, Dr. Vetrovec. But whether it's mean or median, the difference was not significantly different.

DR. PAGE: And just for my own clarity, this unprotected, that's that 2%?

DR. LEON: Yes, that's the --

DR. PAGE: So it's a tiny little part of the brain.

DR. LEON: A tiny little part of the brain.

DR. PAGE: That's the way to analyze this.

DR. LEON: That's the posterior inferior cerebella artery on the left side.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, a minor point. While it's certainly not common to see non-inferiority trials of safety, I'll just remind you that last month the PRECISION trial was published in the *New England Journal*, a 25,000-patient study designed with the FDA, specifically comparing the adverse effects of three NSAIDs, and it was designed as a non-inferiority trial. So it's done. I don't see any problem with having done it here. It's just unusual.

DR. PAGE: Dr. Borer. I'm sorry, Dr. Somberg.

DR. SOMBERG: It seems everything comes down to, in my mind, the meta-analysis because when you add in the extra patients, then there is an imaging difference. And if you accept that, then you have to correlate the imaging difference with some sort of benefit beyond the neuroradiologist and the guys who do the imaging. So can you, the Sponsor, provide me, someone who's really unschooled and uneducated in neurologic imaging, that that correlates with a benefit? Because I think that would go a long way to convincing the unconvinced at the moment, that there is a benefit for this device.

DR. LEON: I think that's a very important point. There is very little literature to suggest that with the neuroimaging analyses, that you have a direct association with clinical strokes or even stroke severity. There is a single study, Bonati's trial in carotid stenting published in the *Lancet*, which suggests that beyond a certain threshold of neuroimaging size lesion, that there is, at that point, a much higher frequency of ischemic strokes. But that relationship that you're looking for is simply not in the literature. I can show again, and

it is a post hoc analysis, but we think it's appropriate just to demonstrate a 63% reduction in neurology assessed, CEC-adjudicated strokes in the first 3 days.

So I do think that this is at least partial clinical evidence that relates to a difference between the two arms but is somewhat supported by the imaging data, especially if you accept the meta-analysis. I mean we'll, of course, talk about heterogeneity, and we'll talk about all of the things that you've requested with regard to the robustness of the meta-analysis. And similarly, we'll be glad to share all of the patient-level data with the FDA.

DR. SOMBERG: I appreciate that, and that's very useful, but I remember some of my colleagues on that side were mentioning, okay, that's in 3 days. What happens a little bit later? If that's the thing I'm going to have to base it on, I'm willing to do that. But what comes a little later?

DR. LEON: But that's when the DW-MRI studies are done. It was an average of four and a half days. So it's 2 to 7 days.

DR. SOMBERG: Okay, but in terms of total patient benefit, I mean, yes, you may have a 63% reduction and Day 1, Day 2, Day 3 summed up. But if 1 or 2 weeks later or a month later or 6 months later it all equals out, you know, what are we doing?

DR. LEON: Well, that gets back to Dr. Brinker's question, and we'll show you data from 30 days, and we'll show you data from 90 days to show you that the difference in strokes is preserved, at least over the course of that 90-day follow-up.

DR. PAGE: Great. Dr. Roberts, please.

DR. ROBERTS: My question relates back to, again, the issue, and I think it's very important what we're calling protected and unprotected and partially protected in these definitions, and one thing that's said here and kind of implied is unprotected is 2% of the brain. But in actuality, if you have a patient with a right vertebral artery that ends on PICA, which commonly happens, the unprotected part of the brain is the whole posterior

circulation. So I think that this plays a very important role and also has important implications for what the efficacy actually is.

And so I have a question for the FDA. Was the choice of the way the neuroimaging was analyzed, was that, you know, an automated method versus a manual method? Was that predetermined ahead of time, agreed upon in terms of it's the best method?

DR. BUCKLEY: I'll let the Sponsor speak to the details with regard to the analysis with the actual lesion volume detection and subtraction techniques and correlation with ADC mapping.

With regard to deciding on what territories are called what, what's protected and what's partially protected and what's unprotected, that was generally Sponsor defined. Kind of the protected correlates with the primary function of the device in covering the right carotid and vertebral arteries and the left carotid. As far as the distinction, if you want to go to Backup Slide 11, with regard to what is considered protected and unprotected, because the only artery that comes off before the basilar is the PICA on the left, that was categorized as the only unprotected or 2% of the territory.

So with regard to these definitions, I don't think FDA has much disagreement per se, but we probably consider this a little more interesting and secondary as opposed to what we would consider. One of the primary areas of interest is the entire brain. So we did not specifically focus on the distinctions between partially protected because you only get half the flow. And no, we don't have additional -- and to your question before, with regard to who has complete or incomplete circles or dominant vertebrals, etc.

DR. ROBERTS: Well, the reason why it's so important is because if you look at the data -- and I think Dr. Somberg asked this earlier, is that if you look at the data with the protected territories, there is some benefit. But then if you look at the data with all territories, all of a sudden that benefit looks like it's lost. And, of course, these are all

numbers that are not statistically significant, so that's, you know, probably the reason. But it's based on what we're calling protected and not protected, and I think that if we looked at what actually was protected and not protected in individual patients, then that would drive how the Sponsor's data looks and could potentially even show better effectiveness in the Sponsor's data if it was done, you know, in a very specific way.

DR. BUCKLEY: I agree. FDA did not perform those analyses or look at specific anatomical issues that would drive individual patient assessments.

DR. PAGE: And for clarity's sake -- because, Dr. Roberts, you're bringing up nuances in terms of individual anatomy that need to be considered. But just for clarity's sake, the issue of protected versus unprotected is the 75/25 range. That was negotiated between the Sponsor and the FDA in terms of the primary analysis. This partially protected and unprotected at 2%, that is a post hoc analysis; is that correct?

DR. BUCKLEY: What I guess is post hoc characterization is the partially protected area. As far as what did FDA agree on with regard to protected versus all-territory analyses, I think FDA made a recommendation that the primary assessment should be all territories. Through continued discussion with the Sponsor, they preferred to look at protected territories. They thought that would be more meaningful. FDA offered kind of a future concern with regard to regulatory approval and needing to look at the totality of the data and that we would be looking at all territories for purposes of approvability.

DR. PAGE: Thank you. But the primary endpoint was what was defined as protected, which was the 74% --

DR. BUCKLEY: Yes.

DR. PAGE: -- for the primary endpoint that FDA and the Sponsor agreed on in terms of --

DR. BUCKLEY: Yes.

DR. PAGE: -- conducting the trial prospectively; is that correct?

CDR TOOR: Yeah. And I wanted to add one point. If we can pull up our backup slide. I believe it's 28, the last one. There's an important note to mention here with regards to FDASIA and how FDA communicates concerns relating to things like the primary endpoint or things that are not specifically patient safety concerns. So we communicated after FDASIA, which was implemented in July 2012. We communicated concerns such as maybe not 100% agreement on the statistical plan's study design considerations. Study design considerations are not concerns that can prohibit enrollment in the study, and the Sponsor can address those, if they wish to. They're not obligated to specifically respond to study design considerations. So FDA communicated our concern with using protected territories in the primary endpoint as a study design consideration because we were a little bit limited with regards to FDASIA as how we could communicate that.

DR. LEON: Can I make just two clarifying points?

DR. PAGE: Yes, Dr. Leon.

DR. LEON: Very quickly. First, cerebral angiograms were not performed systematically. So to be able to get an individual patient-based analysis of the cerebral anatomy to define for each patient whether it's protected, unprotected, partially protected cannot be done, and it was not done in this study.

The second point was, if we had attempted to do a trial with an all-territory analysis, again, it would've been beyond what would've been reasonable in terms of a randomized trial. The variability was so much greater in the all-territory analysis from the predicate CLEAN-TAVI study, it would have doubled the sample size. It's extremely difficult to get these serial DW-MRI studies in patients, particularly elderly, frail patients after a major procedure. And it would have been a study that -- this already took 18 months to enroll. That would've been almost impossible to accomplish.

DR. PAGE: Great. I think this has been a valuable start on our discussion. I'll now call us to a close for the lunch break. We will reconvene exactly at 1 o'clock. I'll ask all Panel members and all participants to be here ahead of schedule. Take your belongings with you, and this room will be secured by FDA staff during the lunch break. I want to remind the panelists not discuss the matter at hand over lunch, and we will reconvene at 1 o'clock.

Thank you.

(Whereupon, at 11:53 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

DR. PAGE: I'm going to call us back to order. We're now resuming this Panel meeting. It's 1:02. We will now 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.

Ms. Washington will now read the Open Public Hearing disclosure process statement.

MS. WASHINGTON: 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 such 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. PAGE: Thank you.

For the record, we originally received 11 requests to speak. One did not appear. The other has left a written comment that will be left at the table out front. That gives us a total of nine presentations. Each speaker will be provided 5 minutes to address the Panel.

We ask you to speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

The Panel appreciates that each speaker remains cognizant of their speaking time. Specifically, there are lights there, a green, a yellow, and a red, green for 4 minutes, yellow for 1, red is when you need to stop speaking. So I hope the most important part of what you want this Panel to hear is at the beginning of your talk or at least in the first 5 minutes because we will cut you off. We have to get on with the rest of this. We appreciate everybody's voice, but we have to be fair to the other, perhaps, eight people after you for this 1-hour session.

With that preamble, I am pleased to invite Dr. Jim McCutcheon from Corpus Christi, Texas. Welcome, Dr. McCutcheon.

DR. McCUTCHEON: I'm Jim McCutcheon, and I have been offered the opportunity to be here, and I appreciate it because I have aortic stenosis, and I have a personal interest in this. Claret Medical told me I might be able to get here, and I said great. They said they'd pay for my transportation and lodging, and I said not if it will impair my integrity. And they said no, the FDA allows that. So that's all they're giving me.

Okay. My story starts 2 years ago when Bob Madry, who has been my long-time cardiologist, told me, Jim, the latest echo shows that you've gone from moderate to severe. It's time for you to look at treatment options. That's all he said. That's all he needed to say. I immediately went home and started looking at treatment options. Obviously, there are three: do nothing, have open surgery, or have TAVR. So I started looking at the risk-benefit relationship there, and I noted that there is a definite decrease in your life expectancy with aortic stenosis, and it's pretty significant when it's symptomatic, not so significant when it's asymptomatic. I was playing tennis three times a week and feeling fine, so I figured, well, I don't need to worry about this right now, but I'm going to keep on looking. I looked at open

surgery, and I looked at TAVR, and I didn't like what I saw with TAVR. I didn't like the risk of debilitating stroke and continuing dementia. I looked at dying, and I'm not afraid to die, but I am afraid of disability and dementia. So I kind of was not so sure. I thought, well, with open surgery it's all washed out. The fragments don't go. I'll go see Sergio Tavares, who did my coronaries 25 years ago, and Sergio said, Jim, you can't have this operation. You're living on your left internal mammary that's plugged into your LAD. It's stuck to the back of the sternum, and if I spread the sternum, you're done for. Okay, Sergio.

So I went home and kept studying, and I read the CLEAN-TAVI, and I read the MISTRAL-C, and I thought, well, I'll go see what they say in Houston, and I went to Houston, and they said the same thing, you can't have open surgery. So I had two choices. Well, I'm asymptomatic, so I waited. But about a year ago, I started having pretty severe shortness of breath when playing singles, and I gave up singles, and I read about the SENTINEL trial, and I looked at Embrella and TriGuard and SENTINEL, and it looked like SENTINEL was probably the best and was going to be available first.

So I e-mailed Claret Medical, and I said do you know when that study will be finished? And they said no. A couple of months later I e-mailed them again. Do you know when that study will be finished? No. I was kind of like the kid in the backseat of the car. How much further, Daddy? Are we at the lake yet? Since Claret wouldn't tell me or didn't know, I went to the Cleveland Clinic website, and it said ask a question. So I put in I know that one of your principal investigators is there. Can you tell me how long this study is going to take? And in 2 days I got a report, and the entire report was at least a year and a half. And at the bottom of that was s-a-m-i-r. I didn't know what that was, but I know now, and you do too.

So then my symptoms progressed. I got to where my buddies on the tennis court were telling me to quit. They didn't want to see me die. So the study came out, and what I

looked at is the risk-benefit relation ratio for me. It looks like SENTINEL has not caused any damage at all, so there's no risk to using the SENTINEL. It looks like 99% of the filters come out with debris that would have gone to my brain. That's a definite benefit. All the statistical analyses in the world don't mean as much to me as the fact that maybe I'll have a chance to run and play again if I can have a new valve and get my brain protected with SENTINEL.

Thank you very much.

DR. PAGE: Thank you, sir.

Our next speaker is Dr. Nicolas M. Van Mieghem from the Thoraxcenter in Erasmus. Welcome.

DR. VAN MIEGHEM: Thank you. First of all, ladies and gentlemen, good afternoon and thank you for giving me the opportunity to present some personal insights on embolic protection with TAVR during this public hearing.

So the case for embolic protection with transcatheter aortic valve replacement: I am the director of interventional cardiology in the Thoraxcenter in the Netherlands, and these are my conflicts. I am part of the advisory board, and I have received research grant support for the MISTRAL-C study, and I was the PI of that study.

So, in general, this was a study that we presented in 2012. It comes from four European centers. And what you can see on the left side is that there is a significant decline in bleeding and vascular complications, but in the middle section is the illustration of what happens with stroke. There was no decline, no significant difference in the stroke rates with the early experience and later on. So that was the incentive, at least for me, to consider embolic protection devices. And for the time being, it is the default embolic protection that we are doing in all our cases. So all our cases are being done in the Thoraxcenter with filter-based embolic protection.

This is data from recent trials that also illustrates that there is no decline in stroke rate with current-generation devices and in the current randomized trials.

Stroke timing post-TAVR, we already heard about that earlier this morning, that the strokes occur within the first 72 hours. So there is definitely something happening during the procedure, and it should be related to the technology that we are applying.

This is a transcranial Doppler study by German colleagues, where you can see on the right end of the slide that especially during the positioning and implantation of a transcatheter heart valve, that is where embolization occurs. We know this by MRI. If you do an MRI before and after TAVI or TAVR, 80% of the patients will have new brain lesions, and brain lesions is brain injury.

Silent infarcts are not trivial, so they are associated with impaired mobility, depression, cognitive dysfunction, even dementia and Alzheimer's, but also associated with future stroke and mortality.

And this is what we experience as operators, what we face when we are implanting a valve. On the left upper side, this is how the aorta looks like, and we need to cross the aorta to reach the valve. And the valve on the bottom left, this is very calcified. It looks like porcelain to me. And on the right side you see what happens when you implant a valve in this degenerated valve, and it's not hard to imagine that debris will dislodge from this valve.

This was the basis and the premise for the MISTRAL-C study. So we randomized patients to the use of filters versus non-filters. Similar to CLEAN-TAVI and also the SENTINEL trial, we found debris in all the filters that we applied. So on the right-hand side in orange you can see the 100% rate of debris captured in the filters.

This is a meta-analysis recently published, combining all randomized trials up to the SENTINEL, and it's clear that there was a significant reduction in total lesion volume but also in number of new ischemic lesions. And it also translated in a reduction of clinical adverse

events.

And this is how I would like to make it visual to you. On the upper side you can see that it's a degenerated valve with a valve implanted. Below is a porcelain cup, and if I drop the cup, it will break, but I cannot predict the size of the fragments. And this is the same thing. When I implant the transcatheter heart valve, I know that I will disrupt some material, that I will dislodge some material. I can only not predict the size of the debris, and it is the size that probably will matter for overt strokes. But we know now that it's not only overt strokes, there are also brain lesions and brain injury that you will not see immediately but maybe later on during a patient's life.

So, to conclude, in my practice I use this device in 85% of TAVR cases. So there are some cases where it's anatomically unsuitable to use the filter-based protection, but the mechanistic concept is sound and valid.

It's relatively easy to use. It takes me 2 minutes to put the filter in. It takes me 20 seconds to take it out again.

The filter has been safe. I have never seen a vascular complication or other complications related to the filter. I have done over 250 cases.

And the debris size is unpredictable, as I referenced already.

And then I also always ask myself, if we know that there is debris, how can it be safe and healthy?

DR. PAGE: Thank you very much.

Our next speaker, and pardon my pronunciation, is Jochen Wöhrle. Welcome.

DR. WÖHRLE: So thank you for the opportunity to present here our real-world experience with the use of the transcatheter double-filter cerebral embolic protection device in patients undergoing transfemoral aortic valve replacement.

This is a complete independent study. There was no conflict of interest. I was paid

for the hotel here, the ground transportation, as well as the flight for this FDA Panel meeting.

So included in this analysis are patients undergoing TAVR at the University of Ulm in Germany since 2014, and the procedures were performed with local anesthesia plus conscious sedation in a hybrid cath lab. The outcomes were defined according to the VARC-2 criteria, and during this period there was no change in operators, technique, or valve types used. For neurological assessment, a neurologist was involved. And we decided to use the double-filter embolic protection device in all patients beginning in 2016. And the rationale, as you have just heard, were the results of the CLEAN-TAVI and the MISTRAL-C trial.

In addition, at the University of Ulm, the radial access is standard for coronary intervention, and the operators performing TAVR are skilled in coronary, structural, and even carotid interventions.

So we present data of 802 patients undergoing TAVR since 2014; 522 patients underwent TAVR without protection, followed by a consecutive 280 patients undergoing TAVR with cerebral embolic protection. And we have 100% 7-days follow-up.

Baseline data between both groups were similar except for a trend towards a higher STS score for mortality in the group without protection, 6.9 as compared to 6.2 in the group with protection, with a p-value of 0.06. There were no differences regarding the diameter of annulus of the LVOT or the calcification of the aortic cusp. There was a trend towards a higher rate of calcification of the LVOT in the group with protection, with a p-value of 0.09.

Device success was high (91.8%), and device success was higher in 2017 (96.3%) when we decided to use the standardized radial access, the ulna and brachial access as well, to introduce the protection system.

Procedural data was similar, except for a significantly larger mean valve size in the

group with protection, based on the more frequent use of self-expandable valves.

Sorry, there's one slide missing here. So here you see the results at 7 days, so 1 week after TAVR. For the overall population, you see that in our experience with 522 patients, the disabling and non-disabling stroke rate at 7 days was 4.2%, and it was significantly reduced to 1.4%, with a p-value of 0.03 in the group of patients protected with the embolic protection device. The rate of mortality or stroke was 5.7% in the group without protection and was decreased to 2.1% in patients with protection, a p-value of 0.02.

And the lower rate of mortality or stroke was not only seen for the overall population, it was also seen in several subgroups such as patients eligible for inclusion in the PARTNER I trial, PARTNER II trial, patients with severe aortic valve calcification, porcelain aorta, male patients, female patients, patients with some STS scores below 8 or patients with some STS scores equal or higher than 8.

In multivariate analyses, the use of the embolic protection system was the only significant predictor for the patient being stroke free within 7 days, and the STS score below 8 and the use of the embolic protection system were significant predictors for a stroke-free survivor within 1 week.

You have seen that in the baseline data the STS score was a little bit higher in the group without protection, so we performed a propensity score matching including the STS score, atrial fibrillation, and other relevant variables.

You see here now, the outcome data at 7 days for the propensity score matched population with 280 patients per group. Again, disabling and non-disabling stroke was 4.3% in patients without protection and was significantly lower in the group with protection (1.4%), with a p-value of 0.04. And there was also a significant reduction of mortality or stroke.

This is a single-center study, and it's not randomized. Nevertheless, we do have prospective data capturing. There was no change in operators, technical issues, or used valve types. A neurologist performed the neurologic assessment of the patients. And this is the largest population undergoing TAVR with embolic protection device so far.

Gentle ladies and gentlemen, in summary, the use of the Claret SENTINEL double-filter embolic protection in real-world use without exclusion criteria resulted in a high technical success, significant lower rate of all stroke within 7 days, a significant lower rate of mortality or stroke within 7 days in the overall population, as well as in the propensity score matched population. And by multivariate analysis, the use of the double-filter embolic protection system was the only significant predictor for the patients being stroke free within 7 days.

Due to the significant clinical impact of the embolic protection device, we try to use the embolic protection device in every single patient at our institution.

Thank you very much for your attention.

DR. PAGE: Thank you.

Our next speaker is David Lange. Welcome.

DR. LANGE: Thank you. Thank you for the opportunity to speak here today. My name is David Lange. I am an interventional cardiology fellow under the tutelage of Dr. Raj Makkar at Cedars-Sinai Medical Center in Los Angeles, California, and I'd like to present a case where we used the SENTINEL device in an otherwise essentially inoperable, non-intervenable patient. My only disclosure is Claret did fly me out here and provide my lodging. I have no other relevant disclosures.

Our patient was a 72-year-old gentleman with a history of ischemic cardiomyopathy, ejection fraction of 20%, chronic kidney disease, hypertension, known severe coronary artery disease, a left ventricular thrombus, and severe symptomatic aortic stenosis. He

presented with acute on chronic decompensated systolic heart failure. He was evaluated by two independent cardiothoracic surgeons and deemed to be extremely high operative risk due to his multiple medical comorbidities. He was evaluated by our heart team and was deemed to be an appropriate candidate for high-risk TAVR.

On May 31st of this past year, he was brought to the cath lab for high-risk TAVR, and as part of the procedure, we did routine TEE, which revealed a highly mobile left ventricular thrombus, shown here on the left in a perpendicular view along the axis of the aortic valve, and on the right, a surface echo cardiogram. You can see very highly mobile thrombus, a high risk for stroke. We felt that due to this extreme risk for stroke, the TAVR procedure could not be safely performed, and the patient was taken off the table. The patient was treated with therapeutic anticoagulation. We had planned to repeat an echo in about a month and proceed with TAVR if the thrombus had resolved. However, the patient unfortunately continued to deteriorate clinically, with worsening heart failure due to his aortic stenosis.

Extensive discussions were then had with the patient, his primary care provider, his cardiologist, and our heart team, and we felt that due to his worsening clinical status, all parties were in agreement to proceed with high-risk TAVR using the Claret SENTINEL cerebral embolic protection device. The FDA was petitioned for compassionate use of this device, and it was approved.

On June 7th, the patient underwent successful transfemoral TAVR using a 23 mm Sapien 3 valve and the SENTINEL device. The patient tolerated the procedure well without complications. He was extubated on the table, and the device was removed. You can see on the left we have a panel of our positioning of the device, and on the right, the deployment of the TAVR valve. The patient tolerated the procedure well, and we had marked improvement in the hemodynamics and symptoms after the procedure, and his

end-organ function improved with increased urine output and increased oxygen saturation. Within 24 hours of the procedure, he was able to lie down almost flat and, though fatigued, he was walking without shortness of breath. The patient was transferred out of our coronary care unit and maintained on IV heparin and Coumadin. He was discharged home roughly 1 week after his procedure, and he suffered no evidence of stroke and continues to do well to this day.

I'm sorry this doesn't project very well, but I'm going to try to read his testimonial which he wasn't able to come and provide, but he asked me to share.

It says, "To Whom It May Concern: At age 72 I had experienced burning in my lungs in May of 2016" -- I'm sorry, I actually can't read this very well. Is there a way it can be projected here?

UNIDENTIFIED SPEAKER: No.

DR. LANGE: All right. Well, I think the most pertinent disclosure is at the bottom here. He described the sense of the same story I shared with you, and he says, "My life was in the balance. I thought of the work I had accomplished and the great joy to have seen my grandchildren. I was positive in my outlook and my confidence in Dr. Makkar and his team of surgeons to do what they had to do. On a rainy day people grab their umbrellas. During the time, my stormy skies cleared up thanks to an umbrella-like device which captured blood clot and gave me my life back. I know that many more will benefit if this procedure can be used. After Dr. Makkar followed up, my ejection fraction has now normalized, and I continue to have my life back and hope others will as well."

Thank you for the time here.

DR. PAGE: Thank you, sir.

Our next speaker is Adnan Siddiqui, M.D., Ph.D., University of Buffalo, representing AANS, CNS, and SNIS. Welcome.

DR. SIDDIQUI: Thank you. Can I have my slides, please? So I'm here to speak on behalf of neurosurgeons and neurointerventionlists that treat stroke. That's my primary job. Claret Medical did provide airfare and hotel for last night.

DR. PAGE: I'm sorry, we're --

DR. SIDDIQUI: We are missing my slides.

DR. PAGE: Did he provide slides?

DR. SIDDIQUI: Yes, I did.

(Off microphone comment.)

DR. SIDDIQUI: Siddiqui, Siddiqui. Yes. So while they go up -- yes.

DR. PAGE: There we are. Let's give him --

DR. SIDDIQUI: Yes.

DR. PAGE: Let's restart the clock. Thank you.

DR. SIDDIQUI: Thank you. So I also represent neurointerventionlists that actually treat stroke, neurosurgeons, the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, the Cerebrovascular Section, and the Society of Neurological -- NeuroInterventional Surgeons.

So this is something which is very familiar to everybody right now. There are a lot of causes for stroke. It's multifactorial. What we are interested in at this particular meeting is preventable strokes during the actual procedure, and it appears that the material either is liberated from diseased vessel segments or from the foreign material introduced during intervention.

Now, if you look at the clinical event rate for strokes, there appear to be multiple trials in low single digits. But if you start evaluating for stroke with appropriate personnel, neurologists who have expertise in stroke, then that rate jumps up. And then if you further look for stroke causes based on imaging criteria, you see a much higher burden. Close to

100% of these procedures is manifest with imaging modalities.

So the question then becomes, okay, well, which one of these is truly reflective of injury or insult to the brain? And the answer to that is all of the above. And there is no one gold standard measure by which we can define insult to the brain. The brain happens to be the most malleable organ in the human body and therefore has the ability to accommodate a variety of insults in a myriad number of ways. And therefore there's no direct correlation between any one particular measure and then outcomes.

So what I heard earlier this morning was there seems to be a signal, but it's unclear. If you look at neurocognition, it wasn't very clear whether there was a direct impact, but the fact of the matter is there is evidence of silent infarcts and changes in white matter that correlate with degenerative activity in the brain with dementia, which we call vascular dementia. Now, does that directly correlate with DWI? It's unclear. But it clearly is intuitively apparent to us. The debris that is released during a procedure that gets lodged in the brain cannot be good. So there are a variety of different things that I looked up in preparation for this talk which are being designed to protect the brain during cardiac interventions.

We believe this is similar to what we went through with carotid intervention. So in carotid cases, we captured debris in 30 to 60%. This was good enough for us to have a mandate, not just from the FDA, but from the CMS as well, that you cannot perform carotid stenting without embolic protection. And in that particular rate, our capture rate was about 50%. With TAVR, it appears to be close to 100%.

So our position would be, well, if it's important enough for us to employ filters during carotid intervention, why would aortic intervention be any different? You have two sets of filters here. Which one's from the carotid where it's mandated, and which one's from aortic disease? We don't really know because both end up releasing debris which

ends up going to the brain and may manifest itself in a variety of different ways. Somebody who has an embolic infarct in the right frontal lobe may look perfectly normal. The exact same lesion in the left basal ganglia may present with hemiplegia. So I think it's not a very linear correlation.

So we believe subclinical ischemic insult is a serious and under-recognized problem. We don't understand fully what the long-term neurocognitive sequelae are of these radiographic findings on MRI, but it's really important to identify stroke acutely and restore flow.

The following statement is endorsed by all the organizations that I mentioned earlier, and I'll take the liberty of reading this.

"These societies are committed to the prevention, management, and recovery from acute ischemic stroke. We're uniquely aware of the inimitable relationship between the brain as an end organ inherently impacted during therapies carried out in the heart or other anterograde vasculatures.

"Currently, the endovascular device-based therapeutic options available to treat cerebral infarcts are focused on large vessel occlusions, which are defined arbitrarily as those occurring in vessels larger than 2.5 mm. And even after successful recanalization, good outcomes are 50%. IV tPA is the only approved therapy for smaller vessels, and the recovery rate is even lower than that.

"So we should consider, again abbreviating all of these, the role of filter-based cerebral protection in the field of TAVR is supported by various studies that demonstrate the safe, effective entrapment." I'll stop right here. "We strongly endorse such endeavors to protect the brain from embolic debris."

Thank you.

DR. PAGE: Thank you very much.

Our next speaker is Dr. Saif Anwaruddin from the Perelman School of Medicine. Welcome.

DR. ANWARUDDIN: Good afternoon, and thank you for allowing me this testimonial. My name is Saif Anwaruddin. I'm an interventional cardiologist at the University of Pennsylvania. I'd like to disclose that my travel and lodging today were provided by Claret Medical.

I won't belabor this point. We know the idea that 30-day stroke rates are associated with TAVR. However, in a carefully or rigorously adjudicated trial such as the SENTINEL trial, I think there's something to be learned. With neurologist participation of carefully adjudicated events, the risk of stroke following TAVR is much higher than what we previously believed.

And this is concerning as an implanting physician. As an implanting TAVR physician, I think about stroke all the time, and I think about 30-day risk, I think about 90-day risk, I think about 1-year risk. But what I'm definitely concerned about is the periprocedural risk, not only because the risk is so high but because as an implanting physician I can do nothing to mitigate that risk for my patients. And as such, we're taking our patients through this procedure, however beneficial, unprotected.

We know that the demand for TAVR continues to rise, and I won't belabor that point. But it's important to understand that even in a procedure that goes extremely well, without hiccups, with an excellent procedural result, the patient can still have a stroke. And the point that remains is that it's an unpredictable event with a potentially catastrophic outcome. So I would encourage you that as we debate the nuances of this study, not to lose sight of this point.

Secondly, as treating physicians, we need an intervention or a device that can help us protect our patients and reduce the procedural risk, which adds no additional risk to the

patient.

Having performed this procedure, I can say it's not any different than original aortic catheterization, which is widely performed across the world for coronary interventional and diagnostic procedures. It's a similar access site, it's a similar sheath size, and I would argue, it's less device manipulation. And the data would suggest that it can be done without added risk to the patient.

So, in closing, we have an unmet clinical need to protect our patients from periprocedural events, which is very important.

We also have a device with a proven safety profile. And if not clinically significant effectiveness, I would argue, clinically meaningful effectiveness.

So as a practicing clinician, my perspective is if this is your patient or a family member, if this is your relative, how would you feel about not utilizing cerebral embolic protection during TAVR?

Thank you for your attention.

DR. PAGE: Thank you very much.

Our next speaker is Larry Ruvo from the Keep Memory Alive and Cleveland Clinic Lou Ruvo Center for Brain Health. Welcome.

MR. RUVO: Good afternoon. My name is Larry Ruvo. I'm here because I want to tell you a story about my mother, 93-year-old Angie Ruvo, and this past year we've had together because of the Claret filter. I am here on my own expense to share our story.

I'm an only child, and I know the importance of care-giving. I learned the hard way. When my father was diagnosed with Alzheimer's in 1992, my mother became the caregiver. Ignorant as I was at that time about care-giving, and after 1994 after burying my father, I had to become my mother's caregiver. I decided to set out to find a cure for these wicked brain diseases that claimed my father's life, and with support of a lot of friends, I raised

over $300 million, and I partnered with the Cleveland Clinic, and the Cleveland Clinic Lou Ruvo Center for Brain Health, named after my dad, was born. It now has five locations in the United States and some of the most esteemed doctors working on finding cures for these terrible brain diseases.

I bring this to your attention because I do know medicine, and although not formally trained, I've become somewhat knowledgeable about the importance of quality of healthcare in clinical trials. God has always been with me through my life, but the stars lined up one afternoon in Las Vegas when Dr. Toby Cosgrove, 5 years ago, was visiting the Lou Ruvo Center. At that time I received a phone call from my mother's local cardiologist and told me that my mother needed a heart valve replacement immediately. That was 5 years ago; she was 87. Toby asked the doctor to please forward the records to him. After review, Toby said there was no emergency and we should follow her condition very closely. We chose immediately another doctor in Las Vegas, and Dr. Ameli followed my mother very closely and last April said it was finally time that the valve now be replaced, 5 years later.

I immediately took her to the Cleveland Clinic where I wanted her to have the surgery. They have an esteemed reputation for cardiovascular surgery, and upon arrival, seven doctors reviewed my mother's case. Three doctors felt she was a little frail and not in the best of health. Four doctors agreed they would perform the surgery, but only with the Claret filter. Immediately I asked, what is the filter? I believed that a large percentage of surgeries on elderly individuals are known to cause strokes, later-onset dementia, and a myriad of other diseases. In my mother's case, the filters trapped the plaque, which I actually saw after the surgery.

Five years earlier, had the local doctor done the surgery, my mother, I believe, would have had some serious problems due to her frailty. The procedure that was used this past April allowed me, her only son, to share a remarkable summer. Photos here with my

children's birthday, her great granddaughter's third birthday. That's the filter that came out of my mother with the plaque in it. And I just wanted to share a moment, take a moment and share how a woman who owned an Italian restaurant, the oldest one in Las Vegas, went on to take care of her husband with Alzheimer's and is still with me today because of the Claret filter.

My personal belief is the filter was the right procedure to do and gave her a quality of life and helped Angie Ruvo Keep Memory Alive. I'm truly grateful, thankful, and appreciative of this remarkable new tool to help those with cardiovascular issues like my mom. Thank you for listening to my mother's story.

DR. PAGE: Thank you very much, sir.

Our next speaker is Robert Eckley from Seminole, Florida. Welcome.

MR. ECKLEY: Good afternoon. My name is Robert Eckley, and I live in Seminole, Florida, and I want to thank Claret Medical for helping me with the expenses of lodging and transportation.

I'm just a regular old guy. I can't follow these acts that just went before me, you know, but I'll tell you my story.

After going through a series of tests, I was evaluated by my cardiologist that I needed a heart valve replacement. He explained the risks of having a stroke or a possible death from the surgery. I then learned about a study they were offering and I asked -- they asked if I would participate. I agreed to have the investigational device used as part of the SENTINEL study with Dr. Robben as the lead doctor and Dr. Spriggs assisting. The device would help prevent a stroke by catching debris that could pass to my brain. I am grateful to have a successful surgery. And the device did capture a lot of debris.

The day of the procedure was very easy for me. I had a short stay in the hospital. In 2 days I was ready to go home, and I did go home after 2 days. I had no complications,

and everything was successful. My biggest fear of having a surgery was having a stroke, and I really believe that if I didn't have the filter, I would've had serious problems.

Now, my brother-in-law, he's waiting for a valve replacement, and he lives in Ohio. So if they don't offer the study in the hospital, he may not get the opportunity without the FDA approval to have the filter put in. I really hope the FDA approves this procedure so others can benefit by reducing the cause of a stroke. And as you are all aware, many people that had a stroke, all their life is really reduced, and that affects the whole family.

Again, I am thankful that I had the opportunity to have the filter, and I hope it will be approved for others. My lifestyle is now back to normal, except I'm so nervous.

(Laughter.)

MR. ECKLEY: And I can do the activities that I used to do without having dizzy spells or shortness of breath or stopping to rest. So I'm very appreciative.

Thank you.

DR. PAGE: Thank you, sir.

The next speaker is Susan Rockenbach from Gobles, Michigan. Welcome.

MS. ROCKENBACH: My name is Sue Rockenbach, and I'm here to tell the story of my mom, Marie Bartman. After getting me to say I would come here with her, she said, oh, well, if you're going, I don't have to go. I hate to travel. So I'm here to tell her story. My travel and lodging expenses are being reimbursed by Claret Medical.

So this is the story my mom wanted me to tell: that she's 88 years old now. She's a mother to 10 children, a grandma to 22, and a great-grandma to 4 currently, with one more due around Easter. And although her heart condition was such that the TAVR was very highly recommended by her doctor, it was really difficult to move forward because I read some of the research studies and I saw the risk of stroke. And her mother had had a stroke, so we knew what it was to help someone who was trying to recover from a stroke as a

senior citizen. And then when my mom was being evaluated for the TAVR, the opportunity to participate in the SENTINEL cerebral protection trial came up, and then she agreed to proceed with the TAVR, knowing that she may be selected to have the filter, but if not, they would be gathering data that could help other people in the future.

So she did have the TAVR on Tuesday, September 22nd, 2015, at Henry Ford Hospital in Detroit, Michigan, by Dr. William O'Neill and a whole team of people. She recovered quickly, and she went home just 3 days later.

And during one of her return visits to see Dr. O'Neill, he told her that she had received the cerebral protection, which she, of course, didn't know, and that a large piece of calcium had broken off and it had been captured in the filter. So there's a picture of the filter and that 3 mm long chunk of calcium, which apparently was captured by the distal filter in this case. That's what had been captured for her. And Dr. O'Neill told us that if that filter had not been in place during the procedure, that that piece of calcium would have gone to her brain causing a devastating event. And I understood that to mean that we would have lost her, whether through death or through severe brain damage. So we were really grateful that Mom had the SENTINEL cerebral protection, and we're glad that it actually functioned the way it was supposed to.

So here's some pictures of Mom since then, making Christmas cookies, going out to lunch with a group of relatives, playing cards, hanging out with some of her grandchildren at a graduation open house. All of these things she can do because of the TAVR and the cerebral protection. She's living in her own home, still cooking, cleaning, doing laundry, telling stories to her children and grandchildren and great grandchildren of days gone by because she can still remember those stories because she had cerebral protection. So her hope and our hope is that this will be available to anyone who is a candidate for it.

Thank you.

DR. PAGE: Thank you very much.

Before I close the Open Public Hearing section, I do want to thank the speakers. All of you kept beautifully on time. The patients and patients' families especially, it's very meaningful to me and the entire Panel to hear your stories. And at the same time, it's our obligation to look at the totality of the data available and to come to our best ability to provide advice to the FDA in terms of safety and efficacy of this device. But we hear what you're saying, and we appreciate your being here.

With that, I'll pronounce the public hearing officially closed and move forward to Panel deliberations. As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak identify themselves each time unless specifically called upon. This helps the transcriptionist identify the speakers.

Now, I believe we gave a little bit of work to the Sponsor and the group to respond to Panel questions. And is the Sponsor prepared to provide those responses?

DR. LEON: Well, we'll certainly do our best to provide as many of the responses --

DR. PAGE: Thank you.

DR. LEON: -- as we can. We think that we caught most of the questions. If we've forgotten any, please, you'll have to refresh our memory, and we'll do our best to be completely responsive and very deliberate in those responses.

First, there was a series of important questions that were posed by Dr. Roberts with respect to specific methodologies regarding some of the MRI scans and the interpretation of those scans. So we've asked Dr. Robert Zivadinov, who's the head of the neuroimaging laboratory, to address those questions.

DR. ZIVADINOV: Thank you very much for the introduction. I'm Robert Zivadinov, director of the core lab center.

First of all, let me briefly review the acquisition protocol. Each site first participates in a dummy run procedure where the imaging protocol was approved by our core lab. All study exams were acquired on a 3 T scanning, and imaging parameters were consistent throughout the study with no software or hardware changes occurring during the study.

Regarding your first question, ADC maps were computed for all scans, and lesions were identified with simultaneous reference to DWI, ADC, and subtraction images.

With respect to your second question about angiography, which we also heard to be discussed in the morning, MRI was not collected as part of this study. However, I would like to clarify that territory analysis was done based on known linear alignment of high-resolution T1-weighted images to the standardized 3D stereoscopic atlas.

FLAIR imaging was acquired at all time points, and the total T2 lesion burden was assessed at baseline and new post-TAVR T2 lesion burden was assessed at 30 days.

In terms of particular questions which were raised in terms of a post-processing method, as you pointed out, the longitudinal co-registration of the echo planar images is really often difficult, mostly due to the distortions at different time points. This highlights the importance of preprocessing, specifically distortion correction via the field map that was included in this protocol.

Additionally, voxel-based traction was used between all longitudinal scan pairs to increase the sensitivity of the new lesions.

In terms of actual lesion analysis, the contours of the lesions were delineated using a reproducible semiautomatic method on DWI images. These analyses were performed by trained medical personnel, and all scans were reviewed by two neuroimaging experts.

DR. LEON: Is that sufficiently responsive?

DR. PAGE: Questions from the Panel? I believe so; thank you. Oh, yes, Dr. Roberts.

DR. ROBERTS: So were all areas identified as lesions reviewed by a radiologist?

DR. ZIVADINOV: Yeah, all the lesions were reviewed by board certified neuroradiologists, and all the analyses were done by two M.D. experts. The adjudication of the lesions was always done by two experts, and there was 95% agreement. When there was disagreement, then there was a third person used in adjudication.

DR. ROBERTS: How did you handle lesions that were bright on DWI but not dark on ADC?

DR. ZIVADINOV: Actually, that's why we used the ADC as a reference, right? Clearly, all the lesions had to be bright also, I mean, on ADC maps. Clearly, the DWI lesions, they're hyperintense on DWI maps, but we used both FLAIR imaging and ADC imaging as a reference, too.

DR. ROBERTS: So if they were bright on DWI but not dark on ADC, were they excluded?

DR. ZIVADINOV: If they were bright on DWI and -- they were excluded, yes, if they were bright --

DR. ROBERTS: In other words, if a lesion is bright on DWI, that doesn't necessarily mean that's an infarct.

DR. ZIVADINOV: Right.

DR. ROBERTS: It's only if it's also dark on ADC. And so --

DR. DWYER: Yeah. Can I just add one thing, too, from a technical perspective? The --

DR. PAGE: Could you introduce yourself?

DR. DWYER: So Mike Dwyer, also from the Buffalo core lab.

So it's a very good point, I think, that you're making actually about the distinction. So generally, if the ADC could be clearly adjudicated as totally isointense, then the lesion was excluded. If there was some question because these are very small lesions, then we

always referred very carefully to the baseline image to be sure that it was not previously there. So if it's bright on DWI, difficult to call on ADC; but if it was not present, then we kept it. Does that make sense?

DR. ROBERTS: It does, it does. Thank you.

DR. PAGE: Dr. Roberts --

DR. LEON: Dr. Somberg had some --

DR. PAGE: I'm sorry.

DR. LEON: Oh, I'm sorry. Dr. Somberg had some very important questions about the meta-analysis methodology interpretation. So we've asked Dr. Roseann White to join us to be able to explain some of her thinking and some of the analytical techniques that were employed in this patient-level meta-analysis.

MS. WHITE: Hello, my name is Roseann White. I'm from DCRI, and I was --

DR. PAGE: Could you speak up a little bit, please?

MS. WHITE: Sorry, I just needed to move the microphone. I'm taller than some of the other people here.

(Laughter.)

MS. WHITE: My name is Roseann White. I'm from DCRI. I'm the Director of Pragmatic Clinical Trial Statistics. I'm here to address some of the questions that Dr. Somberg brought up.

So I wanted to reiterate what we were doing as a single-stage meta-analysis using a mixed linear model. The treatment group was treated as a fixed effect, and the study was treated as a random effect. The data was normalized so that a linear model could be applied. There are currently no accepted methods for nonparametric mixed models for meta-analysis. So, unfortunately, I won't be able to show you anything related to the median. What we did is we transformed the data, and we noted with the observations that

were at 0 mm were set to 5 mm^3, which was half the limit of detection and then log transformed.

I wanted to show you the effect of the transformation. The upper panel is the data on the linear scale, and there is a box plot there. That little squished thing at the very bottom, that little blue thing is the box plot. When we do the log transformation, as you can see, the data is more symmetrically distributed, and it becomes more normalized.

Next, I wanted to show the results of the fixed effect. We believe the heterogeneity is low for the pooling across the three different studies. As you can see, Dr. Somberg, I believe this is the graph that you were looking for. This is the overall where you can see the effect. The overall I-squared is 34%. I'd like to put that 34% in perspective.

With the I-squared, if you have something less than 40%, you've got very low heterogeneity. Between 40 to 70 it's kind of questionable as to whether you would say that they are heterogeneous. If it's greater than 70, then they are definitely heterogeneous, and you have to treat it as a fixed effect. So this was just treating the study as fixed effect, and as you can see, we've got a low I-squared, and several of the other measures of heterogeneity are also low.

This is an expanded version of the random effects model. Again, we've got low I-squared of 15%. The modified X-squared is quite low, etc. So it seemed as if this data could be pooled across these particular studies based on those statistics.

Does this address your question, Dr. Somberg?

DR. SOMBERG: Can you just go back to the previous slide, to the random effects slide?

MS. WHITE: Sure.

DR. SOMBERG: But where is your summary effect? Is that that giant Zeppelin on the bottom there?

MS. WHITE: Yes, that's the giant -- we expanded it. I had to run to get --

DR. SOMBERG: But of course, there's the unity line on the random effects.

MS. WHITE: It's the zero to the right.

DR. SOMBERG: Yeah. So it does cross --

MS. WHITE: Yes.

DR. SOMBERG: -- the unity. So in a fixed effects model, you have significance. In a random effects, you lose that. Why do you think that's the case?

MS. WHITE: In the random effects, we don't lose the significance in the terms of -- you're talking about the overall effect we lose the significance of. So in the random effects model, we didn't lose the overall effect. Yes, I understand. On that particular graph there, it's because of the way it's being plotted right at the moment. Actually, all I'm trying to show here is that the heterogeneity -- there wasn't that much heterogeneity.

DR. SOMBERG: Well, that's why I called it a Zeppelin because I wasn't sure what it was. Do you have a slide with the summary of the effect with the dispersion?

MS. WHITE: Yes, I believe we do. We're looking for it. But if you were to see it, the overall effect was the same actually, whether you looked at the random effect model or the fixed effect model. There was a better version of this graph but we were in a hurry, so it would be a little clearer.

DR. PAGE: I'd like to hear from one of our statistical consultants to explain this to me at least.

DR. NAFTEL: Oh. Well, I'll defer to the other one. This is great having two. Just one thing. You know, when I hear meta-analysis, I'm always thinking of a bunch of papers from the literature with effect sizes and you're combining effect sizes. If I'm understanding, this is a meta-analysis where you actually have the raw data from the studies and you're combining that. So you know --

MS. WHITE: That is correct.

DR. NAFTEL: Okay. So it's really just combining data and making sure that you're accounting for some effect across studies, correct?

MS. WHITE: That is correct.

DR. NAFTEL: Okay. And, of course, that's what we all want, is the raw data instead of just effect sizes. So this, it's not meta-analysis like most of us are used to hearing. It's not an analysis of the literature; it's analysis of raw data, and that's good.

MS. WHITE: Yes. And the definition being meta is these were separate studies. So that's why we called it a meta-analysis.

DR. PAGE: And just to clarify, so the end result of this renewed analysis taken from the three trials and the raw data thereof concludes what?

Dr. Dodd will illuminate this.

DR. DODD: Well, it would certainly be helpful to see the slide with the confidence intervals.

MS. WHITE: Sure.

DR. DODD: And I guess I would -- before I -- well, one question in response to that would be the extent to which you adjusted for the relevant baseline covariates or other procedural differences. I heard earlier some questions about the approach and how that affected outcomes. So I think when we evaluate the meta-analysis, it would be really helpful for me to understand the differences between the three studies and whether it makes sense to combine them.

MS. WHITE: So if we go to the main slide, the first plot that Dr. Leon had put up, that gives you the effects and the confidence intervals across the three studies and then the pooled effect.

DR. PAGE: So this is answering my question --

MS. WHITE: Yes.

DR. PAGE: -- as to this is the raw data --

MS. WHITE: Yes.

DR. PAGE: -- assembled and with all the caveats around the fact that we have one pivotal trial that we're considering, and that's SENTINEL. But these other data were combined in this "meta-analysis" with this result we see here.

MS. WHITE: That is correct. The thing that we should take into consideration, there were no covariate adjustments. The only adjustment that was done is to consider the study as a random effect, which will take into consideration that there may be variability from each of the different studies. So what you end up having is wider confidence intervals because you're taking into consideration that these studies are randomly selected studies from a pool of all the studies we could be doing. So it's a more challenging analysis to do than necessarily the fixed effect.

DR. DODD: And I'm sorry. Is this slide presenting the random effects model?

MS. WHITE: Yes.

DR. DODD: Okay.

MS. WHITE: This is the patient-level random effects. So I also want to remind everybody, this is data that was log transformed and then converted back to the arithmetic scale, so we dealt with the lack of normality or the skew. I think there was some confusion as to the word -- using the word "mean" before as to whether we were really using the mean of the data. We're not. We're actually looking at the means of the transformed data when we're looking at this analysis.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: So along that line -- because clearly, sometimes you have to acknowledge that the log distribution is normal. Sometimes you're not, when it's

nonparametric. And I don't blame you for that at all. But in the whole study, instead of looking at this non-parametrically, if you do what you said, analyze it in the log domain, are you getting the same kind of p-values as you do for the Wilcoxon?

MS. WHITE: Very similar.

DR. NAFTEL: Yeah, I would expect you to.

MS. WHITE: If you think about it, the geometric means are fairly close to the medians, and so you get a similar type of result.

DR. NAFTEL: Thank you.

DR. PAGE: Thank you.

Dr. Leon, why don't you continue?

(Off microphone comment.)

DR. PAGE: Oh, sorry. Dr. Ohman.

DR. OHMAN: Yes. Sorry, I'm a little bit confused because on the first -- on the slide that Dr. Leon showed earlier, that's obviously a significant finding. And then the additional slide you showed, is that dealing with the protected territories only? So we don't have any idea what's the totality, that is to say, all areas within PARTNER. So in the other studies, the CLEAN-TAVI and the MISTRAL, there may actually be a significant effect, but we don't know that. So that's one question.

The second question is that the two p-values didn't seem to jive, and I'm kind of struggling with that, just as a matter.

DR. LEON: I think this is the slide you're asking -- so this is the same analysis but was done log transformed, mean new lesion volumes. This is all territories. No, it's not statistically significant. The p-value is 0.017.

DR. OHMAN: Okay.

DR. LEON: Driven largely by the SENTINEL trial. As you can see, there was a lot more

variability in the all-territory analyses. These were similar but not identical studies. The patient populations were different in Europe in that they were lower on more intermediate-risk patients. The MISTRAL-C study was 4 centers as opposed to 19 centers in SENTINEL, 1 center in CLEAN-TAVI. There were some differences in procedural techniques and the valve types used. So there were some differences. And also some methodology differences, particularly with MISTRAL-C, in terms of the sensitivity of being able to discern differences on the DW-MRI imaging.

DR. OHMAN: Okay, so that's very helpful. Yet I'm trying to reconcile the two p-values; p equals 0.135 with the big Zeppelin, to use Dr. Somberg's analogy. What did that p-value refer to?

DR. LEON: I think it was a heterogeneity reference.

MS. WHITE: Roseann White.

That was the test of heterogeneity. If it was significantly --

DR. OHMAN: Okay.

MS. WHITE: -- heterogeneous, then the p-value would have been less. I mean, it was a test of the I-squared.

DR. OHMAN: Thank you.

DR. PAGE: Thank you.

We'll ask Dr. Leon to continue with the responses to the questions -- Dr. Somberg.

DR. SOMBERG: Sorry about that, but just go back to your overall slide, all territories again, because I'm going to ask you to editorialize. If you look at the protected territories you see in the meta-analysis -- because I'm willing to say that the meta-analysis is the most revealing here. It's adequate numbers, but you have in the protected territories a benefit. In the non-protected in the overall, you have no benefit by using the meta-analysis. So since in real life you're looking at the entire patient, how do you reconcile that? Because

you have no benefit in the entire patient, but in the protected part of the patient, you do.

DR. LEON: Again, that speaks to the adequacy of the surrogate for being able to discern what we think are clinically meaningful neurologic events.

DR. SOMBERG: That's the only surrogate we got to make a decision on today.

DR. LEON: Yes, but we do have some clinical endpoints. We have several other factors, but I think it's the totality of data that really speaks to the value of the device. But this is the best data that we can piece together using the DW-MRI imaging.

DR. PAGE: And Dr. Somberg, that will be a valuable discussion point for the Panel. I do want to ask Dr. Naftel -- Dr. Somberg, you said there is no benefit here. It clearly does not reach statistical significance. I'm interested in Dr. Naftel's and Dr. Dodd's perspective, but whether they agree with what you just said in terms of our subsequent discussion. Does this show there's no benefit?

DR. SOMBERG: I don't want to be quoted. I didn't say that. I said that there was no benefit when you look at this particular meta-analysis dealing with brain imaging, right, lesion amount and with overall taking all territories into account. I wasn't trying to say that there was no benefit for the device, period.

DR. PAGE: Maybe I misunderstood you, but the issue of failure to demonstrate benefit as opposed to whether there's any signal seen by our statisticians. And then I want to move on with Dr. Leon's responses.

Dr. Naftel, were you going to say something?

DR. NAFTEL: Well, I would certainly be fine if there's a signal. Usually, in something like this, when you look at the overall -- the red -- that's where you think, well, when I put together these three non-significant studies, they're going to come together and look significant with a larger *n* and all, and that actually did not happen.

DR. PAGE: And I'm seeing Dr. Dodd agrees.

DR. DODD: Yeah.

DR. PAGE: Great.

DR. DODD: I agree with that.

DR. PAGE: Great. Thank you.

Dr. Leon, why don't you continue?

DR. LEON: Thank you. We want to respond to Dr. Peavy's questions regarding the neurocognitive function analyses and whether or not it was influenced by a floor effect, and we're going to ask Dr. Ron Lazar from Columbia University to respond.

DR. LAZAR: Thank you, Marty.

My name is Dr. Ronald Lazar, and I'm Professor of Neuropsychology and a clinical neuropsychologist at Columbia in New York.

So I want to address the matter of the baseline to try to understand better why we did not see a treatment effect as a result of the intervention. And so in doing that --

DR. PAGE: Could you lift up the microphone just a little bit there? Thank you.

DR. LAZAR: I am sorry. So the first slide I'm going to show you here is a look at how the overall Z-scores were for the entire group. This is the composite of all patients in the study before intervention.

So what we have here along the x-axis is the baseline lesion volume, which we're not going to discuss at the moment, and along the y-axis is the overall Z-score. So the higher you are, the better you're functioning; the lower you go, the worse you're functioning. And the red line across is exactly average for age, the 50th percentile. If this was a normal population, you would see an equal number of dots above and below that zero line, and as you can see, there's a significant skew in the negative direction for this patient population. It turned out that there was a significant correlation with the baseline FLAIR lesion volume, which turns out to be the variable that counts most for these data.

So the question we then wanted to answer is, well, what proportion of patients were actually impaired below 1.5 standard deviations both for the composite as well as for the individual domains? And that is shown in the next slide.

So here we have a composite baseline as the top domain, and then attention, executive function, processing speed, verbal memory, and visual memory. And so we're asking if the population, the normal population, would be expected at a rate of 7%, 1.5 standard deviations below the mean, how many of them exceeded that threshold compared to those who we would see in normals. So it turned out, in the composite baseline, 13.2% of the patients were below 1.5 standard deviations. There is no significant difference in attention or processing speed, but executive function, verbal memory, and visual memory had a significantly greater prevalence of patients below 1.5 SD than you expect with the population as a whole.

So in our judgment, even though not all the domains were equally affected, as a composite, these patients were worse off than the normal distribution in the patient population. So we think that there was a contribution towards a floor effect here.

DR. PAGE: Yes, Dr. Duff.

DR. DUFF: So one point standard -- 1.5 standard deviations below the mean equals about 7%?

DR. LAZAR: That's correct.

DR. DUFF: So in the overall composite, we're only seeing 7% more than we would normally expect to fall below that point?

DR. LAZAR: That's correct.

DR. DUFF: To me, that doesn't suggest floor effect. There still seems to be lots of room for people to go down if only 7% more fall below that point. If we were talking executive functioning as our sole measure, then yeah, that's more than, you know, 30% of

the subjects falling below the point that you talk about. But for the overall composite, it doesn't seem that it's floor that's affecting that.

DR. LAZAR: Well, one of the things we learned in the study that we did note beforehand was how little impact the baseline FLAIR would have on attention and processing speed. And so it does turn out that some functions are affected more than others. And so I mean, if I were to run the study again, I would probably take those out and just focus on those that really show the most significant effect. And this is interesting because when we look at our own published data and those of others in heart failure, carotid disease, and in hyperparathyroidism, we do get effects in attention and processing speed which we didn't find here, and we don't have an explanation for that.

DR. PAGE: Yes, Dr. Peavy.

DR. PEAVY: This is a detail, but especially since executive functioning turned out to be a little bit different, I would question the tests that were actually subsumed under that. So one of them is a copy test, which we often consider visual and spatial functioning, so there's no language. I don't know if there was a clear decision to take out language as a domain. I mean, the way that's divided up would contribute to these numbers.

DR. LAZAR: So you raise an interesting point actually. With regard to the very complex figure test, we've done analyses of those patients. Where you look at focal disease, then visual spatial skills are clearly affected by right hemisphere stroke, for example. But when we find it in widely distributed disease, that's not the effect. The effect is --

DR. PEAVY: When you find --

DR. LAZAR: In widely distributed disease in the brain, such as white matter disease, silent infarction, the effect of anoxia, then it's the organizational aspect of that testing, the putting together sequential aspects of that that seem to be most affected. So based on our

own data and some of the other data in the literature -- but yes, there is controversy in the field about where some of these tests go. I completely acknowledge that. The other question you had was with regard to -- which test was it?

DR. PEAVY: Language.

DR. LAZAR: Language. So it turns out that you really need -- if you're looking at vascular disease, you have to have a large focal event in order to have an aphasia with left hemisphere disease and visual spatial dysfunction with right hemisphere disease. You do not see it in widely distributed disease. It's just not seen at all clinically, and it's not reported in the research, so that's why we didn't include it here. So given that, and the less likelihood we're going to get a signal because we're dealing with this older population, we wanted to make sure that they could do a battery which we felt was most targeted to the functions likely affected in this syndrome. And so we left out visual spatial skills and language skills to target what we think would be most affected by this widely distributed vascular dysfunction. Does that answer your question?

DR. PAGE: Dr. Duff and then Dr. Posner.

Dr. Duff.

DR. DUFF: So a couple times you've mentioned about the relationship between cognitive Z-scores and brain volume lesions. But I think, as the FDA pointed out, those correlations are around -0.2. And so that's about maybe 5 to 6% of the variance that's accounted by those two things, which leaves an awful lot of variance sort of unaccounted for. Did you look at those separately between the test group and the control group to see -- because what has been presented is for all the subjects together.

DR. LAZAR: We have looked at it, and we don't have the data here, but we don't see any differences, and it's probably attributable to the fact that there were small lesions in both groups. And so since there was no significant difference in the small lesion volume

attributed to the very, very small strokes, very, very small infarcts, that's why we didn't see an effect in the two treatment groups. So we're not making any claims as far as that's concerned.

DR. DUFF: Okay. And then just one more point. So assessing cognition in 82-year-olds is tricky because not a lot of normative data goes to that point. And in reading through the materials that we got, it looked like maybe you were using local norms or Columbia norms for that information.

DR. LAZAR: That's not correct. We used the national norms for this.

DR. DUFF: So the test manual norms?

DR. LAZAR: We used the test manual norms in every case.

DR. DUFF: And alternate forms of tests?

DR. LAZAR: When alternate forms were available, we used them. Absolutely.

DR. DUFF: So that means sometimes you did and sometimes you didn't, depending on what was available?

DR. LAZAR: There's only one very complex figure unfortunately. There's only one version of trail making unfortunately. So in those cases we do not use alternate versions.

DR. DUFF: Right. And so when you repeat the tests, obviously there is going to be changes due to exposure multiple times, but you keep using baseline norms each time. You don't have to change norms on these subjects?

DR. LAZAR: Well, we're looking to see whether or not there's change, and so the change is in reference -- in our judgment, was to the population as a whole. And so we wanted to see whether or not there was a significant difference in the outcomes between the two treatment groups.

DR. DUFF: Right.

DR. LAZAR: So we did not have -- we used the national norms to establish what the

standard deviations would be for each particular case, and then we subtracted the Z-scores. So that's how we look at change. So yes, we did use the same norms for both baseline and follow-up.

DR. DUFF: Right. So I guess what I'm saying is by the time the person has gotten the test four times, it's understandable that their score improves, and that is, I think, where you started to see the Z-scores increasing is at that 90-day point.

DR. LAZAR: We don't think there really was much change even at 90 days. And one of the things you have to look at 90 days also is that there was more dropout between 30 days and 90 days. And it's well known in clinical trials of this sort that the patients who are functioning best are the ones who come back.

DR. DUFF: Yeah. Thank you.

DR. PAGE: A brief clarifying comment or question, please, Dr. Peavy, because I want to move on from the neurocognitive in just a moment. Go ahead.

DR. PEAVY: Okay. I was wondering if your norms included education. Did that vary?

DR. LAZAR: All the norms were corrected by education.

DR. PAGE: Dr. Posner, did you have a question?

DR. POSNER: Actually, you've asked all of my questions just now. The only one I had is how far out you went, and did you look at the environment that they went into when they left the hospital? Because I would expect, with an increase in blood flow, an increase in cardiac output, that things should be getting better depending upon where they went and how long they've been out of the hospital.

DR. LAZAR: Well, I think that's a fabulous question, and so I'm pleased to say that I was just funded by NIH to look at that exact question. And so we're looking at cognitive scores --

(Off microphone comment.)

DR. LAZAR: No, I did not.

(Laughter.)

DR. LAZAR: So we're looking at cognitive function as a consequence of before and after TAVR, looking at transcranial Doppler mean flow velocity and pulsatility, and we're also looking at vasomotor reactivity. In our review of the literature in our application, there is not a single published study yet, to date, to demonstrate a change in perfusion to the brain as a result of TAVR. Not one.

DR. PAGE: This has been a very rich conversation. I'm going to ask for Dr. Leon to step back up and address the other questions that we asked the Sponsor to address over the lunch break.

Dr. Leon.

DR. LEON: Thank you. I don't know if this will be quite as rich, but we're going to go through a series of questions, and I'll try to quickly go through the answers.

First, Dr. Cigarroa asked some very probing questions about general anesthesia and also about pre- and post-dilatation. So, first, I'll tell you the general anesthesia were no different in the device arm -- which is the test and safety arm -- and the control arm, and it was 64.3% in the SENTINEL arm and 64.4% in the control arm. So almost two-thirds of patients had general anesthesia. About one-third did not have general anesthesia. I will say that when we look at some of the results in patients, and I'll show you these with and without general anesthesia, there is a difference, and generally, the patients who had conscious sedation were too sick for general anesthesia. So understandably, they had higher MACCE rates and higher stroke rates.

Second, pre- and post-dilatation: Pre- and post-dilatation was frequent. There were no differences overall between device, which is again test and safety versus control. So pre- or post-dilatation was used in 46.7% in the SENTINEL arm and 46.2% in the control arm.

If we look at the results of pre- and post-dilatation relative to clinical endpoints -- the slide should be coming up in just a moment -- I think you can see that any dilatation, pre or post -- or pre and post -- was associated with a higher MACCE rate and a higher stroke rate. When we looked at univariate predicators of median new lesion volume, pre- and post-dilatation was a univariate but not a multivariate predictor of increase in new lesion volume. And as has been suggested, any time we traumatize the aortic valvar complex, we expect that deleterious consequences may result.

Next, Dr. Naftel asked some questions about the distributions of new lesion volumes, and I'll try to show you some slides that hopefully will provide some insights. So this is a slide showing protected territories. This is percent of total frequency looking at the volume of new lesions, and there is, as has been mentioned by the FDA -- in fact, this is derived from the FDA figure. There did appear to be some evidence suggesting that there's a trend, from the standpoint of frequency distribution, of larger lesions associated with the control versus the test.

DR. PAGE: Dr. Leon, can you explain what those multiple dots are, the yellow dots?

DR. LEON: Those are patients with strokes.

DR. PAGE: Total numbers?

DR. LEON: So those are individual patients that have a stroke event. So it's interesting to speculate again --

DR. PAGE: I don't understand. So a blue with a single blue diamond as opposed --

DR. LEON: So a blue diamond is a patient that had a stroke within the window of 20 to 55 mm^3 sized lesion.

DR. PAGE: Got it.

DR. LEON: But what it does show is that yes, there may be more strokes with larger lesions, but there are still many strokes with relatively smaller lesions as well. We'll get

back to this when we talk about the imperfectness of new lesion volume as a surrogate endpoint.

Dr. Naftel also asked about the more standard box plots showing more of the variance in protected territories. And this is new lesion volume. This a log scale. It's not correctly represented, but it is truly a log scale of imaging, test arm and control arm, showing that the medians are somewhat different. You see the interquartile ranges and the min-max data in this box plot to give you at least some sense as to the variance of the data. I will mention that, again, the FDA was -- I think, did a very nice job trying to point out that there is a great deal of overlap in many of these box plots, and we'll get back to that in just a moment.

DR. PAGE: Dr. Dodd.

DR. DODD: Sorry. Before you go, can you go back to the slide with the yellow and blue bars?

DR. LEON: Sure.

DR. DODD: I just want to make sure I understood, just following up. So it looks like there was one patient in the control arm which had a zero volume of new lesion that had a stroke.

DR. LEON: Um-hum.

DR. DODD: That's correct?

DR. LEON: Um-hum.

DR. DODD: Okay. So how did the volume miss it? How did the MRI --

DR. LEON: It easily could've been a small stroke, the window, the timing of the MRI study. These are the data and it's --

DR. DODD: Okay, thank you.

DR. LEON: I think you can have a clinical stroke without a discrete lesion due to

hypotension or due to other things. These are all neurology CEC-adjudicated events. I wish I could say that there was a complete clustering of all of the stroke clinical events towards the right, but it's fairly dispersed.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: So I really appreciate this. Can you stick with that depiction because it's --

DR. LEON: Can we go back to that slide, please, because I think that those provide a lot of information.

DR. NAFTEL: It does. It's just beautiful. A number of things. The statistician that looked at this, as soon as she or he saw this, said oh, my gosh, I've got all of that stuff lumped at zero, and then I've got actual measurements of non-zero. So t-test. Actually, even nonparametric methods are not good for this because a nonparametric method assumes the same distribution but just shifted. So the statisticians actually don't have great ways to analyze this.

But a really good point here is even if we go with the nonparametric, which we have to probably, so we looked at a shift in the midpoint and that's great, and a lot of the statistics look at reduction and all. But this is so important because it shows there's incredible overlap between the two groups and nobody's surprised, but you never see that from the summary statistics, and this is really good to see. So if you don't have this filter, look at all the yellows over there with the small amount. You had a good chance of not much bad stuff happening. With the blues, you've got a bunch of large ones. So it's important in everything we do medically is there's overlap, and that's almost always true. You wish there was a total separation, and we almost lull ourselves into thinking that when we just compare medians or means, but the fact is incredible overlap.

DR. PAGE: Thank you, Dr. Naftel.

Dr. Leon, why don't you continue?

DR. LEON: I just wanted to point out that the FDA, I think, very graphically demonstrated with the box plots and the patients with and without stroke for both protected and all territories, there was tremendous overlap of the data in those box plots, again suggesting our frustration with the robustness of this endpoint.

There were important questions. Someone asked --

DR. PAGE: I'm sorry, Dr. Leon. Dr. Roberts had a comment or a question.

DR. LEON: I'm sorry.

DR. ROBERTS: I was wondering if you have that same chart with all territories.

DR. LEON: I'm sure we can get you that same chart. All territories.

DR. DODD: So does that explain the one stroke at zero, right? So that volume was captured in a non-protected territory?

DR. LEON: Yes, I'm sure that does.

DR. PAGE: That was Dr. Dodd just speaking. I don't know how that stroke would go away.

DR. DODD: I just mean in terms of evaluating the potential surrogacy of the lesion volume for the protected territories versus all territories. So when we looked at the protected territories, there was a volume at zero for the -- that wasn't accurately sort of correlating with a risk of stroke. So now when you look at all territories, you see that there was actually volume for that one patient who had a stroke.

DR. PAGE: That's a very good point. Thank you.

Dr. Leon, we'll ask you to continue.

DR. LEON: Yes. Dr. Ohman asked a question about learning curve effects, which I think are obviously important. It's interesting. We did try to study this, and it's a little complex because some of the highest-volume sites were integrated later during the course

of the study. So the time-dependent learning effects are more problematic, so we looked at the number of cases that were done, and if you look at the higher-volume sites that had more than 20 devices used, it was interesting that there was no significant difference in procedure time between control and device, whereas in the low-volume sites, there was a very significant difference. So part of the learning process is you get more efficient and more effective at being able to actually implant the device.

But in addition, we didn't see any significant differences in MACCE, depending upon whether or not it was a high-volume or a low-volume site. So even though it may have taken longer, it didn't reflect itself in an increase in clinical events. We looked at the roll-in population for the randomized trial versus the high-end, low-volume users, and we didn't see any differences in MACCE. We also looked at device malfunctions, and there were no reported differences in the roll-in patients versus the randomized patients, again, those done in sequence. And if there were a learning curve, we might have seen some of those differences. And device success was still greater than 90% even amongst the first five cases attempted at every center. So that's the best answer that I can give you, Magnus, on learning curve.

DR. SOMBERG: Can you just clarify that --

DR. PAGE: Dr. Somberg.

DR. SOMBERG: Can you just clarify that for a moment? Are you talking about the high volume/low volume for the device that we're discussing now, the de novo device? Or is it high volume/low volume for the TAVR?

DR. LEON: No, this is -- these are all high-volume TAVR sites.

DR. SOMBERG: Okay.

DR. LEON: This is SENTINEL, this is use of the SENTINEL. Is there a learning curve associated with using the SENTINEL device from the standpoint of safety, MACCE events,

procedural time, and other factors such as device success? What we're suggesting is that there is a learning curve in terms of being able to complete the study, but it didn't reflect itself in important differences in clinical outcomes.

DR. PAGE: Yes, Dr. Ohman.

DR. OHMAN: Yeah. I guess linked to this, Dr. Leon, was the idea that when the device was randomized in the EU setting, it looked like it performed a whole lot better. So the question becomes, then, so what is your explanation for this sort of Atlantic divide, if there is any? What would you attribute it to?

DR. LEON: You know, it depends what you mean by better. It's kind of interesting. Certainly, if you look at the CLEAN-TAVI study and you look at the specific surrogate endpoint we used, which was, of course, median new lesion volume in protected or all territories, the results were definitely better. There was much less variability, the treatment effect was greater, and it was statistically significant, the difference.

However, at the same site, if you look at MACCE events in the SENTINEL trial, that same site in the SENTINEL trial, the MACCE events were not better. In fact, they tended to be even a little bit worse. It may have reflected that these were more complex patients. When we looked at the baseline patient characteristics, they may have been a little bit sicker. So there may have been other extenuating confounders that contributed to that, but there was no correlation between what was a tighter and more impressive neuroimaging result with the MACCE and stroke outcomes.

DR. OHMAN: So that's very interesting. That actually is the best explanation I got so far for the discrepancy. So really, as you evolve this into a more complex patient population, you might actually see different results. I thought that's very insightful. Thank you.

DR. LEON: I wanted to deal with the question of surrogacy. This is something that

we struggle with because we went in here in the best of intentions to try to do what we thought was a rigorous trial. We tried to do the most sophisticated neuroimaging study that's ever been done in this field with 3 T units and with multiple serial evaluations, including baseline and subtraction techniques, and we came out with results that were less than what we had expected obviously, and with much more variability in the data than we had intended. So it really spoke to us again as to the rigor of this particular endpoint as a surrogate marker, and this question has been asked.

The only data that we have pointing to surrogacy with respect to DW-MRI, as I mentioned earlier, was the Bonati study in *Lancet* in 2010 with carotid stenting. That did suggest that there was a higher likelihood clearly of having hemispheric ischemic strokes when the DW-MRI lesions were larger. So that is the only predicate data we have. But I must say that we've struggled in this trial, and I think that carotid stenting and classical stroke studies are different than this study and this clinical scenario. And that is again shown very nicely on that example of three control patients that have clinical strokes, where not only size but obviously number vary dramatically and even location appear to be extremely important.

So I think that using it as a simple unitary surrogate, just total new lesion volume, was problematic for us. And when we think about it, the DW-MRI study is really at a point in time. The average time was 4½ days after the procedure, which accounted for, yes, the periprocedural period, but probably also some dilution with other causes of strokes which were not just peri- but post-procedure as well. So I'm not sure that it is truly a proper surrogate for the device effect in and of itself.

I think there are a variety of lesion types, as I've shown here, that we've seen with DW-MRI scanning that we hadn't expected. We saw a dramatic association with the baseline FLAIR brain injury burden as the strongest univariate and multivariate predictor of

new lesion volume. We hadn't imagined that that would be the case, but that was one of the interesting new findings in this study. So the sensitivity of baseline brain injury burden seemed to sensitize many patients, and it's very difficult to sort that out as a confounder. And there was much more variability in the new lesion volume than we had expected.

So we don't believe that this is a perfect surrogate endpoint. We feel that the clinical results with strokes, if not compelling, are certainly an important clinical indicator of treatment effect.

Now, you might ask why didn't we do the study just as a stroke study?

DR. PAGE: I'm sorry, Dr. Leon, have you answered all the questions that we left for you over the lunch break? I really want to be addressing those.

DR. LEON: Okay, so let me go on because I think there's one more question.

DR. PAGE: Thank you.

DR. LEON: I'm sorry. There was a question about -- that Jeff Brinker asked about not just early but later analyses of clinical events, specifically strokes. This study was a 90-day study, so we don't have 6 months, we don't have 1-year data. Perhaps if we go to the TVT registry we can get 1-year data, but not all the patients have even been followed for 1 year yet certainly. But I just wanted to show you the analysis from 72 hours. We did present before the 30-day data, and these are the 90-day data that we do have. So the reduction that was seen early on seems to be preserved for the duration of the study with stroke frequency reduced by 47%, from 12 to 6.4%.

DR. PAGE: Anybody have any questions about that?

Dr. Somberg.

DR. SOMBERG: Can you go back to that slide?

DR. LEON: Could you go back to that slide, please?

DR. SOMBERG: If I may, it's no longer significant at 90 days, though; is that right?

DR. LEON: Yes, the p-value is 0.11.

DR. PAGE: And you're not showing the 30-day, but the 30-day likewise was nonsignificant.

DR. LEON: Was not significant. That was 9.1 versus 5.6%.

DR. PAGE: Dr. Naftel.

DR. NAFTEL: So I assume -- tell me if I'm wrong. I'm going to assume, assuming the correct statement for the 90 days is assuming you're alive, assuming I haven't lost you to follow-up, assuming you're evaluated, then bam, this is it. Am I right?

DR. LEON: That's correct. Yes, you're absolutely correct.

DR. NAFTEL: Yeah, it's very conditional. Good, but it's always important because you look at this, and you think you know exactly what it is, but you don't. It should at least have a footnote on there.

DR. LEON: That's a very good point. We hastily put this together, but you're absolutely right. I guess the point here was to show that with the stroke difference that was seen early that we thought reflected the device effect or effectiveness, that some level of that seemed to be preserved out as long as 90 days. The question was, is it lost over time? And what we're suggesting is that it seems to be somewhat preserved over the course of at least the first 3 months.

DR. PAGE: Thank you, Dr. Leon.

Dr. Cigarroa.

DR. CIGARROA: And if you just go back to that slide, Dr. Leon. And this is not a pre-specified endpoint; this is a post hoc analysis at 72 hours?

DR. LEON: Yes, definitely the 72-hour analysis is a post hoc analysis.

DR. CIGARROA: Thank you.

DR. LEON: The pre-specified analysis was at 30 days, yes.

And the last question that I wanted to answer -- I just had one more -- was a question about flow and whether or not flow could have somehow influenced the potential even for shunting to a non-protected vessel like the left vertebral. So you've all seen this slide. Obviously, the filters are in the arteries themselves, and we did careful animal studies, a GOP animal study, where we actually macerate a thrombus and injected them into the implanted filters in animals, and we injected a worst-case scenario of large amounts of material, larger than anything that we had seen clinically, and the degree of blood pressure change across the filter varied from 0.8 to 2.8%. So we don't believe that flow is importantly impaired, and if flow is not importantly impaired and the filters are in the arteries, we don't see any reason why there should be shunting to the left vertebral artery.

DR. PAGE: That's very helpful. Thank you.

In this last section, I just want to ask our FDA colleagues -- thank you, Dr. Leon, for the time being -- our FDA colleagues, did you have any other -- I don't think we left you with any homework, but I want to give you an opportunity to address the Panel before we go into the break and then the questions.

(Off microphone response.)

DR. PAGE: Okay, great. And I want to make sure that I've allowed our Patient, our Consumer, and our Industry Representatives to ask any questions they might have at this time of either the FDA or the Sponsor. If you don't have any, that's okay, also.

Yes, Dr. Posner.

DR. POSNER: It's not a question, just a comment. But just because there has been no published article that there's a change in blood flow with the change in aortic valve doesn't mean there wasn't one. It just means nobody studied it.

DR. PAGE: I didn't hear what you just said, sir.

DR. POSNER: Well, I said one of the comments that we had was that there's been no published data that shows that there's a change in cerebral blood flow following aortic repair. It doesn't mean there wasn't one; it just means that nobody has studied it and gotten it published.

DR. PAGE: Fair enough. Thank you.

DR. BROCKMAN: Dr. Page?

DR. PAGE: Mr. Frankel, did you have a comment?

MR. FRANKEL: Two quick questions for the FDA, one being that the data that's been published for the estimates annually show that up to 51% of patients with bypass, up to 17% of PCI, 17% with angiogram, all of them have decreased cognitive reserve. Did you feel, as part of the analysis, that could be a confounder in terms of the neurocognitive assessment afterwards because you had this mixed bag of, you know, some patients having that history and some not? How strong of an effect do you think that would've had on the neurocognitive testing afterwards?

And the other question is, just in terms of the outcomes from the PARTNER II trial, the 2.7% overall stroke rate over there. That was with a clinical trial with careful neurological assessments throughout. Is there an explanation of how that jives with what we saw in this trial?

DR. BROCKMAN: Mr. Frankel, can you repeat your first question? We're going to have another responder come up and answer it.

MR. FRANKEL: In summary, it's just there is a correlation between whether it's bypass, it's up to 51% of cognitive reserve being decreased with patients that have suffered from those events, and there's a number of them, a substantial percentage of them, who were the patients within this trial. So how much of an effect was that thought to have had on the neurocognitive assessments after the device was implemented?

DR. BUCKLEY: I can tell you we did not do that subanalysis to look at bypass patients separately from the rest of the neurocognitive patients with regard to specific differences in neurocognitive decline.

MR. FRANKEL: In terms of the sharp discrepancy between the most recently published PARTNER II trial, in terms of the stroke rates?

DR. BUCKLEY: I'm not sure I have a specific comment on that. Dr. Laschinger, our CT surgeon, isn't here, but I can try to get back to you on that.

DR. PAGE: Dr. Hammon, did you have a comment?

DR. HAMMON: Yeah. I'd like to ask you a question. Where did you get the data on a 50% decrease in cognitive reserve in bypass surgery patients? Because I know that literature very well, and that is way off the top of the list.

MR. FRANKEL: So I was quoting from an estimate that Dr. Daryl Gress published in *JACC* 2012. There was a paper there where there were national estimates, and there was a range, and it was up to 51%.

DR. HAMMON: So you said it's an estimate?

MR. FRANKEL: Yes, a national estimate. Yeah.

DR. HAMMON: Okay. Well, the national data have been published repeatedly since that time, and we're talking somewhere in the range of 10%.

MR. FRANKEL: Okay.

DR. HAMMON: Sorry.

DR. PAGE: Thank you, sir.

Mr. Thuramalla, did you have a comment or a question?

MR. THURAMALLA: No, not at this time. Thank you.

DR. PAGE: Okay. With that, we're a little bit ahead of schedule, but I think you'll forgive me --

DR. BROCKMAN: Dr. Page?

DR. PAGE: -- if we now go into break.

DR. BROCKMAN: Dr. Page?

DR. PAGE: It's a quarter of 3:00.

DR. BROCKMAN: Sorry.

DR. PAGE: Dr. Ohman, hold on for just one second and we'll hear from Dr. Brockman.

DR. BROCKMAN: Thank you. Randy Brockman, FDA.

Before we leave the questions, I wanted to make sure that the panelists got all of their questions answered. I had a couple written down here, and it wasn't clear to me that they were addressed. So the ones that I had written down, I think a couple of people asked for results stratified by TAVR devices. Did you get a response to your question? I mean, I know that there was some discussion, but I was under the impression we were going to hear more. So that was the first one.

DR. YUH: It seems like the stratification, if any, was quite limited, and so we didn't really have that as official homework to do.

DR. BROCKMAN: Okay.

MR. FRANKEL: I'd appreciate seeing it, though, if it's possible.

DR. BROCKMAN: It was to the Sponsor. I just wanted to make sure the questions had been addressed.

MR. FRANKEL: Yeah, that was --

DR. BROCKMAN: So that was one. The other one I also had written down, it was a question about what data supports protected territory lesion volume supporting clinical benefit. And I know that there has been some discussion around that. I just didn't know if you actually had your question addressed. So I put those on the table.

DR. DODD: Yeah, I don't think -- I mean, I think the data that are available were shown, and it did not address that question. I did have one other question I wanted to just bring up with regard to the last plot that they showed with the 72-hour stroke. And as I understood it, that was with the analyzed intent-to-treat population, right, which is -- there are 30 lost to follow-ups in the SENTINEL arm and 20-something in the other arm. So I mean, I think as we look at those numbers, we have to make sure that we keep in mind that there are losses to follow-up. We don't know what happened to those patients. That's incorrect?

DR. LEON: That's absolutely incorrect. It was part of the safety analysis. There were a total across the three arms of 18 patients. None of those 18 patients that were randomized among the initial 240 patients, none of those 18 patients had a MACCE event. So there were a total of 18 patients across the three arms that were not included in the analyzed ITT population for the clinical events.

DR. DODD: So in that last slide, could you just show that again? That's including --

DR. LEON: Sure.

DR. DODD: This is really helpful, so I would appreciate --

DR. LEON: Sure.

DR. DODD: -- the clarification.

DR. LEON: Sure. You can show the 72-hour stroke data. Sorry, it takes a moment to get these up.

DR. DODD: So it says analyzed ITT here.

DR. LEON: It's the analyzed ITT population. Again, it's a little bit confusing in terms of the nomenclature. The entire patient cohort, of course, was 240 patients. But there were a total of 18 patients that were either lost to follow-up, withdrew, didn't have a TAVR device, didn't have a SENTINEL device, that were not included in the analyzed ITT

population. But none of those patients had a MACCE event, at least as far as we know.

DR. DODD: Okay.

DR. PAGE: Dr. Brockman, were your questions addressed?

DR. BROCKMAN: If the panelists are comfortable that their questions were addressed, I'm fine with that.

DR. PAGE: Great. And Dr. Ohman, did you have another comment or question?

DR. OHMAN: No, I'm just trying to draw the Chair's view to the end of the table.

DR. PAGE: Thank you. Does anybody from the Panel have another comment or question, or are we comfortable going into break?

(No response.)

DR. PAGE: We will reconvene at 5 minutes after 3:00, and we'll start in with the questions. Thank you.

(Off the record at 2:48 p.m.)

(On the record at 3:05 p.m.)

DR. PAGE: Okay, I'll ask people to take their seats, please, and I'll call the Panel back to order.

At this time we're going to focus on discussion of the FDA questions. Panel members, copies of the questions are in your folders. I'll ask that each Panel member identify him or herself unless called upon ideally before they speak. Commander Toor is going to be reading the questions to us.

Just in terms of the remainder of today's meeting, we have a number of questions to go through, so I'm going to try to keep us from getting hung up on the first of the nine that we have to go through. At the conclusion of the questions, I'm going to provide an opportunity for the FDA and then the Sponsor to give a summary statement, hopefully 5 minutes or less. And then before we close, there is not a vote because this is a de novo

request, but before we close I will go around the table and ask for any comments from each individual member of the Panel who wishes to speak.

So with that, Commander Toor, would you please read the first question?

CDR TOOR: Question 1, Safety Results: Primary safety analysis included comparison of the 30-day MACCE rate to a literature-based performance goal of 18.3%. The ITT with Imputation population is the pre-specified primary analysis population. A secondary qualitative comparison of the patients in the Test Arm (treated with the SENTINEL System) to the Control Arm was conducted as Secondary Safety Endpoint 2.

Question 1: Please comment on the clinical significance of the safety results.

DR. PAGE: Thank you.

I'm looking for members of the Panel to speak up as to their perspective, and I'll get a feeling for the group, and then as we always do, I'll provide feedback to Dr. Brockman, representing the FDA, in terms of the adequacy of our addressing these specific questions.

Dr. Cigarroa.

DR. CIGARROA: So I believe that as the data was presented and as it was performed according to the structure of the clinical trial, that I'm not concerned there would be a signal of potential harm as it relates to safety. I think that the analyses that were done and then the inclusion of those individuals that were not in follow-up did not raise any concerns to my eye.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Good.

DR. GOOD: I agree. I think any risk is because of the primary procedure, not because of the device that we're looking at here. I believe that the SENTINEL device itself does not provide -- it doesn't have any significant safety concerns.

DR. PAGE: Thank you.

Does anybody else wish to -- Dr. Posner?

DR. POSNER: Just a positive statement that mentally I agree with all of that, but the amount of training and learning that is being offered to the users of the device is really very well thought out and, I think, useful since there is a learning curve in using the device.

DR. PAGE: Thank you.

Other comments? I'm looking around for head nods perhaps as to whether you're comfortable with a fairly concise response, that we see this as meeting adequate safety criteria in terms of this device. I'm looking around. I'm seeing many nods; I'm seeing no one shaking their head.

So, Dr. Brockman, the Panel I think unanimously is expressing a sentiment that, as evaluated, this device appears to be safe as used in the context of the TAVR procedure. There wasn't given the opportunity to discuss fully the safety endpoints, but during the discussion there was minor concern about the criteria used, but I think among all of us we're seeing that this device appeared to be safe in the hands of well-trained individuals and not adding significant risk to the overall procedure for which it's designed to be an adjuvant part of that procedure.

Does this meet the needs for you and the FDA, Dr. Brockman?

DR. BROCKMAN: Yes, thank you.

DR. PAGE: Thank you very much.

With that, Commander Toor, I'll ask you to read Question No. 2.

CDR TOOR: Question 2. Sorry, I'll advance the slide.

Question 2: Effectiveness Endpoints. The goal of the SENTINEL device is to maintain the benefits of TAVR while reducing embolic cerebral ischemia. Because a clinical trial designed to focus on clinical stroke reduction alone would be overly burdensome given the anticipated large sample size and trial duration in this dynamic field, a surrogate was

considered to evaluate the effectiveness/benefit of the SENTINEL device as measured by cerebral infarct volume on DW-MRI. FDA created box plots displaying the observed Day 2-7 DW-MRI total new lesion volume in protected territories only and in all cerebral territories by 30-day clinical stroke status. New lesion volume measurement does not seem to differentiate patients with clinical stroke as the ranges for the two groups overlap greatly.

Question 2a: Please comment on the appropriateness of DW-MRI as a primary effectiveness endpoint for the SENTINEL study.

DR. PAGE: Go ahead and read No. 2(a) -- 2(b), please.

CDR TOOR: Sure. Question 2b: Please discuss any recommendations for future trial design/clinically significant effectiveness endpoints.

DR. PAGE: Thank you.

I asked for both to be read because they're somewhat intertwined. And again, Question 3 is for the effectiveness results from this trial. Right now we are assembled, and if you think of the wonderful brain power we have at this table in different areas, we're here to provide our collective expertise in terms of not just how this endpoint was constructed but how future trials might be put together, so this ought to be a valuable discussion. I'm looking for anybody who wants to make the first comment.

Dr. Somberg had his hand up first, and then Dr. Hammon.

DR. SOMBERG: Well, I think we had very different training, Dr. Hammon and myself, so we'll see how this correlates here, but my impression is, from listening to Dr. Leon and the Sponsor's presentation, that when the study was put together in '12 or --

DR. PAGE: I'm sorry, Dr. Somberg; it's my hearing perhaps. I'm not understanding what you're saying. So if you could speak clearly and so we can get it for the record --

DR. SOMBERG: It's my --

DR. PAGE: -- and in case I can hear it.

DR. SOMBERG: Okay, can you hear me now?

(Laughter.)

DR. SOMBERG: I've never been accused of being shy or not heard, but I will speak up here. So anyway, my understanding from the Sponsor's presentation was when this was put together, there was an article in the literature that suggested that this type of imaging would be useful in assessing the concept of brain damage from embolic events, and that the early work with the SENTINEL device and their European experience suggested there was a difference using this assessment technique. It turns out that, from the Sponsor's own multiple statements, is that this became problematic when one looked at the data, and it didn't exactly evolve into their field, and apropos what was brought up earlier, you know, we asked the question about what's the correlation of the standing with clinical outcomes, and it was very nebulous and not an exact answer, so I think, in retrospect, it was not as good as it was thought to be. We have the data, and the data is what it is, we can discuss that, but I'm -- but my impression is, as the Sponsor has moved towards stroke -- assessing outcomes using stroke, that it will be probably very important to, in any future studies, not just look at an imaging outcome but look at neurologic evaluations of the patients in a systematic way, and that might be more informative. So I'm giving, what should I say, a workload to my neurologic colleagues in this matter because I don't think imaging is, at this point -- and I have to say, they said it was a state of the art -- gave us adequate data.

DR. PAGE: Thank you.

Dr. Hammon, then Dr. Good, then Dr. Yuh, then Dr. Roberts.

DR. HAMMON: Well, I agree with the general thrust of Dr. Somberg's response, but what I would like to point out is that certainly stroke volume, the volume of this tissue that's been infarcted is important, particularly if there's a huge difference. But I also would point out that it's the location that is the most important. So if you have a 3 cm lesion in

the frontal lobe, they're not going to present with the same kind of stroke as if you have a 0.5 cm lesion in the internal capsule, and in that particular patient, they might not be able to walk or talk or use their arm. So I would have to say that this is not a very sensitive way of measuring the injury that has occurred, particularly in a patient that -- where you have this basket of potential emboli sitting there just waiting to go someplace.

DR. PAGE: Thank you.

Dr. Good.

DR. GOOD: Well, I essentially agree with much of what Dr. Hammon said. I don't think that looking at the lesion volume is going to be a very good marker for clinical stroke. Now, obviously there's a lot of overlap, and we talked about the variability here at great length today. But as he pointed out, it really is where the lesion is, is what causes the symptoms. Now, I don't think we should be lulled into thinking, though, that all of these multiple emboli are of no significance; they are strokes. I mean, they were confirmed with ADC images, and they clearly are small strokes; they just aren't presenting with major clinical symptoms acutely. Now, over the long run, that may not be -- that may be a problem. You know, we know that the small vessels, these white matter disease multiple small cortical strokes, in cross-sectional studies, are correlated with cognitive problems, and it may well be that some of these people have a poor cognitive reserve, and adding multiple little small strokes over the long run might be detrimental. Now, we don't know. There's no real follow-up studies to look at that. But as a marker for clinical strokes, it's not very good. I think I'll leave it there.

DR. PAGE: Thank you.

Next is Dr. Yuh.

DR. YUH: Yes. My comment was really echoing Dr. Hammon and Dr. Good, and just to extend it, you know, might be relevant with respect to Question 2(b) in terms of location,

but any future studies may want to look at the distribution of the lesions as opposed to volume and see if there's any -- either with overt stroke or a more subtle decline in neurocognitive function.

DR. PAGE: May I ask microphones for Dr. Hammon and Dr. Borer be turned off, please?

Thank you, Dr. Yuh.

Dr. Roberts.

DR. ROBERTS: Again, I think I'm going to echo what other people have already said. I think that on DWI, if it's ADC dark that's representing the brain tissue -- and, you know, as clinicians, we should not do any harm, and so regardless, if we don't know the clinical significance of it, that's still dead brain tissue, and so I think that that's very important. So I think that any future studies should continue to include diffusion imaging along with these other clinical assessments. But the issue of diffusion imaging is that it's problematic. The mean time that the imaging was done here was 4.5 days, and so the DWI doesn't necessarily represent what was associated with the procedure. And also there are other issues, such as strokes that don't show up on -- that aren't DW positive, DWI positive. So I think that these studies should include diffusion-weighted imaging but that we should be very careful and think about how we're going to analyze the data and process it.

Again, I think I raised this in the discussions earlier, but I think this issue of assigning these territories to protected and unprotected and particularly this category of partially protected is a bit problematic, particularly when we have no idea about the patient's vascular anatomy. I think if we are going to continue to use DWI in these type of studies, while they're in the scanner they could undergo a 3-minute MR angiogram procedure so we can at least have an idea of what their vascular anatomy is as approximately 30% of the population has variant vascular anatomy.

So I think those are my main concerns, and another concern is that whenever we start doing procedures such as normalization, particularly in sequences that are highly susceptible to artifact, that can also be problematic and so can lead to systematic errors, and so I've done these longitudinal studies before where you're trying to align patients' images over time, and it's very difficult, even in the best of circumstances with wonderful T1-weighted images, much less with these diffusion-weighted images. So I think consideration should be taken into whether or not we're going to do this in an automated method versus have a radiologist sit there and do it manually as well. So I think those are my concerns.

DR. PAGE: Thank you very much.

I have Dr. Posner, Dr. Cigarroa, and Mr. Thuramalla, as well as Dr. Borer.

As we're discussing, I'm seeing a lot -- I'm hearing a lot of dissatisfaction with the diffusion-weighted imaging, which is a surrogate. We need to give future sponsors and the FDA advice as to how they would move forward, and is the Committee rejecting the idea of a surrogate? Because we've seen or we could model a very large study that would be required to account for the clinical endpoint of stroke, and that's why this trial was done with the surrogate. So let's just keep that in mind in terms of the reality of what the next trial might look like and whether that could be conducted.

Dr. Posner, Cigarroa, Thuramalla, and Borer, and Dr. Good are all on deck, for this is Question No. 2.

DR. POSNER: Let me be very simple. We all assume that fragments from the valve procedure can get into the brain and cause damage. What this device does is just filter it and reduce the amount of stuff that comes off the valve and gets into those particular vessels that it's placed in. So I think an endpoint would be is it effectively filtering out the materials that it's supposed to filter out in those two vessels? I don't think we need to be

fancy about what's happening for stroke, what's happening in the brain, what type of imaging that we're doing. The number of lesions doesn't necessarily reflect function, as was pointed out, depending on location, location, location and size, size, size, and this is a simple filter. So I think if you want to measure an effective endpoint, measure how much is coming off the valve and how much it catches.

DR. PAGE: Thank you very much.

Dr. Cigarroa.

DR. CIGARROA: As I look at the appropriateness of DW-MRI as a primary effectiveness endpoint, one has to ask what is the clinical relevance and how predictable is reduction of embolization to that clinical endpoint. In disease states, we do know that silent ischemia is associated with cognitive dysfunction, so I ask myself two simple questions: Will it predictably reduce stroke if studied in a sample size that's adequately powered, and can one extrapolate that? Number 2: If one can't do that, can one predict that it would reduce cognitive dysfunction? In hypertensive patients, we know that the overall volume of abnormalities by diffusion-weight imaging is associated with cognitive dysfunction. Now, it becomes challenging, in that disease state, to extrapolate to a manufactured disease state, and that is when we, as operators, embolize components. So I am challenged by this as an endpoint because of the differences. I am challenged by the predictability or the lack of predictability of what embolic event at what volume will manifest in a clinically significant stroke. As an operator who does procedures, I would always be happy to have less embolic material because I can never predict, and that is a conundrum.

DR. PAGE: Well said.

Mr. Thuramalla.

MR. THURAMALLA: My point was briefly covered by your comment, Dr. Page, and

that is if this device was to be approved and if it falls into Class II, then expecting a stroke outcome study which would have a significant sample size would be overly burdensome for the industry. Thank you.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Thank you. Quite honestly, as I read through this, I wasn't so concerned about whether there were more strokes or fewer strokes; strokes tended in the right direction, although there were too few to see anything. I would have been perfectly happy with the result that showed less neurocognitive dysfunction, but this imaging surrogate didn't seem to correlate very well with that either, and in fact, the correlations that were shown were quite weak, so I'm concerned about that, and the question is why, because intuitively it seems reasonable that the worse the image, the worse the neurological situation. So if I were going to redo this, I would, as Dr. Roberts said, rethink the timing of the imaging, if imaging is going to be used, and I would be as certain as I could that I had good baseline information not only about the image but about neurocognitive function. Dr. Peavy mentioned that it was well presented in the panel pack that floor effects are a problem. It may be very difficult to show something if there's already sufficient damage so that there's not much margin to be able to show anything, so that's -- I'm concerned about this as the endpoint. I don't care that it's a surrogate; I'm concerned about it as an endpoint, and I would do these things if I were going to redo this study.

DR. PAGE: So let me ask, if we didn't see any neurocognitive difference in this trial, do you believe it's because the trial was too small, or do you believe it's because the device doesn't have any effect? Because if it's an issue of trial size, we can do the math, but this would be a pretty big trial if we are going to find statistical significance.

DR. BORER: Well, neurocognitive improvement was shown in one of the three

studies that was presented to us. It wasn't shown in the other two, and it wasn't shown in the biggest, so there seems to have been some difference in the way people were looking. And I do believe that sample selection may have been very important here. Screening of people for their baseline abnormalities should have been done.

DR. PAGE: Okay.

Dr. Good and Dr. Ohman and then Dr. Duff and then Dr. Hammon. We're on Question 2 here.

DR. GOOD: Yeah, this will be the longest question, I'm sure. I agree with much of what Dr. Cigarroa said, he said it very eloquently, and I also agree with some comments that Dr. Roberts made earlier. You know, the question of what is a surrogate comes up. You asked, Dr. Page, is this an appropriate surrogate for stroke, and probably it's not, but I don't think we should throw the baby out with the bathwater either and just ignore the fact that these DWI abnormalities are present. It may not be a real good surrogate for clinical stroke, but I would say it's still important. Now, again, you pointed out it's a real problem to get a large enough sample to be able to pick up clinical stroke, and that's, of course, why we have this other DWI marker that was thrown in here. But I think we -- again, I don't think we should be blasé about saying that this is not important, and I'd be interested in what my neurocognitive colleagues say about whether this is something that in the long range could be a problem. We're only going up to a short period of time. We don't know long term if this is going to be important or not in these elderly people who have other causes for cognitive problems.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: Yeah, this is kind of sad because this is science and evolution, I think. Actually, FDA, a number of years ago brought together a panel to define surrogate

endpoints and how they should be used and interpreted, and so they should be biologically plausible, and I think everybody here thinks that a spot in the brain is not a good thing, so I think that that's biologically plausible. Is it reproducible? Yeah, it is reproducible because you can repeat the MRI imaging, so that is all well and good. Now, where we get into this is, is it related to a measurable clinical meaningful outcome? That is the challenge.

We've seen the data on stroke, the overlapping imaging with the individual stroke, and I think my assessment is that this is not an adequate surrogate endpoint not because somebody picked it and it was wrong; it was simply that the knowledge of science at that time and how that relates to actual strokes or clinical strokes are much less clear. And it's even so with cognitive function, which would have been a perfectly acceptable linkage had it occurred, but I haven't seen any of this. One has to say that using the FDA's own definition from a number of years ago in another co-related field, actually this does not fulfill that criteria unfortunately.

DR. PAGE: Thank you.

Dr. Duff and then Dr. Hammon.

DR. DUFF: This is related to Question 2b. So I think we need to keep in mind what Dr. Hammon said about location, location, location in that we should not expect neurocognitive dysfunction in all patients that experience stroke because it depends; where the stroke occurs may determine whether there is neurocognitive dysfunction or not, so using that as our only endpoint, it sounds strange for me to say as a neuropsychologist, but maybe isn't the only thing we should be focusing on or put so much effort on. That being said, I would just encourage, for moving forward for future clinical trials, I think it's important to look at normative data that incorporates cognitive change, that you can't use baseline scores to interpret the third, fourth, or fifth time somebody's taken the exact same cognitive test.

I think that it was problematic in the battery that they had some tests that had alternate forms and other tests that didn't, because that means some of the measures are going to show practice effects and others are not. And also, we expect to see differential practice effects at different time points. So if somebody gets a test repeated closer together, they're going to show larger practice effects, but if you spread it out over 90 days, they're going to show smaller practice effects. And I don't think any of that was really incorporated into the study design and maybe moving forward could be.

DR. PAGE: Fair enough.

I'll ask Dr. Hammon to have the last word before I do my best to summarize.

DR. HAMMON: Let me try and go fast here because all I want to say is that I think, after I read through a lot of the studies that were done here, I didn't see a big attempt at standardization that would cover the entire study, and what we're talking about is doing the same tests on all of the patients. So I just happen to have in my hand here a reprint from the January issue of *The American Journal of Cardiology,* and the title is "Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials," and that's what we're trying to do here. And it's a very well thought out, well-presented paper with pretty much a blue chip list of neuroscientists and neurologists, although I don't see a lot of people here, except Dr. Virmani, who is on that study, and I would think that we ought to make a statement that standardization is really important. And I'll rest my case.

DR. PAGE: Thank you very much.

Dr. Brockman, the Panel I think unanimously is dissatisfied with the diffusion-weighted MRI imaging, and I think everyone would wish to have a clear clinical benefit demonstrated for any device, but the issues of the fact that even if it's not demonstrable with any testing, none of us want little infarcts in our brains, and the location of the embolic event may make a huge difference. We saw beautiful pictures of small emboli or small

volume lesions having significant effect, and in other cases no clinical effect, for example, was demonstrated even with lesions visible.

There is a wish for better anatomic definition; there is a wish for a better neurocognitive evaluation at baseline and in subsequent evaluations. Standardization is important, and no one can argue with benefit in terms of stroke. At times like this, I'm glad we have a transcript, and you and other members of the FDA can pore over the wisdom that has been shared over the last 15 minutes in Question No. 2 because it's impossible to fully summarize all of it, but I think you're getting a clear message that the diffusion-weighted MRI is not an adequate endpoint in and of itself as a surrogate, but the reality of designing tests, this one in particular, and trials in the future are going to depend on the reality of being able to identify a difference between two groups studied, if that were to occur. Is this adequate, Dr. Brockman?

DR. BROCKMAN: So I agree with you that we're going to need to look at the transcript.

DR. PAGE: I'm so used to saying Zuckerman, but does that meet your needs?

DR. BROCKMAN: So for Question 2a, yes, we certainly got our information --

DR. PAGE: I'm sorry, I can't hear you.

DR. BROCKMAN: For Question 2a, we certainly got the information that we need. For Question 2b, it's a difficult question. I would love to hear a more definitive description of what we could use in a future study. I understand the struggles, and I'm willing to accept that it's a difficult thing for you to provide. If there is anything else that you could give us, that would be great; if not, I understand.

DR. PAGE: I don't know that we have an answer for that. I think you've heard good recommendations, and you're receiving that endpoint paper, which I agree, I read this week, is a valuable one.

I'll ask to move on to Question No. 3.

CDR TOOR: Sure. Before I read Question 3, I just wanted to point out that if you have difficulties with the tables that are presented on the next couple slides, they're also in your panel pack in Tab 10.

So Question 3: The SENTINEL study effectiveness assessment included 2 Criteria. Statistical superiority with regard to DW-MRI median new lesion volume reduction in protected territories (which was Effectiveness Criterion #1) was not met. An observed treatment effect greater than 30% in protected territories (Effectiveness Criterion #2) was achieved. FDA also plotted the frequency distribution of the observed total new lesion volume in both protected territories and all territories. In log scale, the distribution of the observed total new lesion volume in protected territories for the Test Arm shows a small shift to the left, suggesting a slightly lower total volume in the Test Arm. This observation is consistent with the results based on medians. However, the total new lesion volume in all territories are similar for the Test Arm and the Control Arm, suggesting no difference between the two.

Question 3a: Please discuss whether the reduction in new lesion volume in protected territories observed in the Test Arm is clinically meaningful.

And Question 3b: Please discuss the clinical appropriateness of reporting the effectiveness outcomes for protected territories versus all territories in the labeling, if the De Novo request were to be granted.

DR. PAGE: Okay, Dr. Naftel.

DR. NAFTEL: I just want to bring up one point, and it's part of 2b, but it's 3a also. If you look at Table 3 that we were looking at, there's the row of ITT with imputation so that 121 patients with imputation, the row below that, just ITT, the patients that actually have measurements, it's 91. So that's 30 patients that either didn't have a pre- or a post- and

you couldn't get a change; in the control arm, it was 21 that didn't. So, first of all, going forward, that's way too many. So I'm going to say that's 51 patients, they didn't show up for the second visit because they had a stroke, because they couldn't find the room, they couldn't leave home. So that's just way too many. It just -- we haven't had that discussion about this whole weird imputation because it doesn't seem to affect the results, but it's too many patients.

DR. PAGE: Dr. Naftel, did you find it compelling at all that the Sponsor said, and I'd be interested in any of the interventional cardiologists to comment on this, that this is a very sick patient population and obtaining a repeat MRI, even in this percentage of patients, was very difficult. Do you or did you find that at all compelling? And I very much want the interventional cardiologists to comment on whether that is compelling.

DR. NAFTEL: I don't find it the least bit compelling. I work in a lot of quality-of-life studies, and it's the same thing. We look at quality of life in people on a ventilator, we look at quality of life in people that are too sick, and we can't, we can't get them to answer the questionnaire. There's no buy here whatsoever that the patient -- that this is a sick population, that gets me nothing.

DR. PAGE: Is anybody else on the Panel more sensitive to that perspective?

Dr. Ohman.

DR. OHMAN: Yeah, I was starting to worry about the Chair having visual defect on this side of the table. I'm just kidding. So the imputation is imperfect. Unfortunately, when you get to surrogate endpoints, that's what you have to sometimes use because for better or worse, you will not be able to get the right reading in all the patients. But one thing that is important to recognize is that you really have to adjust your sample size, so in cardiac MRI, it's very frequent to see a dropout rate of about 22-25% when cardiac MRI is used as an endpoint in a study. That means that the sample size needs to be up-adjusted to

accommodate for the expected and known loss. It doesn't get away from the ones that can't find the MRI standard because they had a stroke, but it does actually help you ascertain what an effect might be because you're now enriching or adding more patients to your sample size. You can make a better interpretation.

DR. PAGE: Thank you.

Dr. Naftel, why don't you comment, and then Dr. Cigarroa.

DR. NAFTEL: Yeah. So a lot of the times we say that let's just get a larger sample size and we don't care as much about the missing. Again, that doesn't buy me anything because the issue isn't that there's missing data; the issue is that it's missing for a cause that's related to the very thing we're trying to study. So inflated sample size lulls you into thinking you've got something, but you don't.

DR. PAGE: Dr. Cigarroa and then Dr. Roberts and Dr. Somberg.

DR. CIGARROA: So when I look at this Table 3 in reduction in median total new lesion volumes and look at the issue of the sample size, as a sensitive interventional cardiologist, I do understand that it is challenging, either for technical reasons, that is a person has had a pacemaker implanted or there are other complications as it relates to the procedure and/or delirium that challenges acquisition of an MRI within the time frame of Days 2 to 7, and as a consequence, I think that one has to adjust despite the lulling of the sample size to be able to discern that difference. A second thing is, I would say, is during that period there are many other etiologies that can result in new lesion volumes, thrombosis of the valve, which is present in up to 10% with reduced leaflet mobility, injuring atheroma around the aortic arch and other components, so I think, you know, these are all the challenges of trying to execute a very difficult clinical trial.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Roberts.

DR. ROBERTS: Just speaking from a radiologist's point of view, it is so incredibly difficult to get these very sick patients inside the scanner and, you know, with all their equipment that's never MI compatible, and dealing with respirators and all this other issue, and then if you do get them in the scanner, getting them still. So I think it's, you know, I'd like to applaud the Sponsor for being able to get as many patients into the scanner as quickly as they were, but again, the issue with MRI is that it's so very nonspecific, and so many other events could've happened in that time period, that 4-day time period that could've caused a positive DWI. It would be nice to look at other things such as was it FLAIR, was the FLAIR positive at the time or not, just things that can give us an idea of yes, this was really an acute lesion and therefore not associated with the procedure.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: And tell me if you can't hear me. I want to address these two questions: 3a, I think the simple answer is no, that between the test and the control, the reduction in new lesion volume does not seem to be clinically meaningful, but that is this particular study, and I think you have to put it in the context of adding the two other studies and using a systematic analysis or meta-analysis in that case. So I think it's a problem of sample size. 3b, I think, once again it comes down to sample size, and this is what I mean by that, that the protection device can't work where the filter isn't and --

DR. PAGE: Can't work with what?

DR. SOMBERG: It can't work where the filter is not present, right? So if it can't work there, it can't work in the control group, it can't work in the test group, so it should be like a placebo subtraction. That it doesn't seem to be that way is -- once again, small numbers give you deceptive results, so I think it's a sample size factor. So, therefore, I think it's appropriate to look at the total protected -- I'm sorry, all the territories, but to look at it in

terms of a systematic analysis. And there, I think we have a signal that there is suggestion of benefit if we take the volume of the lesions as an adequate surrogate, and that's very flimsy.

DR. PAGE: So thank you for bringing us back to the questions that we're being asked, and again, whether the reduction in new lesion volume is clinically meaningful. Your concern is that the sample size wasn't large enough for both the protected territory and the overall evaluation, but are you still believing there's some signal that there is some evidence of effectiveness?

DR. SOMBERG: In this particular study, the differences are not significant, so therefore it is non-informative. And I'm saying it's non-informative in all likelihood because the sample size is too small based on the assumptions that were made earlier on with a larger effect size in the first study they did. But you take that study plus one of the other studies -- sorry, I don't memorize names -- and the SENTINEL study, put it all together, and we saw, in that, you know, patient level meta-analysis, that there was a signal that there's a difference. Remember, that's still based on the surrogate of lesion volume, and that surrogate is a very weak surrogate. But that's all we have, and we didn't really come up with such a great alternative except maybe a 3- to 5,000 patient study where we look at stroke.

DR. PAGE: Other comments?

Dr. Good, Dr. Borer.

DR. GOOD: So regarding Question 3b, I personally think that the labeling should include all of the brain. I think this is outcomes -- make sure I read this correctly. I was going to say --

DR. PAGE: I'm sorry, I'm not hearing you.

DR. GOOD: Sorry. I think that it should talk about all territories in the labeling. I'm

sorry, I'm reading while I'm talking, sorry. And again, despite the small sample size, I'm concerned about Table 3, the bottom half of Table 3, and it really does not, to me, show any major difference when you look at all territories. And so I would think that the labeling ought to mention something about that.

DR. PAGE: Fair enough.

Dr. Borer.

DR. BORER: With regard to 3b, I agree completely with Dr. Good, but with regard to 3a, I don't think that this is a clinically meaningful result. We can't relate the imaging results to strokes, and we can't relate the imaging results in any quantitatively meaningful way to cognitive dysfunction. If we can't interpret the images as indicative of clinical results of one sort or another, then I don't see how they can be considered clinically meaningful. Maybe they might be with a different sample size, but I think Dr. Naftel pointed out, you're going to have a sample size, you got to test them.

DR. PAGE: Fair enough. Both your microphones are on.

Dr. Vetrovec.

DR. VETROVEC: I guess in answer to the question, particularly -- well, both 3a and 3b, I think we would really be helped by knowing, you know, having a body count: who's alive, who's functioning well, some other information to give us whether these dropouts were real or not. It's sort of amazing to me that we don't have that data.

DR. PAGE: Dr. Yuh.

DR. YUH: I'm going to take a little bit of a different view on what clinically meaningful means to me. Certainly, the definitions that have been proposed are valid, and I probably would adhere to them, but looking at it from another perspective, does clinically meaningful mean that it would alter my management in some way, shape, or form? And although there's not a statistically significant reduction in new lesion volumes, there is a

qualitative difference, in my view at least. And given the choice, if I had this device and I had to maybe organize putting a TAVR in, would I use it or not use it? I can't say that I wouldn't use it, and in that respect, I think it is clinically meaningful in that it would affect how I conduct that procedure.

DR. PAGE: And we will talk about the collection of embolic material in a subsequent question as well.

Mr. Thuramalla and then Mr. Frankel.

MR. THURAMALLA: So Dr. Yuh actually just now touched on the point I was going to make. The fact that 99% of the patients that debris was captured, as shown in the study, I was just about to ask, having this device, which is shown to be safe and was capturing debris in 99% of the patients, would you use the device if an option was available, so I think Dr. Yuh already touched upon it.

DR. PAGE: And that's not the question right now, but it's a very important question.

Mr. Frankel.

MR. FRANKEL: I think that the analysis that was noted by the other question is applicable here also in the sense that you can have multiple patients that have the same baseline in the cognitive testing and you have a substantially different outcome with those different patients that may have, on imaging alone, the same appearance, but because of perhaps prior to the baseline their history and age and other characteristics they will have a different outcome, even though everything represented on the imaging is the same, and because of that, I think that there is a somewhat weak argument to say that this is indicating one way or another in terms of whether there will be a clinical benefit because of that discrepancy, which obviously goes back to Question 2 in the sense that you noted as one of the recommendations to FDA for better baseline analysis of those patients for cognitive testing.

DR. PAGE: Thank you.

Did you have a comment, Dr. Cigarroa?

DR. CIGARROA: I wanted to provide my response to Question 3a. And what I would say is, for me, whether it's clinically meaningful, often as a proceduralist, there are things that I would want to use, and the question is can I state that clinically the patient has a benefit? And at least the data presented don't demonstrate to me a reduction in stroke, although it wasn't designed to do so, doesn't demonstrate a change in the neuropsych testing. And it may be here that the key here is the reduction, and that is the baseline, the control segment also has an augmentation in total new lesion volume. And so for me, it's does the delta demonstrate measures that are meaningful to the patient as studied by this clinical trial? And although I'd like to say yes, and as an operator, I'd like to use the device, I can't answer yes.

DR. PAGE: Fair enough.

We're being asked in 3b whether -- comparing all territories to protected territories, and I'll remind you, the last slide the FDA showed us, before lunch I guess it was, demonstrated -- the recommendation to the Sponsor was to use all territories, and the Sponsor chose, independent of the recommendation -- it's their right, by law, to choose the endpoint that they wanted, and they chose the endpoint protected territories. So this is a very important opportunity for us to give the FDA guidance as to if one were doing a trial like this again, is -- I won't even ask whether or not you'd use diffusion-weighted MRI, but let's say if you were, whether you would want to use all territories or what we call, for this trial, the protected territories. I'd like to hear from someone who has a strong feeling about one or the other and then look to others, because I think we probably have consensus as to what you want, but I -- that's just what I believe.

Dr. Somberg.

DR. SOMBERG: I just --

DR. PAGE: All or protected?

DR. SOMBERG: Well, I wanted to hark back to what I was saying earlier. I think that if you had an adequate sample size, they should come out similar because the device can't protect the area it's not in; therefore, in the control group you'll have a certain amount of damage in that unprotected area, and the intervention group you'll have a certain amount of damage. So if the sample size is large enough, that damage will be about the same. If it's small, you might have aberrations, and you'll have a bias introduced, so that's why an adequate sample size is important. But to ask the device to protect in an area that it's not seems to me inappropriate. Now, you might go ahead and say, well, okay, but the overall effect -- well, the overall effect was, once again, not seen here because the sample size was too small. So I don't know why my colleagues are not willing to use a systematic analysis where that is used in many areas, when your sample size is too small, to introduce additional material, unless you're asking them to go back and start again for 2, 3, or 4 years, and I think that's to the detriment of the population. There was a benefit seen in many areas with the meta-analysis addition.

DR. PAGE: I hear you. So again, if it's the sentiment of the Committee that either one is fine, let me hear that.

Dr. Good and Dr. Dodd.

DR. GOOD: Well, I'll be a little more dogmatic, I guess.

DR. PAGE: Say again?

DR. GOOD: I'll be a little more dogmatic. I really --

DR. PAGE: I'm sorry, I cannot hear you.

DR. GOOD: I'll be a little more -- you can't hear me?

DR. PAGE: Just say it slowly, and maybe I'll hear you.

DR. GOOD: I'll be a little more dogmatic in my opinion. I think, in retrospect, that it would've made sense to look at all territories, and obviously, it's too late now to do that, but I think that would've made more sense.

DR. PAGE: Thank you.

Dr. Dodd.

DR. DODD: Yeah, I just want to ask, how do you know that the device itself is not introducing new lesion in the unprotected area? How do we know that that is not part of what's going on here? And if so, then that's a strong argument for looking at all areas, all territories. And also, when you think about what you're trying to measure with a surrogate endpoint, you're trying to measure the total effect. So I would think you would still want to capture that, all territories.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: Yeah, I want to echo that because realistically, I think it's totally on who gave the best explanation for the discrepancy of what is going on, and now that I can see what he means, that is that maybe a lesser sicker population where you only examine the area of interest, the impact of the non-covered area, so to speak, is less. But in the sicker population where there's maybe more threshold effects from circulation, that's more dependent on one or the other. You can actually start understanding the discrepancy between two other trials and the current one we're reviewing. So from my vantage point, I think it has to be all; you could certainly share the protected, but leaving out all territories would be a mistake.

DR. PAGE: Fair enough.

Dr. Roberts.

DR. ROBERTS: Just to say again, I'm sorry, but it's very hard to define protected

versus non-protected if you don't know the vascular anatomy, and so I don't know how you could even divide it into those groups. And the issue that you just brought up about a sicker population, with a sicker population, their vasculature is going to be even more aberrant, so again, it's that much more important to know the anatomy.

DR. PAGE: So looking around, Dr. Brockman, in terms of Questions 3a and 3b, the -- there's significant concern about the clinical meaning of what was seen, although there is some perspective that we -- this trial may have been underpowered and that there is a signal that at least in the protected areas there appears to be a reduction of volume. In terms of 3b, there's likewise a perspective that sample size may show concurrent -- a large enough sample would show concurrent results, but there is concern that if there's a meaningful signal here, overall the number of lesions should be reduced or the volume of lesions should be reduced, and going forward, I believe there's advocacy for at least having all the territories as opposed to just the protected territories. Is this adequate?

DR. BROCKMAN: Yes, it is. Thank you.

DR. PAGE: Thank you.

We'll move on to Question 4, debris capture.

CDR TOOR: Question 4: The sponsor cites debris was captured in 99% of cases. Histopathology and histomorphometry results from the Test Arm patients showed a broad range of debris sizes and debris type. Acute thrombus with tissue and foreign material was the most commonly captured debris (98%) followed by arterial wall (94%), valve tissue (50%), calcifications (50%), foreign material (35%), and myocardium (15%).

Question 4: Please comment on the meaning and clinical significance of debris capture. Specifically, please comment on the discernment of the debris captured from TAVR versus that related to placement of the SENTINEL device.

DR. PAGE: Who'd like -- Dr. Cigarroa.

DR. CIGARROA: So with regards to the debris capture as it might relate to the transcatheter delivery system and deployment of the valve versus that related to the placement of the SENTINEL device, I would state, from a probability perspective, most would be related to either transversing the arch with the bulky transcatheter delivery system and nose cone and/or the acute deployment of the valve. And I doubt that the actual filter system and the guide and the wire are likely a source for injuring debris.

DR. PAGE: What about the clot? Do you see clot as being different from pieces of calcium, pieces of artery? Do you think there's that much clot being formed in the absence of the SENTINEL device?

DR. CIGARROA: I think that the SENTINEL device is unlikely a precipitant of clot, and I think the debridement of atheroma and aorta is a cause for clot both acutely and subacutely. So I think that harm is more related to the implantation, the delivery implantation system as opposed to the protective device.

DR. PAGE: Just for the record, the implantation system you're talking about, the implantation system of the valve, not the protective device?

DR. CIGARROA: Correct, the transcatheter delivery system, nose cone and device.

DR. PAGE: I'm looking for interventional cardiologists or cardiologists who want to weigh in.

Dr. Borer.

DR. BORER: In terms of the clinical significance of the debris, it's hard to say for certain because we didn't have good measures of outcome, but those are scary. The largest piece of debris was 5.4 mm. That's almost the lumen size of the capillary. Now, we don't know how many were quite that big, there certainly couldn't have been very many, but we did hear that a fair proportion of greater than 2 mm -- that means, to me, there's potentially great clinical importance to the generation of these debris, and I find that

frightening, and I would intuitively like to not have it there.

DR. PAGE: And your perspective is that that's -- that is material that came from the valve and not from the protective device, either growing a clot or collecting material or causing this debris to be formed?

DR. BORER: Yeah, given the degree of manipulation that's needed with a TAVR device versus what it seems like the degree of manipulation is needed with the SENTINEL device, I think it's far more likely that the TAVR procedure was the genesis of much of the debris. I can't be certain of that, of course, but I think that that's right.

DR. PAGE: Thank you.

Dr. Vetrovec.

DR. VETROVEC: Yeah, first I think almost all of the debris has to come from the valve or the structures related to that because the major time of disrupting artery and breaking off a plaque, the device isn't deployed so it's unlikely to capture anything, so I think to put this on the device is unlikely. Doesn't say that it didn't happen, but it wasn't able to be measured by this technique. I think this is a huge amount of material; I'm frankly struck by the fact that 35% of this is some other matter. I don't know what the standard is or if there's an FDA standard, but I think that's quite concerning if that happens in all procedures, which was an implication made. So I think this is very useful data. I don't quite know what to do with all of it, but it is concerning.

DR. PAGE: We'll have an opportunity to chat about what we might do about it.

Any other comments?

Mr. Frankel.

MR. FRANKEL: I think to address this question, the two sentences actually in the manuscript by the investigators seem to be very reasonable, which was "The observation that residual new lesions are still present in the protected territories after neuro protection

indicates either that current transcatheter devices are suboptimal in debris capture or that post-procedure particulate embolization is ongoing and occurs after filter removal. It is possible that some of the retrieved material in the filters was not directly related to TAVR but rather was the result of placement of the device."

DR. PAGE: Okay. So anybody else have comments about this? We're being asked to comment on the meaning and clinical significance of debris capture. And this is a quandary, isn't it, because this stuff is -- we can't argue that this isn't there, and we pretty much know where it would've gone if the device weren't in place, but at the same time we see a failure in the primary endpoint, we see a failure in terms of neurocognitive outcomes. So what is the clinical meaning of this, and how would it help you make any clinical decision, such as, for example, giving advice to the FDA as to whether this ought to be available to an operator doing a TAVR?

Dr. Hammon.

DR. HAMMON: Well, there are devices now that you can buy, and they're not that expensive, that use Doppler technology to measure the emboli going by in the carotid arteries, the intracranial carotid arteries, and we've used those in our institution, and believe me, it gets your attention when that balloon goes up or the automatic self-expanding device expands. It sounds really pretty scary listening to all this stuff zooming up there. So on the other hand, does it tell you how big it is? No. Does it tell you what it's made of? No. It just tells you that it's going someplace up in the brain and --

DR. PAGE: And some of the Panel may recall being on a panel where an ablation device based on carotid imaging really at the eleventh hour made the Panel pretty conclusively uncomfortable with that device.

Dr. Duff. And is your hand up, Dr. Somberg?

Okay. Dr. Duff, then Dr. Somberg.

DR. DUFF: Just briefly, to address that discrepancy that you were talking about. I keep reading this over, and what it says is that of all the cases, 99% of the protective device caught something, but what it doesn't say is that it caught 99% of all the debris that was flying through, and I think that's the part that we don't know and maybe that's what some of the discrepancies do. But some is still getting through, clearly, and causing problems in both groups.

DR. PAGE: Fair enough.

Dr. Somberg.

DR. SOMBERG: We don't know what the clinical consequences are of seeing these defects in the brain imaging. We know even less about the particulate matter. It might be scary to people, but it might -- I mean, it might scare you, the operator and the physician, but it may not hurt the patient; we don't know this. So this can't be used as a surrogate; it can't be used -- you know, you say, hey, look, look what I got from the strainer; therefore, I got to approve the strainer. I think that's a real reach.

DR. PAGE: Dr. Posner, you had kind of a patient's common sense perspective about these MRI lesions. As a patient, how do you feel about the clinical meaning of collecting this debris?

DR. POSNER: Well, as I said earlier, that's what the filter does, and we all agree that debris going to the brain is not a good thing. I have MS. I do MRIs all the time. And I look like I've had a shotgun put through my brain, but my function's fine except for my left leg. And so from the MS community, we're not great believers in looking at imaging in the brain to see what's happening functionally. Imaging the brain tells us if we have active lesions that are going on, so it's good to monitor. So as an endpoint -- I'm going off on a tangent -- I don't think that's very good for this, but I still believe as a filter, we all believe, from day one when I was on the open heart bypass team, if I saw a bubble going into a coronary, I

worried about it. And if I see anything going up to the brain, I worry about it. So this is a filter, and if it's filtering something, it's doing something good.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: I agree. I think that the only problem with this device is that it's not a complete filter.

DR. PAGE: It's not --

DR. BRINKER: Not complete, it doesn't filter everything, and there's parts of the circulation that doesn't get filtered. Now, is it better to have some of the stuff removed if you can't have all of it; is it better to have some rather than none of those, none? I think it is; I think it's better to have it. I think it is the obvious fulfillment of what the device is supposed to do; it's just the sequelae of that that hasn't been correlated with what it does, and that's a function of a number of things, one of which we've already argued for way too long, the ability of DWI imaging or DWI to be able to detect this, and it's just not there. And as far as the cognitive testing, that's also not there for any of a variety of reasons. But I think that there are other devices, as been mentioned previously, that were designed to filter down downstream from where things were occurring, interventional devices being used, and they've been approved because they caught things in the filter. I think that it would be hard not to say that this is a very important piece of the puzzle, and what we're struggling with is that we're not sensitive enough to pick up the physiologic or anatomic benefit that might accrue from this.

DR. PAGE: Thank you, Dr. Brinker.

Dr. Ohman.

DR. OHMAN: One of the things that come to mind as this being the first device of its type is that because it's relatively low risk, that future devices will be measured against this

device, so now I feel that I'm even further out on a slippery slope not knowing exactly how much this device does. It captures a lot of things, but it doesn't tell me that the next device that's being compared to this device, how that will perform really, because I'm on a slippery slope and I don't know where this goes, and that's one of my concerns, that we have so much uncertainty that I'm not entirely sure that this -- I would like to see this to be the predicate device for all future devices in the field given the imperfect scenario that we're in, and it's not the fault of a lot of --

DR. PAGE: We're not quite there, and really, we can't go there on the regulatory perspective, but right now let me just keep you focused on this Question No. 4, clinical significance.

DR. OHMAN: So it's wonderful to see that things are captured, there's no doubt about it, but I just don't know that it captures enough, and there you're left with the uncertainty.

DR. PAGE: So, Dr. Brockman, with regard to Question 4, generally I would say the Panel would rather have this debris caught in a filter than caught in their cerebral vasculature. The tough part is whether -- it clearly isn't blocking everything, and the failure in terms of the various outcomes gives pause in terms of demonstrating the effectiveness of this device. Does that meet your satisfaction?

DR. BROCKMAN: I think this has been a helpful discussion. Thank you.

DR. PAGE: Okay. Let's move on to Question No. 5, neurocognitive outcomes.

CDR TOOR: Although it is observed that the Neurocognitive Battery Composite z-score decreased at 30-day follow-up and then increased at 90-day follow-up, it is unclear whether the small change represents a clinically meaningful change in neurocognitive function or if it is merely due to random variation. Note that a positive z-score indicates improvement. No obvious difference between Test and Control Arms were noted with

respect to changes in overall z-scores at both 30-day and 90-day follow-up. This is also true for change in component z-scores for all five component domains at 30 days. Again, no meaningful clinical changes or trends regarding comparisons between groups were noted.

Question 5: Please comment on the clinical significance of the neurocognitive outcomes.

DR. PAGE: So Dr. Peavy.

DR. PEAVY: I don't think that the outcomes are clinically significant, but I also don't think it's random variation. I think that there are reasons for the results that we don't understand, but we do have some ideas, so things that we can learn from the results that have occurred.

DR. PAGE: So in terms of future evaluation, how would --

DR. PEAVY: I have a short list.

DR. PAGE: Okay.

DR. PEAVY: I think that, you know, everybody's talking about the dropout being a problem, so I think that one thing that has to be addressed at the very beginning of doing more on this topic is to come up with retention strategies, and I think that's important, and most people in science don't really want to deal with that that much, I don't think, but I think it's important. Another thing is looking at the floor effects, it may be that you initially get some idea of where people stand cognitively because some of these people are clearly impaired before they have the procedure, and there could be a two-tiered kind of cognitive assessment possibly as a strategy because what you're looking at is changed.

And also, I think it's important to be really clear on the norms, what norms are used, and put that in publications so that people can assess that. And the last thing is to do more longitudinal analysis, which I think people, you know, are hesitant about that. And Dr. Good brought up the fact that we don't know what these, whatever it is, the damage that gets

done does over time, and there is a growing pretty big literature about the relationship between neurovascular or -- yeah, neurovascular disease and Alzheimer's disease and probably other kinds of neurodegenerative disorders as well.

DR. PAGE: Fair enough.

Other comments about the neurovascular outcomes?

Yes, Dr. Hammon.

DR. HAMMON: We've been studying coronary bypass patients in our institution now for over 10 years and doing neuropsychological studies on all of them, ones that we get permission and so forth. So question one was how to get them to come back. Well, we pay them, and we arrange transportation if they don't have any, and we have almost 100% success in getting them back. Second thing is what does all this mean? Well, one thing that we got from our data was if patients have a deficit, and we do our studies a little bit different than this, but it means the same thing, a verbal memory is considered to be not normal or has a negative slope at 2 weeks or a month or even at 3 months; it may not be permanent. But at 6 months, if it is still impaired, it won't come back. So it's a healing process in the brain, and it just lets you know whether or not that healing has taken place. So it does give prognosis, and I think prognosis is very important.

DR. PAGE: And we've had some good discussions about the neurocognitive evaluation in this trial. Is there anybody in the Panel who sees a signal for some benefit or harm coming from the SENTINEL device in terms of neurocognitive outcomes?

(No response.)

DR. PAGE: I'm seeing none.

So, Dr. Brockman, you've heard the discussion about ways to potentially do this better in terms of the secondary outcomes of this trial. We're in agreement with the Sponsor and the FDA that we're not seeing any signal that's measurable; that could be due

to a number of different things. Perhaps these are not random issues, and they could be studied better, but at least in the context of the trial as it was conducted, we don't see a signal here. Is that useful?

DR. BROCKMAN: Yes, thank you.

DR. PAGE: Thank you.

We'll now move on to indications for use.

CDR TOOR: The sponsor has proposed the following indications for use: "The SENTINEL Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain periprocedurally. The diameters of the arteries at the site of filter placement should be between 9-15 mm for the brachiocephalic and 6.5 mm-10 mm in the left common carotid."

Question 6: Please comment on the appropriateness of the proposed Indications for Use and discuss any revisions to the indication that you would recommend based on the information in the Panel Pack and/or discussed today.

DR. PAGE: And just as when we do a PMA panel, this discussion is as if the device were going to be approved. What does the Panel think of this indication for use?

Dr. Borer, Dr. Good, Dr. Naftel.

DR. BORER: I think the indications for use as they're written are fine. What we've been discussing here is whether the device actually does the thing that you're trying to prevent, whether it actually reduces ischemic injury. If we determine that it does, then I think the indications are fine.

DR. PAGE: Thank you.

Dr. Good.

DR. GOOD: Well, as a follow-up to Dr. Borer's comment, I personally would remove

the phrase "in order to reduce ischemic injury to the brain periprocedurally" because I'm not sure we've completely been able to show that. That would be my opinion. The rest of it, I'm okay.

DR. PAGE: Fair enough.

Dr. Naftel.

DR. NAFTEL: I'm going to disagree with the name of this device, Cerebral Protection System, so this is in the indications for use. I looked up the word "protection," the state of being kept from harm. You're protected, it means something's not going to happen. This is not a protection device. If I were going to have this aortic valve implanted, I personally would want this to perhaps reduce the probability, but this is not a protection device in my opinion.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: So the "device to capture and remove embolic material while performing transcatheter aortic valve procedures" and I would put a period right there primarily because only Criteria 2, the observed treatment effect, was met whereas the lesion volume reduction was not met. And so as it relates to the clinical trial, I would find it hard to follow through with this IFU.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: And I would like to add a comma after that to say that it's limited to the areas where the device could be deployed, recognizing that in 5% only one of the filters were deployed. Sorry, 90% the filter was deployed in both, and there was 5% or so, I forget the numbers exactly, but it's not giving the full protection as this leads you to believe.

DR. PAGE: So, Dr. Brockman, if I may summarize, the issue of calling it a protection

system, and not to parse the words, but if you're protected from those emboli, are you protected? I don't know, Dr. Naftel, that we can let that be navigated. There is concern about the phrase "in order to reduce ischemic injury of the brain periprocedurally" because there is concern that that was not necessarily demonstrated. Is this adequate?

DR. BROCKMAN: Yes. And just to clarify, Dr. Ohman, you were suggesting that the indication statement note the limits of the protection or whatever word that was used --

DR. OHMAN: Exactly, yes.

DR. BROCKMAN: -- of the territories? Thank you.

DR. PAGE: All right, let's move on to No. 7.

DR. GOOD: Mr. Chairman, can I ask something?

DR. PAGE: I'm sorry, Dr. Good.

DR. GOOD: Sorry.

DR. PAGE: And Dr. Posner.

DR. GOOD: So a couple other comments about this. I think at some point it should say something similar to what was said over here, that the left vertebral system is not protected, and it doesn't really say that anywhere here. And the other problem I have is on page 4, they talk about -- wait a second, let me get this. It's page 5, they're talking about the overall Z-score, but there's nothing at all that talks about the neurocognitive testing. The Z-scores have to do with the neurocognitive testing. All of a sudden it shows up as the Z-score, and you're kind of going what is this? So I would suggest that some clarification -- that should be removed or something should be said about the neurocognitive testing.

DR. PAGE: I'm sorry, I'm not clear. This is on the --

DR. PAGE: -- indications for the device?

DR. GOOD: Indications, yeah. Page 5 on the --

DR. PAGE: We're not there yet.

DR. GOOD: Oh, I'm sorry.

DR. PAGE: We're not at the package insert; we're just on the indication.

DR. GOOD: My bad.

DR. PAGE: No problems.

DR. GOOD: Apologize.

DR. POSNER: Just a verbiage suggestion that rather than prevention or whatever, use the phrase "risk factor reduction," as we do for a lot of the cardiac stuff, because by removing the amount of debris that goes up, that's a major risk factor, and it's reducing that particular risk factor.

DR. PAGE: Thank you.

So we'll move on to No. 7, labeling, and I'll call on Dr. Good first. Why don't you go ahead and read the question, please?

CDR TOOR: Draft labeling has been provided by the sponsor in the Panel Pack.

Question 7a: Please comment on the appropriateness of the contraindications, warnings, and precautions.

And Question 7b: Please comment on the appropriateness of the SENTINEL data included in the labeling, and discuss whether there are any analyses or data not provided in the labeling that would be important to provide to the user in the labeling.

DR. PAGE: And let's take these one at a time. Let's do 7a first, commenting on the appropriateness of the contraindications, warnings, and precautions.

Dr. Vetrovec.

DR. VETROVEC: Yeah, I would actually extend sort of -- Magnus made the point about the 5% or so that can't be successfully cannulated, but I think there's a more important issue that really wasn't talked about at all today, it is in the package insert, it's kind of a one bullet, but it seems to me that this issue about not putting it in patients who

are anatomically not correct in terms of having vessel damage or tortuosity and so forth is very important because we talked about the fact that some of the events could've been related to the device itself, and I think the worse anatomy you try to put this in, the more likely you are to see that, so somehow I think that needs a little bit bigger description here, and there's been no description about how that was assessed, and maybe, I don't know whether that's important or not, but it seems to me that's something that should be thought about.

DR. PAGE: So, again, assessing the appropriateness of the anatomy?

DR. VETROVEC: Correct.

DR. PAGE: Okay, thank you.

Other comments about --

(No response.)

DR. PAGE: Then let's move on to 7b. Specifically, I don't know if you read the description of the SENTINEL data as proposed for the Sponsor, the draft labeling, Dr. Good?

DR. GOOD: Yes. I apologize, Mr. Chairman, for jumping ahead earlier.

DR. PAGE: No problem.

DR. GOOD: So a couple of comments. First of all, I didn't see and maybe I missed this, anything about the left vertebral not being protected, and I think maybe it would be reasonable to state that somewhere here; I think that's a fair thing to have in labeling, at least in my opinion. The other concern was on page 4 -- whoops, I'm sorry. Did it again. Page 5, figure 2, talks about the overall Z-score, but I didn't see any comment about neurocognitive testing anywhere in the label; it just showed up. If I missed that, I apologize too. But I would either change that figure -- I'd add something about the neurocognitive in the verbiage.

DR. PAGE: Other comments?

Yes, Dr. Dodd.

DR. DODD: Yeah, so looking at label -- in the tables that refers to the protected areas, and I don't see any -- or protected territories rather. I don't -- what's that? Is this --

(Off microphone comment.)

DR. DODD: Yeah, I had to look -- yeah, I can give you my computer, if you want. So I guess, given the discussion that we've had, would people feel comfortable including the protected territories and adding all territories, or would you want to only include the all territories or remove the protected territories?

DR. PAGE: Comments about that? As I read the description, it certainly, I think, had a certain perspective on the data.

Dr. Somberg.

DR. SOMBERG: It certainly did, and I think it would be good to put in -- if you think there's benefit here, you have to base it on benefit in the protected territories, so I think a label has to reflect that, but if you are concerned that that was vitiated by all territories, that could be put in as well, so anybody who is going to use this device who reads the label will have the angst of this Panel and weigh, you know, the pluses and the cons. So I think all that information should be in there, and I would just add I would think the meta-analysis should be in the label as well, that when you compare the three studies, there was this finding.

DR. PAGE: Other comments?

(No response.)

DR. PAGE: Dr. Brockman, do you need me to summarize those for you, or did you get them?

DR. BROCKMAN: No, I have the --

DR. PAGE: Okay, fair enough.

We'll move on to No. 8, risk-benefit. And I'll ask for that to be read, please.

CDR TOOR: A reasonable assurance of safety and effectiveness can be achieved, in part, if it can be determined that the probable benefits of using the device outweigh the probable risks. The sponsor has identified death, peripheral ischemia, stroke, systemic infection, and vessel perforation as potential risks. The SENTINEL System met its primary safety endpoint. The study also showed the device had low (0.4%) vascular injury complications and high delivery success (99.6%). The sponsor has also shown that the device successfully captured embolic debris in 99% of Test Arm patients. However, the probable clinical effectiveness benefit of the device is unclear.

Question 8: Please discuss any additional benefit-risk considerations.

DR. PAGE: And just for the Panel's sake, we will -- I will ask everyone, when we're done with the questions and summary statements, as appropriate per FDA and the Sponsor, I'll ask to go around the room. But right now let's discuss this very question, risk-benefit considerations, any additional or from your perspective how you would balance risk and benefit.

Dr. Somberg.

DR. SOMBERG: I would think that if this was approved, you would like to insert the additional consideration of the stroke reduction that was 63% at 72 hours and was significant, but retrospective data analysis, not pre-specified, and that at 30 days it was 47%, no longer significant, but pre-specified, and I think that would be informative to those who are making the decision to use it or not.

DR. PAGE: Other comments?

Dr. Cigarroa.

DR. CIGARROA: So I would beg to disagree on the inclusion of the post hoc analysis of the 72-hour data. I think that when thinking about the -- you know, I think there's a key

word here, "determined that the probable benefits," or I should say phrase, "of using the device outweigh the probable risks." So let me tackle the risk first; that's easy. I think that the risks are as low as they can be for any device that we introduce into an arterial circulation. I think that the engineering of the particular filter type has been demonstrated to be safe when implanted in carotids.

I think that the risk is lowest when approached radially, and avoiding the brachial is important as we avoid brachial for all procedures for we know the vascular complications are higher. To me, the word "probable" is easier when I use the word "possible," given the challenges of the endpoint and the desire to capture whatever percentage of debris that is embolized. And so there is possible benefit, given the inability to predict who's going to stroke and who's not going to stroke, and where that embolic material goes, whether it hits an area of the brain that's plastic and recoverable or one that is not. And so I think it's possible that it has a clinical benefit.

DR. PAGE: Thank you.

Mr. Frankel.

MR. FRANKEL: In terms of the risk, I think that that's clear that there is that open question that has to be watched in terms of that potential of there being debris caused by the device; it seems that it's not, but there seems to be somewhat of a possibility. In terms of benefit, just to echo on the actual word of "probable," if my understanding is correct in terms of the FDA criteria, when we look at benefits, we look at patient satisfaction, reducing the probability of loss of function, duration of effect, but in terms of alternative treatments, if there are none that are available, I mean, at least per the guidance documents, significant uncertainty about that benefit can be still a basis of approval if there is no available alternative treatments.

That goes along with, also, the guidance document that cites on novel technology

addressing unmet need, we may tolerate greater uncertainty. So I think that, you know, there is a strong basis in terms of the wording, at least as far as our guidance that we have from the FDA, that even if there is this question mark, based on the potential benefits, there's a strong argument to approve it.

DR. PAGE: Thank you.

Yes, Dr. Hammon.

DR. HAMMON: Sorry to be so noisy. I would like to propose that somebody in the FDA could decide who they want, take patients that they are putting at risk because of doing a TAVR procedure, even though they have this device in place, because we know that all of the patients have emboli, and the way I would do it is I would study them with what's called transcranial Doppler, two electrodes here, and they image the intracranial carotid arteries. Now, theoretically, if those filters worked, you wouldn't have many emboli going up to the brain no matter when, but clearly, they don't work all the time, and you'd like to know when they don't work and maybe then you could come up with some sort of an answer to stop it.

DR. PAGE: So you're talking about possibly No. 9, postmarket data, at this point?

DR. HAMMON: I'm talking about Question No. 8, any additional benefit-risk considerations.

DR. PAGE: Okay. At this point, we're talking about the data we have at hand, so --

DR. HAMMON: Okay. Well, then let's go to No. 9, then.

DR. PAGE: -- any other -- but I want to retain what you were commenting on for No. 9 as we give further advice.

DR. HAMMON: Okay.

DR. PAGE: Any other risk-benefit considerations that we have to address?

(No response.)

DR. PAGE: So, Dr. Brockman, the issue of the 72-hour stroke rate being a post hoc analysis is compelling to some and not to others in the Panel. There is considered to be significant uncertainty, but certainly also the consideration of is there possible benefit, perhaps not probable. I think people are thinking there might be, especially if you're collecting debris that otherwise would be going to the brain. And likewise, what is the alternative in terms of the level of risk-benefit balance, and again, we need to reiterate that the issue of risk, I think there's agreement this is a relatively low-risk device, especially in the context of undertaking that procedure. Is that adequate?

DR. BROCKMAN: Yes. I appreciate the reference to our benefit-risk guidance, and yes, it's adequate. Thank you.

DR. PAGE: Thank you.

So let's move on to No. 9, again, postmarket data.

CDR TOOR: FDA may consider the collection of post-market data as a way to develop additional information regarding benefits or risks for certain device types or in specific patient populations when making a benefit-risk determination. FDA has the authority to require post-market data collection for De Novo devices.

Question 9: Please discuss any recommendations for post-market data collection, if the subject De Novo request for the SENTINEL device is granted.

DR. PAGE: Okay. Again, this is as if it were approved. What would we like to learn about this? And I'll go to Dr. Hammon first in terms of your -- just if you want to restate your suggestion in terms of further study and cranial imaging.

DR. HAMMON: Well, I'll just repeat what I said, hopefully more briefly. Since the one thing that we're all sitting here worried about is the patients having small infarcts in their brain, and sometimes they're bigger than small, that occur in the areas where the filters are supposedly removing the embolic material -- and it would seem to me to be a

wise thing to know when these events occur and the volume, and then after that, we know where they go. But with the transcranial Doppler you could certainly see these things and see where they go in the proximal carotid intracranial circulation, and so I would strongly recommend that we favor that.

DR. PAGE: Thank you.

Dr. Borer and then Dr. Good.

DR. BORER: As I understand it, we cannot, given the fact that this is a de novo request, suggest specific studies because --

DR. PAGE: Go ahead and blue-sky it, but --

DR. BORER: Okay, that's fine.

DR. PAGE: But --

DR. BORER: That's fine, but I'm going to suggest collection of data. The concern that I have is that 2,000 of these devices have been put in elsewhere and less than 1,000 total in all the studies that we've heard about here, so that's less than 3,000 of these devices have been deployed. That's a small number from which to draw inferences about benefits and risks. I would like to see extended collection of data if this is approved so that we can determine the long-term outcome of patients who undergo the procedure with this device.

We actually need more data. There was one vascular incident only. Clearly, there will be more than that. There will be other things that will happen; we don't know them. So we need to refine the label with more data, and the way to get it is to extend the follow-up and collect outcome data, and I think that's the number one requirement. I could suggest studies, but I'll stop there.

DR. PAGE: Just so I'm clear, extending collection of the data on patients who have already been randomized?

DR. BORER: That's right. Well, if -- no, no. If the device is approved, then it's

collection of data on patients who get it going forward. That's a registry.

DR. PAGE: So -- yeah, that's certainly a registry, but you were also suggesting longer-term follow-up on the patients who were randomized before?

(No audible response.)

DR. PAGE: Okay, great.

Dr. Good.

DR. GOOD: I agree with Dr. Borer. I was going to say the same thing. Certainly, having some sort of registry, I think, is going to be important. I mean, you could certainly eventually have thousands of patients and get some idea about the stroke, although you don't have any control population. But I want to come back for a second to Dr. Hammon's blue-sky suggestion with TCDs. Actually, I think that's a very good idea and, you know, you could suggest in a future study, but you could actually check TCDs not only periprocedurally but afterwards and see if there's any change intermittently over the first 24-48 hours and you see more emboli during that time. But that's just a blue-sky suggestion.

DR. PAGE: Great, thank you.

Dr. Somberg.

DR. SOMBERG: I think what is most needed is clinical demonstration of benefit and the way to do that is by having a large sample size and a registry is a very good idea, and I think what one has to do is look at the easily obtained metrics. And one would be stroke, and two would be neurocognitive function, not that it's easy, but compared to MRIs, etc., which are not going to be done clinically routinely. And I also think it's critical, critical to have everyone in the registry who was considered for the device, so those people who don't get the device, those people who can't have it deployed, those people who only have it partially deployed, that is a good comparator group so you know what happens.

So if they have appreciably more strokes, even though that number may be small,

that will tell you something as opposed to there's really, you know, no difference when you have 5,000 patients between the two groups and then you're saying, well, maybe we ought to do a 50,000 patient study. It's getting to a point where there may not be clinical benefit. But I think if you look for stroke and neurocognitive function in those two groups in a couple of thousand patients, you will see something.

DR. PAGE: Mr. Frankel and then Dr. Posner.

MR. FRANKEL: I'd like just to echo in terms of a long-term registry, of the --

DR. PAGE: Say that again, please.

MR. FRANKEL: I'd like to echo also in terms of a long-term registry for the collection of postmarket. That data hopefully will enlighten a lot of the questions that we're facing. I also think that it should go hand in hand, I'm sorry for quoting from the FDA literature again, but in 513(a) (3)(C), I just noticed that, you know, in that same guidance document, that's actually a balance to the uncertainty that exists, so you know, there's this question of possibility or to use the word probability, so let's say for argument's sake that it's possibility versus probability that that postmarket data is essential.

DR. PAGE: Thank you.

Dr. Posner.

DR. POSNER: Yes. This is just a naive question, that is how long you leave the filter in place during the procedure, and this can probably be done with an animal study, but typically, it's going to go in, the valve is going to be placed, and then the valve catheter is going to come on out, but do you want to leave that in a little bit longer in case -- how long does it take that debris from the valve ring to get up to those vessels? And I don't think they mentioned how long it would stay in. I'm not talking about days, but I'm talking about 30 minutes, and is that sufficient?

DR. PAGE: Again, I'm not asking you to ask the Sponsor at this point, but you raise

an interesting question, and I think that would need to be discussed.

Dr. Brockman, let me summarize. In terms of any post-approval evaluation, there's a mention of transcranial Doppler, both acutely and then some short term after that as being possible; follow-up of the randomized patients already enrolled in terms of longer-term follow-up; a registry, which would be certainly looking at CVA and neurocognitive outcomes, perhaps collecting those patients who, for whatever reason, were not also subject to the use of this device and see whether there would be any information added there. Is this adequate?

DR. BROCKMAN: It's helpful. I have two questions. One, in terms of the long-term follow-up that several suggested, do you have some guidance as to how long is long enough? And the second one in terms of the endpoints, is there a role for imaging? PW-MR [sic]?

DR. PAGE: Great questions.

DR. BROCKMAN: PW --

DR. PAGE: So who would give me a number in terms of duration of follow-up that would hopefully be reasonable?

Dr. Brinker, we haven't heard from you lately.

DR. BRINKER: One year.

DR. PAGE: One year. I hear 1 year.

Dr. Borer.

(Laugher.)

DR. BORER: I would draw from experience with sports injuries, concussions. It takes more than 1 year to see the outcomes. I think we ought to go for as long as we can, but being realistic, I would say 2 to 3 years would be appropriate.

DR. PAGE: How many?

DR. BORER: Two to three.

DR. PAGE: Two.

And Dr. Brinker.

DR. BRINKER: A realization that the population that gets this device isn't known for longevity, so -- and they're not like sports injuries. So I think that if we can't find a difference by 1 year, it's not going to make any difference.

DR. PAGE: Thank you, Dr. --

DR. BRINKER: And it's expensive the longer you go.

DR. PAGE: Thank you, Dr. Brinker.

Dr. Somberg and then Dr. Peavy.

DR. SOMBERG: There's merit to what both people said, but I think if you think that this -- the TAVR device is that it will improve life expectancy 3 to 5 years, following people for 1 to 2 years is appropriate.

DR. PAGE: Fair enough, thank you.

Dr. Peavy.

DR. PEAVY: To try to get a balance between the difficulty of doing a study and as much time as possible, I would say 2 years.

DR. PAGE: As much time as possible, but how many?

DR. PEAVY: Two years.

DR. PAGE: Two years, thank you.

Dr. Hammon.

(Off microphone response.)

DR. PAGE: Dr. Hammon said 6 months.

I think you're getting a span here. In terms of imaging, should we expect people to be imaged and over a long term, and how long and how often?

Dr. Cigarroa.

DR. CIGARROA: So we have seen, in a randomized trial, imaging. We have discussed the challenges in interpreting as a surrogate the diffusion-weighted imaging, the reduction in overall stroke rate, and so I don't see how serial imaging will help here given that there are also many other causes of strokes beyond the acute procedural embolic event rate that would be protected at the time, so I would not advocate for additional imaging.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah. I agree completely with Dr. Cigarroa. We couldn't interpret the images we saw; why would you get more of them?

DR. PAGE: I bet Dr. Roberts might have an idea.

Dr. Roberts.

DR. ROBERTS: Well, I do agree with what you're saying because if we're -- we're going to get long-term imaging follow-up, we won't be able to associate it particularly with the device, but as far as imaging in general goes, I do think that we should continue to image these patients in the immediate periprocedural area because, number one, again, I don't think the issues of protected versus non-protected has been fully addressed, and so I would strongly recommend getting MR angiograms or some type of angiogram, CT angiogram, whenever you do -- before you do this procedure so you can interpret that data because I think it's important for us to understand what this device is actually protecting, and we can't do that without knowing the vascular anatomy.

Your second part of that question was about imaging. Did you say PWI?

DR. BROCKMAN: I had trouble reading the handwriting.

DR. BUCKLEY: I wasn't -- it was my handwriting. DW. I wasn't interested in perfusion imaging.

DR. ROBERTS: Okay, yeah, because, you know, I mean, that's a separate question too. Yes.

DR. PAGE: Okay, thank you.

Dr. Somberg and then Dr. Peavy.

DR. SOMBERG: I think it would be inappropriate not to collect the data if it was available. I think the primary data is stroke; the secondary data is neurocognitive. If an institution is imaging before and after, that is additional useful information, but I don't think, given the cost of that, it can be mandated.

DR. PAGE: Thank you.

Dr. Peavy.

DR. PEAVY: I was referring to neuropsychological testing when I said 2 years, not to imaging. I may have misunderstood the question.

DR. PAGE: Dr. Roberts.

DR. ROBERTS: And I'm sorry. The other point, too, is -- you know, again, kind of maybe in disagreement with other people. I do think that if we see a lesion on DWI that's positive showing injured brain tissue, even if we don't see specific clinical outcomes, I still think that's a clinically relevant finding, and so therefore in addition to all the clinical exams, this just adds one more point to that.

DR. PAGE: Thank you.

Mr. Frankel.

MR. FRANKEL: Just a quick point in terms of those that are raising the issue of longevity. I just wanted to really understand that because, I mean, as everyone here knows, these are devices that are progressively being used in younger populations, so I'm not sure if that should be any type of decision-making process in this regard.

DR. PAGE: Okay, thank you.

So, Dr. Brockman, in terms of imaging, there is some perspective that more imaging would be nice, although there is a perspective likewise, I think, by a larger group, that it may not be realistic to prospectively expect imaging collection of events, and imaging in and around those in terms of opportunistic data would certainly be welcome, and we don't want to forget neurocognitive evaluation in the follow-up of any post-approval surveillance. Is this adequate?

DR. BROCKMAN: Yes, thank you.

DR. PAGE: Great. So we're going a little bit -- Dr. Borer.

DR. BORER: I just want to point out that, according to the newspaper this morning, a study published in Britain indicates that by 2030 the average survival age will be 90, so just got to keep that in mind.

DR. PAGE: That is --

DR. BORER: Everybody's living longer except in the United States.

DR. PAGE: I don't know whether that's encouraging or not, but we will move on to --

(Laughter.)

DR. PAGE: What we're going to do -- this has been a very useful discussion. We'd like the FDA to provide any concluding comments, and then the last word always goes to the Sponsor. And then I am going to go around the table and ask people to give their bottom-line perspective on what we're dealing with here. We're not going to have a vote, de novo does not require, expect, or allow a vote, but I think it will be valuable for everybody to give their perspective. We will ask for as much brevity as possible from all speakers. And with that, I welcome the FDA for any concluding remarks.

DR. BUCKLEY: Other than to thank the Panel for their thoughtful input and the Sponsor for their very thorough presentation, FDA doesn't have any further comment.

DR. PAGE: Thank you so much.

I'll ask the Sponsor if they have any concluding remarks.

Dr. Leon.

DR. LEON: Thank you. Again, I'd like to thank the Panel for their very deliberate discussions, very, very informative for all of us. One of my close colleagues advised me that enduring an FDA panel is like being on a roller coaster. Well, since I am prone to motion sickness, you can imagine my current state of queasiness.

I'd been the principal investigator for the PARTNER trial for the last 10 years. We have enrolled over 10,000 patients with aortic stenosis and FDA control clinical trials, some registries, some randomized trials. I have never experienced a trial that's been more difficult to enroll in this population of octogenarians who are high surgical risk. To be able to do serial DW-MRI imaging, to be able to do serial neurocognitive function in these kinds of patients is extremely difficult. Therefore, I'm not really apologetic; in fact, I would defend the quality of the clinical trial design and the fact that only 5% dropout on clinical endpoints at 30 days, I think is more than acceptable, and the 21% dropout in the neuroimaging study, I also think, was acceptable. In fact, this was better than most serial MRI imaging studies that have ever been reported in the literature.

I want to thank the co-PIs that did a superb job in managing the study, and that includes Susheel Kodali from Columbia, Samir Kapadia from Cleveland Clinic, and Axel Linke from Germany. It was very difficult to manage this trial, to enroll these patients under the current circumstances. It certainly was a learning experience. We learned that the neuroimaging studies were less robust than we had expected from the standpoint of a surrogate clinical endpoint. We learned that the neurocognitive function studies, even bringing the greatest level of expertise to try to design these studies and execute them was less than robust in terms of being able to discern important clinical differences. So from the standpoint of the study, I think it was a learning experience.

I would urge the Panel to consider that as you deliberate risk-benefit, that you consider the totality of all the data. I have no uncertainty that this is a safe device. I believe we demonstrated that more than adequately for the single vascular access site complication. I have no uncertainty that we can train physicians to use this device properly, and as you saw, we were able to implant both filters in 95% of patients, there was not a significant learning curve, and I think that we can certainly train physicians to use this device appropriately. This device does not disrupt the clinical workflow. It takes a short time to insert; the dwell time of the device is only 15 to 30 minutes. There's been uniform debris capture, which we do think is significant. I know people wonder about this; it was independent of valve type, it was independent of everything, and much of the material could not have been related to the filter itself and had to be from either the vasculature or the aortic valvar complex. It is concerning to me that one in four patients had an average of 25 particles that were collected but were at least a half a millimeter in size, and that's visible to the naked eye, so I think that is concerning, and those particles have nowhere to go but to the brain. The MR data was inconclusive, disturbingly, disappointingly inconclusive for a variety of reasons which I won't reiterate. I will say that the meta-analysis at least helps me to be able to put some perspective on the MR data, again, still not perfect but at least trends towards demonstrating some level of effectiveness.

And I think the clinical data, although again imperfect because it was not powered to show clinical endpoints, was important to consider as part of the overall evidence. A 63% reduction in neurology adjudicated strokes at 72 hours I think is important; the fact that we were able to maintain much of that difference by 90 days is equally important, and the fact that there was a postmarket surveillance study that was presented from Germany in a large number of patients, again showing what appear to be an improvement in clinical endpoints, I think, adds to the totality of data that we're considering.

So my final comment is one of perspective. I've been an interventional cardiologist for many years; I care desperately about these patients. Strokes are devastating. They are random, they are unpredictable, and anything that we can provide as an alternative accessory device to reduce, not eliminate but reduce, ischemic brain injury in strokes is extremely meaningful, and therefore, looking at the totality of data, we would strongly urge the Panel to consider, from a risk-benefit standpoint, with a device that's safe, that the potential benefits outweigh the risks and that this device should be available to American interventional cardiologists.

DR. PAGE: Thank you very much.

So now we're going to go around the table, and I'll start with our Patient, our Consumer, and our Industry Representatives for any brief comment and kind of big picture perspective on this device.

Dr. Posner.

DR. POSNER: Hate to go first. As I said earlier, I think it does what it said it was going to do. It's a filter, it gets a lot of junk out of the system that won't go to the brain. And basically it's like my taking my aspirin every day. If I were going to have my valve replaced, I'd want to have the filter in as an added thing; whether it actually is going to prevent my stroke or not, I don't know, but it can't hurt. There is minimal risk from what they've seen, and intellectually, stopping that junk from getting into those vessels, I think, is a really good thing. The only thing, as a patient involved in wise use -- and we're not allowed to talk about that at FDA -- is I might consider if it costs me a lot more, it was worth the risk. But otherwise, go for it.

DR. PAGE: Thank you.

Mr. Frankel.

MR. FRANKEL: So in terms of the benefit-risk, we discussed that already, but I think

that just to really encapsulate the idea which has already been stated, we don't know exactly who's going to benefit from this, the extent of the benefit, but there is a pretty broad consensus that there is a likelihood or at the very least a possibility of benefit, and there is also a consensus that there will be no one that will argue that to avoid one stroke is certainly a worthy cause.

The pooled data showed some 8 million neurons that were saved in terms of the lesion size. The meta-analysis -- one death or stroke may have been averted for every 22 patients. This is the type of data that I think that a lot of patients and a lot of consumers out there, it would weigh very heavily with them in their judgment. Just one sidebar: in closing, I think that it's very encouraging that there is such caution being voiced in terms of avoiding any stroke, any size of the stroke in the context of TAVR, and I would urge that that discussion has the same volume when discussing the procedure, TAVR itself, in comparison to traditional surgery, something that in recent days, months, and years, it certainly has changed, even in the context of this trial. There was "a debunked notion that TAVI carries a higher risk of stroke than SAVR." I think that the 9.1% stroke rate of the unprotected patients is something that should be -- that's a substantial alarm bell that people have to think about when discussing with their patients regarding the risk and benefit of TAVR versus traditional surgery because that obviously is substantially a higher number than what was seen in the PARTNER II trial.

DR. PAGE: Thank you.

Mr. Thuramalla.

MR. THURAMALLA: I'd like to first thank the Sponsor, the FDA, and the public speakers for their excellent presentations. I'd like to also thank the Panel for the thoughtful deliberations. Based on all the discussions and the data that we have seen, I strongly feel that the de novo should be granted. We saw that the primary safety endpoint was met and

debris was captured in 99% of the patients, and some panelists also mentioned that it is definitely better to capture some, if not all, of the debris, so there is only a positive side to this; hence, I strongly feel this de novo should be granted. Thank you.

DR. PAGE: Thank you very much. And thank you, the three of you, for your important voices in this Panel.

Now Dr. Roberts.

DR. ROBERTS: I thank the Sponsor for conducting this very important study. I know it's a difficult study to perform, having trying to get these very difficult patients into MRI scanners for much of my career. So I, you know, I really applaud you on that. You know, it just comes down to, you know, would I want this device myself, and whenever I see those scans and, you know, regardless of whether or not down the road I'm going to have a difference in some neurocognitive test, I see those DWI signals as injured brain tissue, and so, to me, that's extremely important to protect the brain tissue, particularly given the fact that this device is safe. And so there is really no large risk associated with this, so why would you not want to go ahead and protect this brain tissue. I have expressed my concerns about the neuroimaging component of it earlier.

If the Sponsor would be willing, I think it would be very interesting to go back and look at the data that they already have and reanalyze some of that data, particularly in any patients who might have had angiograms done; many of those patients, I'm sure, given how sick they are, because I still have concerns about protected versus non-protected territories and how that could be potentially even making this data not look as good as it potentially could be, so maybe that's something that could be addressed, but ultimately this is a device that I would want to have.

DR. PAGE: Thank you very much.

Dr. Good.

DR. GOOD: I would also like to add my thanks to the Sponsors and the FDA. This was a very, very informative panel meeting today and very well, very well done. I think that I have to say that there certainly is a signal towards effectiveness in preventing stroke, even though it's not statistically significant between the two groups. Obviously, as everyone said, the device appears to be safe. It's disappointing that there's no clear connection between the diffusion-weighted volumes or numbers and the clinical strokes, and I know the Sponsor feels that very strongly that that's a disappointment. I am concerned about the DWI images. With all the abnormalities, I think long term this could be a problem; some longitudinal study might be helpful. And any damaged brain is a bad thing. There's no question that the device does capture debris, and even though it doesn't seem to capture it all, and strokes seem to occur for whatever reason, even in the treatment group, so putting this all together and considering that there are really no other alternatives, I would be in favor of approving the device, especially because of its safety.

DR. PAGE: Thank you, Dr. Good.

Dr. Borer.

DR. BORER: Intuitively, it seems like a very good thing to me that these debris, which are released during a TAVR procedure, are taken out of the circulation pretty effectively by this filter, and I think that's a good thing. And even though I really can't interpret what it means, I intuitively believe that it's better that the images that were done looked better after a filter was used than when a filter wasn't used. So I think that's all very good. What troubles me is that I can't relate those results clearly to clinical benefit.

There's a suggestion, but it's not as clear as I would like it to be, and I don't know why that is. It may be that the study could have been designed a little differently, it may be that the measurements could've been made a little differently, or it may be that I don't really understand the pathophysiology of what's going on here all that well. So with that

having been said, I'm troubled that I don't have a clear position that I can take; however, if I had to, if I were forced to, I'd rather have this thing in than not have it in if I had to have a TAVR.

DR. PAGE: Thank you.

Dr. Dodd.

DR. DODD: So I would tend to agree with Dr. Borer, and I think that the discussion that we had earlier was very good, so I don't want to reiterate all that. I do have one thing that is in the back of my mind. I have in my notes that there is a risk of stroke and dementia associated with TAVR, and that was shown in the *New England Journal* paper. I haven't read the paper, but my question is if there is an increased risk of stroke and dementia associated with the TAVR procedure, if this protection device is approved, is that going to send a message that TAVR is now safer than the open surgery, from the *New England Journal* paper, and I guess that's just one of the things in the back of my mind is, you know, I know -- I heard some people from the public presentations talk about, well, they weren't eligible for the open surgery, but for -- you know, who is this going to be used on, and is it going to send a message that it is now safe, and that would be a concern. And presumably, labeling could address that, but -- that was my only other comment. Thanks.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: This is a challenging question. There's a motion, there is a desire to mitigate embolic material to arguably the most important organ that we all have. It's unpredictable. We are precedent for the excitement of filters capturing device that -- rather, emboli or catheters that suck out clot, aspiration thrombectomy that we all used to perform routinely that proved to be negative in terms of patient benefit, in that case a signal potentially of harm, although the biologic plausibility was difficult. So I have no

concern here about safety.

I have concern about efficacy, but I don't know of a good clinical trial that is doable to overcome what I thought was a very well conducted, very well designed trial. And because it's unpredictable and because I think preventing any stroke or potential for cognitive dysfunction in a patient population that is, one, currently already full of comorbidities and, two, moving to lower and lower-risk patients, as an interventionalist, I would use this device. I can't tell you that it is effective in reducing clinical endpoints, but I believe the totality of the data suggests that it might, and the outcome, when it occurs, is so devastating that I would want to prevent it.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: So let me say first that if we really were voting right now, I would vote in favor of approval, and that might temper my real remarks. So I think it was a very good study, I do understand the challenges of getting everybody back, but the challenge to you is to convince us that the people that don't come back for whatever evaluation, that they're not different from the ones who did come back, that they didn't have more death or whatever, so it was a good study, but you did have a lot of missing data. But here's what I mentioned before, but I'm really concerned about this.

If I were to have a valve replaced this way and the doctor explained to me, hey, there's some risk, that we know there's a chance of stroke, there's debris that breaks off, so I have this thing called the SENTINEL Cerebral Protection System, and I'd say, okay, I understand pieces of junk going to my brain, so you have a protection system, tell me more, because this is informed consent, I have to sign, and the first thing here is he would have to tell me is, well, it's not really a protection system, it's a debris catching system that hopefully will reduce your chance of stroke or other brain problems.

But the guy doing the informed consent is going to have to backpedal immediately, and I'd really like to talk to some of you who have had to go through the informed consent for these patients, and I'm guessing on occasion, if you had a really educated person, they had to say, oh, so it's not what you just told me, it's not what it's named, it's something else; something else good, a debris capture system, it's something good, but it is not a protection system. However, I'd vote for it.

DR. PAGE: Thank you. And just to remind us that we are not voting, but we know how you would vote.

Dr. Yuh.

DR. YUH: So the conduct of most modern cardiac surgery over the last several decades particularly has been predicated, the instrumentation, as well, on reducing both particulate and gaseous emboli, so the action of this particular device resonates particularly strongly with me, and I think the Sponsors are on the right track with respect to the device design in their study. I think it's quite laudable in terms of conducting something of this magnitude and complexity.

I think the lack of seeing significance is more in the imperfection of the device as opposed to a flaw in the concept of the device, and I think the study carries a lot of value not only in terms of setting a framework for improvements on this device or subsequent device, new devices, but creating a framework for improving investigational techniques and shedding more light on the value or the faults or flaws in diffusion-weighted MRI for assessing neurologic injuries, so I think all in all I'm very much excited by this device. I would use it in an open cardiac operation, I think it could be. I'm not sure the Sponsors might be thinking along those lines as well, but I think this was a very valuable study even though the results were not statistically as impressive as we would've liked them to be.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: I'd like to reassure Dr. Dodd that people aren't going to be particularly attracted to TAVR at a younger age because they have stroke protection. If they need an aortic valve, everybody's attracted to that rather than open -- except for cardiac surgeons --

(Laughter.)

DR. BRINKER: -- rather than open procedures, and that's without this device. So this device is a helpful step in the right direction, and I believe everything that you said about it's a not perfect device; it's an early clinical, primitive clinical device right now, because when it gets to be really good, it will protect all cerebral flow during the procedure, including obviously the left vertebral. But there are some things also that will probably occur, so the Sponsors, I'm sure, thought already about why there are any evidence of embolic events in the protected area. What's going on there? Is stuff going through a 140 µ filter capable of causing this, or is it the fact that the circumferential pattern of the cage doesn't fit tightly against the wall, especially if the wall's a bit eccentric rather than totally circular? And I think those answers will only make a better device, but it think it's good enough as it stands now to be available.

DR. PAGE: Thank you.

Dr. Peavy.

DR. PEAVY: So along the relatively optimistic comments from the group, I think this is a very important step toward understanding stroke and could be very useful as you go in understanding the peripheral and the central -- the relationships between the peripheral and central nervous system. I'm certain that there will be many advances over the next 5 to 10 years and the sensitivity of measures, including hopefully neurocognitive measures, imaging measures, and other things that hopefully will make it easier to do some of the measurements, maybe less invasive. So I just see this as being a step, but very many

subsequent steps in developing the technology and really being able to learn from it. So thank you.

DR. PAGE: Thank you.

Dr. Duff.

DR. DUFF: So I guess I'll be a dissenting voice. Although I understand the concept and very much wanted to see positive results, I didn't in the primary first outcome measure, and I think that the secondary outcome measure or the second primary outcome measure was, you know, not for me really convinced why 30% was so important. So I hope that the work continues in this, but I don't feel as strongly about it.

DR. PAGE: Thank you very much.

Dr. Hammon.

DR. HAMMON: I want to thank the FDA for inviting me to come to this session, and I've enjoyed meeting all these new people that I met and some of the people that I've known in the past and have reconnected with. And I'm just 5 years from being 80, and I want something available that can help me, so I'm very much in favor of having this device go forward. But I'd like to ask Dr. Leon and his team and his industrial partner to help me out by continuing to improve this device.

I'm sure Dr. Leon can remember when stents first hit the market and these bare metal stents came out and everybody said -- I heard a cardiologist from Brussels say that the days of coronary bypass surgery are over and now we're doing more than we ever did. So we're working together with the cardiologists. This is a wonderful time. We are partners with the cardiologists again, and I am so happy about that. And this would just be another way to increase that partnership, so thank you.

DR. PAGE: Thank you, sir.

Dr. Ohman.

DR. OHMAN: Yeah, I want to thank the Sponsors and the FDA for an incredible day. It really taxes my brain to think how I should interpret this information. We really don't have anything. We would love to have something. We think that things going to the brain are bad for us, and then we have a study that doesn't help us, and we get lost in this sort of conflict of science versus -- maybe emotion isn't exactly the right word, but at least that's this realm we're in. So on the first level, I want to -- would any sponsor do this type of study again? I doubt it. I think somebody might say let's go back to that clinical endpoint; yes, it's a harder study, but you don't have to try squeeze elderly people into MRI machines and try to figure out what it really means, and you can make the study very simple and maybe then get the information that is really meaningful to all of us. Had we had that, it would have been pretty easy. Do we have some signals towards that? We do. There are some signals within this study that actually gives us some hope that this would be the case. The one unsettling part for me, I think, is that if I look at the three studies and the difference between the three studies, it worries me that actually it's the more complex patients that may not derive the benefit, which is actually the last group I would want -- I want them to have a lot more benefit.

This could be a technical issue or some other issues, but that is the one piece that puts me a bit on the worrying side of is this really going to be good, and I already alluded to, but I was shut down, so I still say it again, you know, this is one first iteration. It really depends on what we do after that that becomes even more important, because if we're uncertain of today, we're going to be even more uncertain of tomorrow unless something can be changed and moved in the right direction. So overall, I'm favorably disposed, but I'm highly uncertain.

DR. PAGE: Thank you, Dr. Ohman.

Dr. Somberg.

DR. SOMBERG: Well, a lot's been said today from my colleagues, and I agree with much of it. I'd look at it or I'd ask the FDA to look at it from a slightly different perspective, and that is that there's considerable current pressure to modify or change the acceptance procedure of drugs and devices and to look towards safety predominantly and maybe not to consider efficacy. I disagree with that, and I think we and the FDA must be data driven, and that is a major problem with this particular device because although our doctor sentiment here that we all would like to see the particulate matter "matter," maybe it does, maybe it doesn't, so what I would say is I would favor and had voted for approval of this drug based on some data, not the primary study, because it was flawed, terribly flawed, and yes, probably a sponsor's not going to redo this study in a larger dimension or do it again, or other sponsors. So I think right now we have to look towards the meta-analysis, the compilation, systematic compilation of all the data, that extent, and that wasn't even done. It was only done with the three studies the Sponsor did. I heard there's a German study, there's another study we saw presented, so there is more data out there to harvest, and I commend the FDA to do that. I think the meta-analysis, the 72-hour stroke data, and the 30-day stroke data, although that isn't significant, that's trending, all together gives us an overview that there is enough benefit here and very little risk to favor a risk-benefit assessment in favor of the device's approval.

DR. PAGE: Thank you, Dr. Somberg.

Dr. Vetrovec.

DR. VETROVEC: Well, I'm an interventional cardiologist and sort of straightforward in my thinking. First, I'd like to congratulate the Sponsor for what I think was a really clear, nicely done presentation. I think the FDA did a nice, thoughtful evaluation of the information also in their presentation, so I thank both. As I see it, stroke and/or cognitive impairment are bad things, and given that TAVR's a growing population that's moving into

younger and younger people, I think even more perhaps worrisome than just stroke is this whole issue of multiple debris and how that may or may not impact cognitive dysfunction longitudinally in the future.

The device clearly filters material that I think, at least, I would not want in my brain, which I think is an important factor, particularly again may be more related to late cognitive dysfunction. The device seems to be able to be delivered effectively with a minimal amount of training and it has low risk. And if you put those things all together, recognizing this is not the perfect double blind placebo control study, I would want it if I were having a TAVR. In terms of looking ahead, I got two other thoughts. It's probably hopeless to try to do anything else with the population, but gosh, if anything could be obtained in terms of follow-up on these patients late, I think we could learn a lot from that, even if you didn't get the imaging, even you got neurocognitive information. And then assuming approval, it would be wonderful to see a registry that went out 2 or 3 years with a clinical follow-up. I'm a Magnus believer that we could learn a lot just by knowing what happens to these patients, do they have strokes and particularly their neurocognitive function, and if possible, either in a cadre or across the board, actually get real testing, but at least a subset to try to document what happens. But I think the longer-term follow-up will be really important. Thank you.

DR. PAGE: Thank you, Dr. Vetrovec.

And I, as Chair, have the prerogative of giving my perspective. I agree with the, I think, strong consensus of the Panel in that this is a device that is safe. While we're all frustrated with the outcome of the study, I'm not sure it could've been done better, and I don't think it ever will be done better, so we have the data we have, which I think shows a signal. And in terms of the capture of debris, I think we're all in agreement that we'd much rather have that debris coming out of the body than going to our brain, so for that reason, I

would favor this. And furthermore, this is an adjunctive device.

I had the honor of chairing the first TAVR panel in the highest risk group, and the world's come a long way since then. But we recognized that it's not a perfect procedure, and I think this is an iterative step. Our interventional colleagues, I believe, will want this to be available, and I would postulate it will be used frequently, if not nearly universally, in terms of these procedures, and I think that's the right thing.

Dr. Brockman, do you have any further comments for us, the audience, the Panel, before I conclude this meeting?

DR. BROCKMAN: I would just like to add my thanks to the Sponsor, to everyone who presented. Great discussion from the panelists. I would especially like to thank you for focusing on the clinical and statistical issues. Your comments and discussion have been very enlightening. Thank you.

DR. PAGE: And I would like to acknowledge you. I didn't know anybody but Bram Zuckerman who could sit in that chair and take us through a meeting, and you've done an admirable job in his absence, and we all wish him the best of health. I do also want to thank the FDA, I want to thank the Sponsors. I especially want to thank the people who came here to address the Panel, especially the patients and the family members of patients, and I hope this has given you some insight into the very serious deliberation that we undertake when we consider a device that would be available for the U.S. population.

With that, I want to thank everyone again and pronounce this February 23rd meeting of the Circulatory System Devices Panel to be adjourned. Safe travels.

(Whereupon, at 5:31 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

February 23, 2017

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

TOM BOWMAN

Official Reporter