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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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December 10, 2012
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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KRISTINE R. MATTIVI, M.S.	Consumer Representative
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MEETING

(8:00 a.m.)

DR. HURST: It's approximately 8 o'clock, and I'd like to call this meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee to order.

I'm Dr. Robert Hurst, Acting Chairperson for the Panel meeting. I'm a Professor of Radiology, Neurosurgery, and Neurology at the University of Pennsylvania.

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

The FDA is convening today's meeting to solicit the Panel's input on the current knowledge of the safety and effectiveness of the NeuroFlo Catheter for use in patients with acute ischemic stroke within 14 hours of symptom onset.

Before we begin, I'd like to ask the distinguished Panel members and FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

And I'd like to start on my left with Dr. Eydelman, please.

DR. EYDELMAN: Good morning. My name is Dr. Malvina Eydelman. I'm the Director of the Division of Ophthalmic, Ear,

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Nose and Throat Devices. Prior to reorganization of November 1, I was Division Director of Ophthalmic, Neurological, and ENT Devices. Hence, I'm at the table today.

Thank you.

DR. HAMMON: My name is John Hammon. I am a cardiothoracic surgeon from Wake Forest University, and my research experience for the last 20 years has been in neuroprotection during cardiac surgery.

DR. DORSEY: Good morning. My name is Ray Dorsey. I'm Associate Professor of Neurology at Johns Hopkins and have expertise in clinical trial design as it pertains to neurodegenerative disorders.

DR. GOLDSTEIN: I'm Larry Goldstein. I'm Director of the Stroke Center at Duke. I'm a vascular neurologist and I have various expertise, all related to stroke.

DR. FURIE: I'm Karen Furie. I'm a vascular neurologist and Chief of Neurology at the Lifespan hospitals, and Chairman of Neurology at the Alpert Medical School of Brown University.

DR. TOLEDANO: My name is Alicia Toledano. I'm a statistician with 20 years of experience in medical device clinical trials, and I'm a special assistant to the editor of the *American Journal of Neuroradiology*, a member of the Quantitative Imaging Biomarkers Alliance of the Radiology Society of North America, and President of Biostatistics Consulting, Limited.

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DR. NOONAN: I'm Patrick Noonan, Director of Interventional Neuroradiology at Scott & White Hospital in Temple, Texas.

MS. FACEY: Natasha Facey, Designated Federal Officer for the Neurological Devices Panel.

DR. YANG: Good morning. I'm Lynda Yang, and I'm Associate Professor of Neurosurgery at the University of Michigan, with expertise in general neurosurgery and also in nerve disorders.

DR. ENSRUD: I'm Erik Ensrud, a neurologist and physiatrist, or a specialist in rehabilitation medicine, from the Boston VA Medical Center and Brigham and Women's Hospital.

DR. SUNG: I'm Gene Sung, Director of the Division of Neurocritical Care and Stroke at the University of Southern California.

DR. ZHOU: Xiao-Hua Andrew Zhou, a professor in the Department of Biostatistics at the University of Washington. My research interest is statistical methods in diagnostic medicine.

DR. POSNER: I'm Phil Posner. I'm the Patient Representative, with experience with families with stroke. But I'm also a retired cardiovascular physiologist and pharmacologist who's currently with Oak Ridge Associated Universities.

MS. MATTIVI: Kris Mattivi. I'm the Consumer Representative to this Panel. I'm the manager of analytic services at the Colorado Foundation for Medical Care, and a physical therapist.

DR. LAYTON: I'm Terry Layton, a biomedical engineer from Laytech. I'm also a visiting professor at the University of Illinois, Chicago, teaching the bioengineers the skill sets for industry.

DR. HURST: Thanks very much.

If you have not already done so, please sign the attendance sheets that are on the tables by the door.

Natasha Facey, the Designated Federal Officer for the Neurological Devices Panel, will make some introductory remarks.

MS. FACEY: Good morning. I will now read the FDA Conflict of Interest Disclosure Statement, a particular matter involving specific parties.

The Food and Drug Administration is convening today's meeting of the Neurological 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

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

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees 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 current knowledge about the safety and effectiveness of the CoAxia NeuroFlo Catheter device for the intended use of diverting cardiac output to the cerebral vasculature via partial occlusion of the descending aorta, including in patients with acute ischemic stroke within 14 hours of symptom onset.

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. A copy of this statement will be available for review at the registration table

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during this meeting and will be included as part of the official transcript.

Dr. Terry Layton is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Laytech, 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 that they may have with any firms at issue.

For the duration of the Neurological Devices Panel meeting on December 10, 2012, Drs. Larry Goldstein, Philip Posner, and Gene Sung from the Peripheral and Central Nervous System Advisory Committee in the Center for Drug Evaluation and Research have been appointed as temporary non-voting members. Also, Dr. Posner will serve as the Patient Representative for this meeting. 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.

Dr. Erik Ensrud is a regular Government employee also from the CDER'S Peripheral and Central Nervous System Advisory Committee and has been appointed as a temporary non-voting member who has undergone the

customary conflict of interest review and has reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on December 7, 2012.

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

This entire meeting will be transcribed, and in order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time you speak. Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Information on purchasing videos of today's meeting can be found at the FDA registration table.

The press contact for today's meeting is Michelle Bolek.

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 presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

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

Dr. Hurst.

DR. HURST: Thank you, Natasha.

We'll now proceed with the presentations portion of this meeting, and our first presentation will be from CoAxia, Incorporated.

MS. KVISTAD: Good morning, Mr. Chairman and distinguished Panel members. I am Sharon Kvistad. I'm a consultant to CoAxia. I was also the Vice President of Regulatory Affairs for CoAxia for the past nine years. I am a shareholder in the company.

As already discussed, we are here today to talk about the safety and effectiveness of the NeuroFlo Catheter in acute ischemic stroke.

CoAxia is here because we seek a label for use in ischemic stroke for the NeuroFlo Catheter. The basis for our request is that we have an existing 510(k) device which is labeled for general use. That device cannot be labeled for use in stroke. We have submitted a de novo petition and are seeking addition of stroke labeling based on trial data. That trial data discusses safety and patient benefit, and we think it's a valuable body of information.

The patients indicated for this device are those with acute ischemic stroke, a very large patient population in need, with no effective treatment alternatives.

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Here with me today as presenters are Dr. Susan Alpert, Dr. Louis Caplan, Dr. Jeffrey Saver, Dr. Helmi Lutsep, and Dr. Raul Nogueira. Also here as responders are Mr. Chris Mullin, Ms. Lisa Thackery, Mr. Rick Schallhorn, and Ms. Kay Zander.

Our presentation today will be led off by Dr. Susan Alpert with some discussion context. We will then go through the device history and description, the stroke treatment perspectives, a SENTIS study and interpretation overview of the SENTIS data and clinical interpretation of that data, followed by a conclusion from Dr. Alpert.

And with that, I will turn it over to Dr. Alpert.

DR. ALPERT: Thank you, Sharon.

Good morning. I'm Susan Alpert. I am a paid consultant to CoAxia. I've filled a number of positions in the medical device industry in the last 25 years, including six years as the Director of the Office of Device Evaluation at the Center for Devices and Radiological Health at FDA.

You've heard that we're here because CoAxia is looking for a claim for the NeuroFlo Catheter for use in ischemic stroke patients. The submission is based on preclinical and clinical data. And you're going to hear about the large SENTIS trial that was conducted to study the safety and efficacy of the device in ischemic stroke patients with best medical management and compared to best medical management.

What I want to spend a few minutes doing, however, is talking

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about the regulatory context. As you're probably aware, this is a unique Panel. This is the first time that the de novo process has actually been discussed in a public panel meeting, so I want to spend a few minutes with you talking about the de novo process itself.

As Sharon has said, the product is already in the market under 510(k). It's a moderate-risk product and has been cleared actually several times for a general tool claim, in essence, that it can be used to divert central blood flow to areas of the body needing increased flow. And that includes the cerebral vasculature.

However, FDA has determined that in order to label this device for use in ischemic stroke patients, it's a new claim. It's not covered by the current 510(k). And that's due to the defined population and concerns about the risk and benefit of the product in that specific population. So the product needs its own path to market.

Gaining the clearing for ischemic stroke is very important for making the device appropriately available to the stroke population so the company can properly label, with the appropriate information, patient selection, expected risks and benefits, provide education, provide training, and share the experience as it's gained for the use of the product.

In addition, the use of NeuroFlo today would be considered off label. Off label means the company can't promote, can't train, can't teach, can't support, can't provide additional information. And risk managers and

others in hospitals find that off label usually means higher risk and are reluctant to use the product. So in order for the product to be available for the population, we need to get the claim on label.

So how do we get the product with the right claim into the marketplace? FDA actually has several tools for placing products in the market. And I know you've been trained, so you're familiar with the premarket approval, or PMA, pathway that's used for high-risk devices, and that's the one that panels are frequently involved in discussing. That's not why we're here today.

You're also, I'm sure, familiar with the pathway to market for lower-risk products through the 510(k), or premarket notification process, where a product establishes that it is substantially equivalent to an already marketed product.

In this case, however, since there is no predicate, no similar product labeled for use in ischemic stroke to which NeuroFlo can, in fact, claim equivalence, we've asked FDA to evaluate the product under this different tool, the de novo or original classification process for low to moderate-risk devices.

And I'll just add a note that I was at FDA when, in fact, the de novo was originally proposed and described for these low to moderate-risk devices.

So what is de novo? De novo is a regulatory tool that FDA can

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use to create, in essence, a new 510(k) category of devices for low to moderate-risk products. These are devices that don't need to go through the PMA because they have recognized and reasonably controlled risks. But the devices do need to be safe and have the right benefit-to-risk ratio for the intended population in order to go to market.

The assessment for de novo takes into account several things. First, that they're low to moderate-risk devices and that the benefits are commensurate with the risk. As moderate-risk devices, moderate amounts of benefit are expected. The benefit/risk evaluation is done in the appropriate or labeled population -- and that's why we're here today -- and requires judgment, medical judgment of the clinical data. Consideration includes what alternative therapies are available for the indicated population. And these products will be subject to general and specific controls. And I'll talk about that more in a few moments.

In addition, there are a number of considerations. And this is taken from FDA's guidance document on how to assess the benefits and risks for de novo.

So among the considerations that will be made by FDA are the magnitude and probability of the device impact, so safety and efficacy. But the considerations include the impact on clinical management of products. Are there impacts on quality of life? Is there a reduction in the probability of death as the result of using a product? Or is it an aid to improving the

function of the patient?

When it comes to the patient populations considered for these products, is there an unmet clinical need in the population, what alternative therapies are available, as I mentioned, and that not all patients are expected to have all benefits from these products. The decisions are made on a basis of both clinical and nonclinical data.

I'm going to spend just a couple of moments -- and this is actually -- sorry, I'm going to read a little bit from FDA's guidance document on benefit/risk, again, because it's a little bit different than what you may be used to in the PMA context.

So, first, "It is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the applicant demonstrates a relatively small probable benefit.

"In addition, the development of innovative technology may provide additional future benefits to patients.

"With subsequent iterations of the device, its benefit-risk profile may change (e.g., the benefits may increase or the risks may be reduced), the expected level of safety and effectiveness may change, and later versions may offer significant advantages over the initial device.

"In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, we" --

in this case it's FDA speaking -- "may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available."

FDA also has other tools that they can use to assure, once they've established through de novo a new category for 510(k), that products following on will remain safe and effective. They use general and specific controls. The general controls that apply to all devices include things like manufacturing under good quality systems, design controls, appropriate labeling, and the reporting of failures and adverse events.

In addition, FDA has a tool called special controls, which can include things such as the training, education, and specific labeling. But that's FDA's role, just to give you some background about what FDA is going to do with the information from this Panel meeting.

What's your role today? FDA has convened this Panel, yourselves, of scientific and clinical experts to help them assess the data from the SENTIS trial. The standard for assessing valid scientific evidence, the data from trials like SENTIS, is that it can be fairly and responsibly concluded by qualified experts, by yourselves, that there is reasonable evidence of safety and effectiveness, which for de novo is according to the criteria and considerations that I mentioned before, and that the benefit and risk assessment is appropriate for the moderate-risk device and the population being served.

So for NeuroFlo, what does that mean? The first question is, is there benefit for stroke patients who today have no alternatives? We believe there is, and you'll see that in the data.

Is this benefit sufficient to support marketing, considering the moderate risks of NeuroFlo use? We believe that based on the data you will agree that, in fact, moderate risk and the benefits are a good match.

Is NeuroFlo use reasonably safe in this population? And you'll see that the SENTIS trial has developed the type of data that will demonstrate that safety.

You're going to hear from the presenters who follow me a lot more detail on the data, but I wanted to provide you that context for your deliberations.

Thank you. And now I'm going to turn it back to Sharon.

MS. KVISTAD: Thanks, Dr. Alpert.

I'm going to provide a brief device description and regulatory history of CoAxia.

This is the NeuroFlo Catheter. You've heard us mention that we have a 510(k)-cleared device called FloControl. FloControl and NeuroFlo are the same device. It's a dual-balloon peripheral vascular occlusion device. Balloon inflation is independent. Balloons are large to accommodate vessels 10 mm to 28 mm in diameter, which includes the descending aorta.

During the procedure, the device is placed in the descending

aorta via standard femoral access. The balloons are inflated for 45 minutes of partial occlusion, after which they are deflated and withdrawn.

In this slide you can see the positioning of the device in the descending aorta. First, the infrarenal balloon is inflated. Then the second balloon is inflated. These are above and below the renal arteries when the device is in the descending aorta. In this position, like any vascular occlusion balloon, blood flow is redirected. So blood flow below the balloons is decreased, increased above the balloons, and specifically, in the descending aorta, that redirects blood flow to the cardiac, spinal, and cerebral vasculature.

A brief history of CoAxia.

As mentioned, there's a FloControl device that was cleared in 2003. This device was cleared for a second size in 2009. Both devices are indicated for controlling or stopping blood flow, and in 2009, specifically, the descending aorta was added to that description.

Also added to the labeling at that time was the physiologic effect of that device, that being that placement in the descending aorta resulted in diversion of cardiac output to core organs, including the cerebral vasculature.

In 2005, the FloControl device named NeuroFlo received a Humanitarian Device Exemption for treatment of cerebral ischemia following securement of subarachnoid hemorrhage and resulting vasospasm.

The NeuroFlo device was then studied. Actually, the NeuroFlo device study started in 2002 and, under the study named SENTIS, was the pivotal study that we're going to discuss today.

As mentioned previously, labeling for this device is being requested by a de novo petition.

With that, I'm going to open it up, and I'm going to tell you a little bit about what's going to happen next in clinical discussion.

Dr. Louis Caplan is going to lead off and talk about stroke treatment perspectives. That will be followed by a discussion of the SENTIS study and results from Drs. Saver, Lutsep. And later Dr. Nogueira is going to talk about the importance in patient treatment.

With that, I will turn it over to Dr. Caplan.

DR. CAPLAN: Good morning. I appreciate the opportunity to come and talk to you today. I must confess, I was a little surprised and disappointed that the CoAxia and the FDA presentations are kind of organized in an adversarial way. I just want to remind everybody that we're on the same team, the stroke patients' team, and we're all here really to maximize the care of stroke patients. That's certainly why I'm here today.

I had a stroke fellowship in the late 1960s, and since then I've devoted really my whole career to try to really study seriously stroke patients. I was the organizer and founder of the Harvard Stroke Registry, which was the first registry of prospective entry of over 700 patients. Since

then I was one of the principal investigators of the Stroke Data Bank, which was an NIH-funded registry. We led the Michael Reese Hospital Stroke Registry and New England Medical Center Posterior Circulation Registry. And more recently, I take care of inpatients and outpatients at the Beth Israel Deaconess hospital, and we've been focused really on imaging and stroke diagnosis and treatment. And I thought seriously for a very long time on the best way to diagnose and take care of stroke patients.

I have no financial interest in CoAxia, I'm not an investigator in the SENTIS trial, and I am a paid consultant for this meeting.

Now, my role in this is to try to put this NeuroFlo treatment into perspective. First, I'm going to just emphasize the importance of the problem of the number of stroke patients and the predominance of ischemic stroke and point out the target, which is the ischemic brain penumbra, that area which is under-perfused and will often go on to be infarcted if the circulation is not restored or if there is not reperfusion and emphasize, as everybody has, the importance of time.

As time goes by and the brain is still ischemic, it dies. But it's very important that even late improvements make a difference. And it can make a great difference.

Now, there are two ways now that reperfusion is attempted. One is to try to unblock the artery that is blocked, and the other is to try to maximize collateral blood flow, and that's where NeuroFlo actually fits in.

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So if we look here, if you block a blood vessel, what you do is decrease blood flow and the area directly involved, so-called the core, dies very quickly. With time there's an increasing amount of brain that's infarcted and the patient often gets worse. And this area, called the ischemic penumbra, is usually outside the core. So this is the target of reperfusion. And the need for reperfusion has really been known and recognized for decades.

Now, one effect is by increasing blood flow to the ischemic penumbra. And others have tried to improve tissue resistance to the ischemic damage, that is, neuroprotection. Unfortunately all of the neuroprotection trials have failed and there is not a viable present way to deal with the patients.

So one can use a number of on-label and off-label ways of opening the blocked artery using either intravenous tPA in the approved 3 hours, or some use it in 4 and 5 hours, or using intra-arterial thrombolysis with mechanical clot retrieval.

The other techniques are to try to bring more blood flow there and augment collateral flow. An old technique was just lying the patient head down. That increases blood flow a little bit, but is not dramatic.

A second way that's been used is by inducing hypertension. This has a limited effect because of autoregulation, and the problem is it also poses a risk to the heart with coronary ischemia and congestive heart failure.

An alternate technique that's been used is trying to increase blood volume. This is used in subarachnoid hemorrhage related to vasoconstriction. It does produce pulmonary congestion and sometimes hypoxemia, which decreases the benefit. And it's also a risk to the heart for congestive heart failure and myocardial infarction. So here's where NeuroFlo would be an alternate method of augmenting collateral blood flow.

Now, patients come in if they're early. Unfortunately only about 20%, at maximum, get in early enough for the on-label approved treatment, and now the mid to late strokes are more than 80% of the patients.

The early strokes are eligible for recanalization. The ones that come between 3 and 8 hours, some of them are off-label eligible for recanalization, but the effectiveness is known to be much less. And they also are candidates for collateral enhancement. For example, with NeuroFlo, the late strokes now have no approved treatment and are candidates for collateral enhancement.

If we look at the treatment objectives, they vary by the patient. So in the early strokes you try to get complete recovery, or as best you can, by opening the vessels. By the time 3 to 8 hours go and they're either moderate or severe severity, they really already had a stroke, so you try to improve function and reduce disability. In the late strokes you try to reduce mortality and try to reduce severe disability.

Now, more than 80% of the ischemic stroke patients, unfortunately, get there too late or they're otherwise excluded from recanalization treatment. And sometimes the treatment doesn't work; you can't recanalize the blood vessel.

Collateral flow augmentation is the major reperfusion focus for, now, the excluded and the mid to late patients. Current collateral augmentation techniques, which we've talked about position in bed, hypertension, increased blood volume, have not been shown to be very important and effective and really have important risks.

NeuroFlo, as you'll hear, augments cerebral blood flow safely, even in excluded, mid-late arrived patients. And any improvement in these patients to lower levels is very important. So taking a patient who would've died and having him being at home and be able to be with his family, having a patient who would ordinarily be in a nursing home now be home with health and some disability, having a disabled person now able to do things on their own, this is really critical and very important.

So any benefit that can shift these patients to a different category, even though they're not back to normal, is of enormous importance to the patient and the family.

I'm going to now turn it over to Dr. Jeffrey Saver, who's going to talk more about the actual study design of the SENTIS study.

Thank you.

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DR. SAVER: Good morning. It's a great pleasure to be here. I am Jeffrey Saver, Professor of Neurology and Director of the UCLA Stroke Center, a former chair of the AHA Stroke Guidelines Committee and the Stroke Council.

I have no equity interest in CoAxia. I have been a clinical investigator and a steering committee member for the SENTIS trial since its inception, so I've lived with this data for quite some time. I am a paid consultant for the company at this meeting. And I have an intense interest in clinical trial design and in acute stroke treatment.

I will be talking about the general design of the SENTIS trial, and then Dr. Lutsep will be talking about the safety results from the trial, and then I'll come back and talk about the effectiveness results from the trial.

SENTIS was a study undertaken to evaluate the safety and long-term outcome of collateral augmentation by partial aortic occlusion in acute stroke patients ineligible for other interventions. It really occupies a special place in the history of device clinical trials for stroke. It is the largest randomized trial of an acute endovascular stroke device ever undertaken, with 515 patients enrolled between 2005 and 2010.

It is a clinical outcome study. The Sponsor initially proposed a cerebral perfusion biomarker outcome study to FDA, and FDA indicated that a biomarker outcome would not support a change in label, that a clinical outcome study needed to be done, and so this trial was designed and

undertaken. It had oversight by an international steering committee and a DSMB.

The design was a prospective, single-blind, randomized 1:1 assignment trial comparing patients assigned to best medical therapy plus NeuroFlo treatment versus best medical therapy alone. Patients were followed through the final determination of status at 90 days.

The primary endpoint in the SENTIS trial for effectiveness was the global outcome score at 90 days, and for safety, all serious adverse events at 90 days. So this was a rigorously managed trial at leading stroke centers, a robust dataset for consideration.

The entry criteria for the study. To summarize some key criteria, patients needed to have a clinical diagnosis of acute ischemic stroke with cortical involvement. CT scans needed to exclude hemorrhage and exclude massive infarcts more than one-third of the MCA territory, but not special multi-modal imaging required for entry; broad moderate to severe stroke severity entry with NIH Stroke Scales of 5 to 18, and the time to onset to randomization was permitted up to 18 hours. So this was a very long treatment window trial.

Exclusion criteria excluded patients with cardiac and renal features that might've put patients at increased risk for an aortic intervention, and also patients who were having a recanalization intervention.

In the actually enrolled patient population, the mean time from onset was, to randomization, over 8 hours. This was a late treatment trial. Typical age range for stroke patients, 68 years old. The entry severity was a median on the NIH Stroke Scale of 10, which at this late time point indicates a moderate to severe patient population.

And in looking at subject accountability, the flow of patients through the trial is shown here. In the full intention-to-treat patient population, 515 patients were randomized. Twenty-eight had aortic pathology or early improvement and, therefore, in the treatment assigned group, did not undergo the treatment. They were not included in the modified intent-to-treat population. And then there was the modified as-treated patient population. The follow-up rate at 90 days was 98%. So this was a very high-quality dataset, a very complete clinical trial dataset for analysis.

The baseline characteristics between the treatment and control groups were well matched. Patients in general had a high frequency of hypertension, over 70% of patients; of hyperlipidemia in over half; atrial fibrillation in a quarter. So these were typical stroke patients with the substantial burden of comorbidities that we see, and a well-matched result of randomization allowing us to do reliable study analysis.

So with that brief overview of the SENTIS trial design, I will turn the podium over to Dr. Helmi Lutsep, who chaired the DSMB, to talk about

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the safety results.

DR. LUTSEP: Hello, I'm Helmi Lutsep. I'm a professor and the Vice Chair of the Department of Neurology at Oregon Health & Science University in Portland. And I did receive compensation for my role in the DSMB and for being here today, but otherwise have no financial disclosures, and neither do the rest of the DSMB members.

So our DSMB had quite a typical composition for a trial like this. We had four vascular neurologists, one interventional cardiologist, and one biostatistician. These were very experienced people and, I'll have to say, a very dedicated group.

Our responsibilities included reviewing all of the adverse events for the trial. We served as both the clinical events committee and the DSMB, so we had a broad perspective with which to adjudicate these events. And we were primarily concerned with safety in our role, but we did review efficacy on one protocol-specified analysis. And then one final point to keep in mind is that we were not blinded in the trial. This allowed us to review all of the medical records for these patients.

So we performed these adjudications on an ongoing basis, looking for the relatedness of the adverse event with the procedure or the device. And we included all study-related requirements in making these adjudications and even changes in care that the patient may have incurred by being enrolled in the study. And the procedure-related events included such

things as the groin puncture -- there were related issues -- or even medications that the investigator may have chosen to use, such as heparin or sedation.

So we applied categories to these events. We determined the procedure or device either to be likely related to the adverse event, likely not related, or unknown. And we made that unknown determination when we simply could not tell if they were otherwise related or not. And then there was one more category, which was "not applicable," if the patient did not get the device or the procedure.

So as the trial progressed, this was a novel device, and also we did not know what the rates were in the control arm initially. So there were a number of AEs that we designated as unknown in the beginning. At the end of the trial, we performed a final review in person, again reviewed the results in both of the arms, and applied what we could for consistency to the two arms. And through that we found that most of these events that we had initially designated as unknown were actually likely not related to the device or procedure.

Here is the important safety results slide. And this shows the SAEs through 90 days, and it shows that this did not differ in the NeuroFlo group compared to the control group. There were 43.9% in the NeuroFlo group and 42.8% in the control group.

Likewise, index stroke-related SAEs did not differ. These were

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SAEs that related to neurologic progression as a result of the stroke or death from the stroke. So those were 20.9% and 23.7%.

Despite the addition of the interventional procedure, NeuroFlo did not increase the serious adverse events.

Hemorrhage was of interest, given the physiology of the device, and we found that NeuroFlo use did not increase hemorrhage. So whether it's all hemorrhages through 90 days, serious hemorrhages, fatal hemorrhages, they did not differ in the two arms.

And then, of particular interest to our DSMB, we wanted to know about the symptomatic hemorrhages. These were defined, as they had been in the SITS-MOST trial, based on a 24-hour CT and a four-point neurologic change. These also did not differ in the two groups.

The DSMB had identified a number of areas of focus, and we had chosen these even before the trial started and our first face-to-face meeting. So we particularly looked at neurologic events, we've already discussed cerebral hemorrhage, but also cerebral edema and neurologic deterioration, and did not find a difference in the treatment and the control arms. Renal events were another area of focus for us, as they were for the DSMB. We did not find a difference in the two groups. And cardiac events likewise.

In fact, when we looked at all of the various subcategories in addition to the ones that we've already discussed, there were others,

including vascular, pulmonary, GI events, and so on. There was no significant difference between the two groups for any of these.

Of course, we had also identified procedure and device-related events as being of importance, and we found that there were no serious adverse events that were related to the device only. There was one serious adverse event that was related to the device and procedure, and this was a case of limb ischemia in a patient with very significant peripheral vascular disease.

And then there were seven additional SAEs that we felt were related to the procedure only. Most of these were groin access issues. There were two pseudo-aneurysms, there were two cases of arterial thrombosis, peripherally, and there was a groin abscess. In addition, there was a case of flash pulmonary edema that occurred when the patient was on the table, and a cerebral hemorrhage that we felt may have been procedure related.

So, overall, our DSMB concluded that there was no specific safety concerns related to NeuroFlo treatment.

We'll turn now to mortality. First, all-cause mortality tended to be lower in the NeuroFlo group than the control group. It was 11.3% in the NeuroFlo group and 16.3% in the control group, with a p-value of just over 0.08.

Stroke-related mortality was significantly lower in the NeuroFlo group than the control group. It was 7.4% in the NeuroFlo group, which is

about half that in the control group, 14.4%, with a p-value of 0.0111.

We'll look at the second category, the stroke-related mortality, in the second slide.

So we had been adjudicating stroke-related deaths on an ongoing basis, based on a prospectively defined definition, and we determined that stroke-related deaths could be either due to the stroke itself, such as cerebral edema, systemic complications associated with stroke, such as pneumonia that may be temporally related, or a new stroke. And each of these is lower in the NeuroFlo group than in the control group, numerically. And then stroke-related deaths, in the very bottom row, did not differ in the two groups.

Here's the Kaplan-Meier curve. First for all-cause mortality. The event-free probability is shown on the Y-axis, days from baseline on the X-axis, and there was a tendency for better survival in the treatment group, shown on the top curve.

This is the Kaplan-Meier curve for stroke-related mortality, and here there was a significant difference in survival, with the treatment group having better survival and then deaths occurring early here in the other group and then persisting.

So, in summary, our DSMB found that the NeuroFlo device was safe and that the serious adverse events did not differ in the NeuroFlo and control groups. Index stroke-related SAEs did not differ. All-cause mortality

tended to be lower in the NeuroFlo group, and stroke-related mortality was, in fact, significantly lower in the NeuroFlo group.

Thank you. At this point I will turn the podium back to Jeff.

DR. SAVER: Thank you, Helmi.

And now we'll turn from consideration of the safety outcomes from SENTIS to consideration of the effectiveness outcomes. And in my comments, I will talk briefly about the pre-specified outcomes in the SENTIS trial, then about some of the advances in the knowledge of clinical trial design in acute stroke, and the appropriateness of different outcome measures for different stroke patient populations, and then bring this together in interpreting the SENTIS results.

So, in SENTIS, the primary endpoint was the global outcome score. This is a composite of excellent outcomes on four measures, the neurologic deficit scale NIH Stroke Scale, the activities of daily living scale Barthel Index, and two global disability measures, Rankin and Glasgow.

This was the only endpoint the trial was powered around. It was discussed and selected in 2004 and was chosen back then because it was the endpoint used in the only positive acute stroke drug trial, the NINDS tPA trials.

But, in retrospect, I think most stroke design experts would recognize that it was not the most appropriate endpoint to have chosen for this patient population and this intervention. The global outcome scale is

well designed for a hyperacute intervention, like tPA under 3 hours, that has a powerful effect. It's a return to normal-type outcome, and early treatments with powerful interventions can get patients back to normal. But that type of return to normal outcome is not going to be responsive or sensitive in a later treatment intervention with a more modest effect.

The pre-specified secondary endpoints in SENTIS included analyses of the Rankin Scale, dichotomized at 0 to 2, and a Rankin shift over six levels, and several additional clinical measures.

And in addition to these pre-specified endpoints, I'll be also talking about additional endpoints that have been refined and developed in the decade since the trial was first designed, recognized as informative in later-treated patient populations and widely used today in a way that they weren't when the trial was first designed.

So, first, looking at the pre-specified and some leading primary and leading secondary endpoints, here are the results in tabular format; odds ratio point estimates favoring the NeuroFlo device, but none reaching statistical significance.

Here are the same results in a Forest plot collection, along with the results of the shift analysis. And, again, all endpoint estimates favorable, but none reaching statistical significance.

So this is formally not a positive trial, and it's important to bear that in mind.

Now, however, we are on the de novo pathway, not a PMA pathway. And as you heard and as I understand it, in the de novo pathway, a greater deal of uncertainty is permitted. We're not looking for beyond a reasonable doubt-type results with all p-value primaries 0.05. We're looking for preponderance of evidence. And taking into account all the information from this trial, we have a very robust dataset and much to learn from a detailed analysis.

So with that, let's turn to some of the later-developed approaches to trial analysis. I've talked briefly about why I think the global score is not an informative endpoint for analysis of the SENTIS trial. It's useful when you have a hyperacute intervention. It's not going to be responsive when you have a subacute intervention. It will be informative when you have a reperfusion intervention that completely reperfuses the brain. For a collateral enhancement intervention that partially reperfuses and has a more modest effect, it's also going to be hard to get patients back to normal. That's not going to be the most sensitive endpoint.

So what are the endpoints that are likely to be informative? They're going to be endpoints that are in the mid and lower end of the spectrum of outcomes that look at health state transitions that are achievable for patients treated late with a modest intervention, not endpoints clustered at the excellent outcome range, which are not going to be achievable in this patient population.

And so they include looking at the Rankin dichotomized at 0 to 2, but also dichotomized at the 0 to 4, the standard in the hemicraniectomy late treatment trials. They include looking at the Rankin shift at the health state transitions that are in the mid and lower end of the Rankin range, so a four-level Rankin shift.

And they also include the new approach of a sliding dichotomy analysis. And for this analysis we use the SAS sliding dichotomy developed for the ImpACT-24 trial, a different device trial that looks at several prognostic features for each patient at baseline, their age, their stroke severity, and the side of lesion, and says what's the expected outcome for that patient, based on their baseline prognosis, and then sets a win criterion for beating that expected outcome in each individual patient. So it slides the win criteria based on each patient's individual prognosis.

And for this analysis we removed the 18 stroke mimics from the patient population -- from the analysis. These are patients whose combined information from imaging and clinical course revealed that they were confirmed as not having had stroke causing their deficits, migraine, seizure, or some other cause, and therefore they introduced noise into the analysis. So we removed them. But the results are the same, in essence, if you include them or remove them.

And here are the results of these informative endpoint analyses. This was undertaken in the true intention-to-treat patient

population, but with the stroke mimics excluded. And you can see that, for the dichotomized endpoints I've discussed, sliding dichotomy, Rankin dichotomized at independent 0 to 2, Rankin dichotomized at avoiding severe disability and death at 0 to 4, there were beneficial effects indicated, with absolute differences between the arms ranging from 6% to 9% and p-values approaching or exceeding a conventional 0.05 level.

Here's the same data in a Forest plot format, along with the Rankin shift analysis shown. And you can see on the shift analysis that the deaths at the lower end, the Rankin 5 and 6, severe death and disability reduced and the good outcome, 0 to 2, increased and that occurring without an increase in the intermediate severe disability group. So a generally favorable shift. So, overall, the type of result we would expect to see if this was a treatment that was having a beneficial effect in a later time point.

We also looked at subgroup analyses. If this treatment is having a beneficial effect, we would expect the effect to be magnified in patient subgroups for which there was a physiologic reason to expect them to be particularly responsive to the intervention. And we thought there were three such subgroups to look at.

One are patients who have the more severe range of the mid-severity strokes. These are patients who have a greater range to improve over and whose collaterals were insufficient to protect them into the mild range, but still treatable and therefore responsive to a collateral

enhancement intervention; also the elderly who also have a compromised collateral circulation and therefore a potential to benefit from collateral enhancement therapy; and lastly, early presenting patients because, in all strokes, if you present early, the chance for a better outcome is greater.

And so here's the analyses of those subgroups and each of these subgroups, as would be expected, had an enhanced evidence of benefit; the early treated patients, under 5 hours, a 4½-fold odds ratio increase of good outcome; the severe patients near doubling, and the oldest old, age over 80, a fourfold increase in the odds of a good outcome.

Now, FDA has appropriately pointed out that you will be presented -- are being presented with multiple looks at this dataset today, and we have to be on guard for considerations of Type I error. And whenever you look at a trial in multiple different ways, there's a chance that certain analyses will be positive or negative by the play of chance.

However, if what results you see are solely the result of play of chance, then you would expect to see an equal balance, as shown in the figure on your left, here, of results that are favorable to the intervention and favorable to control, which you'd see significant results indicating benefit and significant results indicating harm.

On the other hand, if you see the pattern that I think we're seeing, where most of the results -- the great majority of the results indicate benefit, some are neutral, and none are indicating a clear harm. That's a very

different pattern. That suggests that the results we're seeing are not due to play of chance. They're due to an underlying true biologic effect of the treatment.

So in the data that we've examined, almost all of the point estimates of the odds ratios favor NeuroFlo among the single primary analysis, the 11 secondary analyses, and the four informative post hoc analyses that I've discussed this morning. Thirteen of the 16, 81%, have point estimates favoring NeuroFlo; multiple significant p-values favoring NeuroFlo and no significant p-values favoring control. This is a clear, consistent pattern suggesting the benefit of this device and not play of chance.

Here's a summary again of the major outcomes that I've discussed to emphasize this point, that they are all falling in the direction that indicates this device is making patients better.

So I will summarize that the results of the SENTIS trial indicate that there's no increase in serious adverse events from this intervention versus medical management, notably no increase in cerebral hemorrhage from this collateral enhancement intervention. There was a trend toward reduction in mortality, a remarkable outcome in an acute stroke trial only seen before in hemispherectomy trials, and a conventionally significant reduction in stroke-related mortality.

The trial was neutral on the primary effectiveness endpoint. However, there were consistent trends to improve functional outcomes that

were amplified when using more responsive sensitive endpoints in this patient population and in key subgroups.

And I think the overall take-home message then is that the SENTIS trial demonstrates safety from the NeuroFlo intervention and provides a totality of evidence indicating a preponderance of benefit.

Thank you very much for the consideration of the SENTIS trial. I'll now introduce Raul Nogueira, who will talk about applying these results in a clinical context.

DR. NOGUEIRA: Thank you, Dr. Saver.

Good morning, colleagues. Thank you for this opportunity. I'm Raul Nogueira. I am an academic neurointerventionalist out of Emory University and Grady Memorial Hospital in Atlanta, and a board member of the Society of Vascular and Interventional Neurology and the Society of NeuroInterventional Surgery, and also part of the AHA Stroke Leadership Committee.

I have no financial interest in CoAxia; however, I am a paid consultant for this meeting.

So what I would like to bring to the table is the perspective of a neurointerventionalist. I will try to focus on just three major topics. I will try to answer you and go over the data that demonstrates that NeuroFlo increases cerebral blood flow in both preclinical and human stroke patients. And then I would like to go over the rationale of why I would like to have

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NeuroFlo on my shelf with an approval labeling for stroke. This is mostly related to the limited treatment options that you have in these patients. Then I would like to explain how do I evaluate the SENTIS results. I think it's specifically important to understand the expected outcomes in that particular patient group, taking into consideration the late time to treatment and the variations in stroke severity.

So starting with the preclinical data, this first paper published in *Cerebrovascular Disease* by Hammer's group utilized a microsphere measurement technique, which is considered the gold standard technique in animals. Unfortunately it's not applicable to humans, usually.

And what you can see here is essentially the baseline cerebral blood flow, okay, quantified over time, and you can see the baseline numbers in these four distinctive areas of the brain. Infrarenal inflation. And at the time of suprarenal inflation, the NeuroFlo device takes its effect, and you can clearly see a statistically significant increase in cerebral blood flow ranging from 35% to 52%, which is quite remarkable. You can see that pretty much happens in all the areas of the brain that were measured, and that was sustained, in fact, all the way through 90 minutes post-balloon inflation.

The next slide, which was not yet provided to the FDA, it illustrates one of the strengths of this model, which is the fact that the rete mirabile of the swine actually is structurally anatomic. It's very similar to the human leptomeningeal collateral flow, in terms of the channel structure and

size.

So one of the great strengths of this model, it's not a stroke model. There is a paucity of stroke models, essentially, the rat model and the primate model being the two that were established. There is a canine model recently established for endovascular treatment. But one of the strengths of this model is the presence of this rete mirabile, which is a structure that connects the cervical circulation to the intracranial circulation in the swine, and it has an anatomic similarity with the human leptomeningeal circulation system.

So moving on to the second experiment, which utilized a stroke model in the rat. That's the work of Shuaib's group. They clearly demonstrate that the aortic occlusion results in both a reduction in the perfusion deficit, but more important, a reduction in stroke volume. As you can see here in the control, 60% deficit versus only 15% deficit in this example.

It's actually better illustrated and better depicted in this graph, where you have the control versus the aortic occlusion, a statistically significant stroke size reduction. This also illustrates another interesting effect, which is the synergistic effect of tPA and the aortic occlusion.

It's important to mention that that was achieved at no cost in terms of hemorrhagic transformation in the area of infarct or activation of MMP-9, which is an index of reperfusion injury.

And why infarct reduction is important, infarct reduction is very important because we have actually recently demonstrated that infarct volume, in any given patient, is the strongest predictor of outcomes.

So what you have shown is that flow augmentation technique with aortic occlusion increases cerebral blood flow in animals, leads to a reduction in infarct size in animals, and infarct size is the most important predictor of outcome in humans.

So moving on to the proof that this technique increases cerebral blood flow in stroke patients. I think you have done so using multiple different techniques. We're going to go over each one, starting with transcranial Doppler.

Again, this slide is not yet provided to the FDA. That's the work of Saquur's group. It's a small study with eight patients with proximal MCA or intracranial IC occlusions.

But what they demonstrated was a numerical increase in the mean systolic velocity in these patients. And they were also able to demonstrate, in this small cohort, that there was a statistically significant difference in good outcome versus bad outcome according to the strength of that increase in blood flow velocity.

The second slide not yet shared with the FDA illustrates actually a case that I have recently treated, of a 47-year-old lady that had this long segment of severe intracranial stenosis. She had failed antiplatelet

therapy and came to the hospital with fluctuating right hemiparesis and aphasia. As you may know, the SENTIS trial was a negative trial. So you actually don't have any other means of treating this patient other than antiplatelet therapy. Intracranial stent failed to show an improvement and you decide to treat her with NeuroFlo.

And what I want to show here is the velocities in the left middle cerebral artery prior to treatment and during treatment. And you can clearly see a twofold increase in both mean and peak systolic velocities.

This patient fortunately stabilized over course. She stopped fluctuating. I can't prove this was directly related to my treatment, but I was glad that I had the device available for this particular patient.

What about CT perfusion techniques? These are study cases performed during an evaluation of the device. This is a CT perfusion at baseline, and after the device was used, showing a marked improvement in perfusion.

Another case of a more distal focal occlusion, where you can see this area of viable brain with a perfusion deficit and a marked increase in perfusion with resolution of that, which was sustained several hours after treatment.

This is a case of a 35-year-old lady that was treated by the Canadian group. Her initial NIH Stroke Scale was 19. She failed IV tPA treatment, which is actually fairly common with M1 occlusions.

Unfortunately only one in four of them will respond to tPA. Only 1 in 5 to 1 in 10 of the ICA occlusions, intracranial ICAs, will respond to tPA. So this is actually a very common scenario that you face.

Fortunately she underwent treatment with the NeuroFlo device, which resulted in this marked improvement in the perfusion on the time-to-peak scan. And that correlated with the clinical outcome improvement with a drop in NIH Stroke Scale from 19 to 2 at 30 days.

As an angiographer, I particularly appreciate this case where you have this bright IC angiogram with machine injection. It demonstrated no cross-filling for the Circle of Willis and very poor retrograde filling of the left middle cerebral artery via collateral flow; as you can see here, very poor and delayed. And after the treatment with the NeuroFlo system, you can see brisk filling across the ACOM with antegraded reperfusion of the middle cerebral artery.

In this other case of a vasospasm patient that was refractory to treatment with triple-H therapy, you can see a clear perfusion deficit. She had some clinical deficits with an NIH Stroke Scale of 6, and this patient was treated with the NeuroFlo device with improvement in perfusion in that area and a clinical improvement as well.

Finally, I think this is one of the most robust examples because it demonstrates the application of PET scanning one of these patients. As you know, a PET scan is the gold standard for CBF assessment in humans, and you

can see here that fact in comparing the baseline with partial, full, and even post-deflation balloon periods, with very noticeable improvement in perfusion.

So whom and how to treat? Who are the patients and how do you select our treatment strategies in acute ischemic stroke? I think you have essentially two options now, direct recanalization, which is a high risk/high reward and probably has a smaller target population. On the other hand, which we haven't really explored as we should, we have flow augmentation, which has a much lower risk, definitely a more modest benefit. Yet, any benefit in this patient population would be greatly appreciated by the patients and their families, I'm sure. And we believe there is a much larger target population that you will neglect by not offering these treatments.

It's very important to also take into consideration the risk/benefit assessment, which then should be very favorable with flow augmentation, and specifically the patients' and the families' expectations.

So we start with direct recanalization, again, the more powerful method, where you remove this occlusive thrombus. One of the problems is, when you do that, dissolving or removing the thrombus, you can cause fragmentation, distal embolization, and more infarcts. But just as important or actually more important is the fact that when you remove that blockage, you suddenly open the high-pressure reperfusion to the dead brain and that makes it prone to cerebral edema and hemorrhage reperfusion injury.

IV tPA has been approved by the FDA in 0 to 3 hours, and it's endorsed by the societies from 3 to 4½ hours. But the main issue there is again the limited use. Only 10% of the population is getting that treatment, mostly related to the short therapy at the end of IV tPA. So unfortunately you can't offer any treatment to about 90% of the patients.

Thrombectomy. A very potent modality. You have four cleared devices. It's important to mention that you have medical arm controls in any of these studies where these devices were investigated. So I think it's important to acknowledge that at least I believe that you have more data about the safety and even efficacy of NeuroFlo than you have for the thrombectomy devices.

Having said that, I'm very happy that you have them available because I really think they have made a big contribution to the outcomes of stroke patients, and the newer technology has only improved our success rate with a better safety profile.

Having said that, direct recanalization suffers from this very limited patient population that you can apply this technique to.

Moving on to flow augmentation. Here is where you expect the clots. So you don't cause additional fragmentation, and because you reperfuse for these smaller channels, we increase flow at the relatively low reperfusion pressure. So that's the reason why in the SENTIS trial you haven't really run into a lot of issues with symptomatic intracranial hemorrhage and

cerebral edema. There are essentially three ways of doing it.

Vasopressors, as Dr. Caplan has mentioned, have a lot of cardiopulmonary complications, CHF, MI, pulmonary edema. Increasing volume is usually used in vasospasm, but actually there is data suggesting that maybe that -- probably for pulmonary congestion regions and increasing oxygenation. So that's really where NeuroFlo emerges as a very unique alternative, since it doesn't really significantly increase blood pressure cardiac work.

I think this schema actually illustrates well how you select our patients and our expectations for the patients and families, based on the time of presentation and the severity and location of the occlusion.

So if you have a patient that comes early with a very severe stroke, I think your risk tolerance for a complication is relatively high and you can really go for a very good outcome and a definite outcome. In the early phases, with a more mild to moderate stroke, most of the time a distal occlusion, that risk tolerance is more moderate. The treatment goal is still ambitious with function in that. And that's for a near normal patient.

Having said that, in the late phases, which were most of the patients actually in the SENTIS trial, we should still have a moderate risk tolerance for the severe strokes because you don't want to make things worse. But you can't be as ambitious as you are early on, and I think that was the main issue with the trial. Our goals here are more survival and avoiding

extreme disability.

Very much like the hemicraniectomy trials, if you're in the late phases with a mild to moderate stroke, the risk tolerance should be low because many of those patients may do well, and the treatment goal should be to minimize disability to a patient that is perhaps ambulatory or better.

So how do you titrate our treatments with these family and patient expectations? We use the more aggressive recanalization technique with intravenous tPA and/or thrombectomy for the patients that can get those treatments. But, again, many patients you have exclusion to those treatments, and we should offer them other treatments that perhaps can bring them into a better situation, such as flow augmentation.

In the early phases, again, with the distal occlusions, intravenous tPA in the first 3 or 4½-hour window -- again, 0 to 3 FDA approved -- we can provide IV tPA. But what about the patients that have contraindications to tPA or are beyond the 3 or 4½-hour window? What to do with them?

More importantly, I think you are really neglecting a lot of these late-presenting patients that still have viable brain. Some of them can be treated with thrombectomy if the infarct core is not too big. But I think the vast majority of them, both the severe and the more mild and moderate strokes, would be a better target for flow augmentation techniques, assuming that they still have any viable brain.

I'll show you a recent case of a patient that had a very large stroke. It's hard to see in this scan, but he had about a third of the MCA already with early findings; very young, so at high risk for cerebral edema and malignant MCA syndrome and herniation; NIH Stroke Scale of 15 because his leg was spared, but it had dense neglect hemiplegia deviation.

And you can see that in the perfusion scan there was a suggestion of an area at risk, not definitely damaged, M1 occlusion with poor collateral flow. You apply the NeuroFlo device. And as in our discussions with the family, our expectation here was to limit this infarct to what you had seen or read dead on this scan and prevent additional evolution of the infarct, because that would culminate in more edema and perhaps herniation and the need for a hemicraniectomy.

And that was our goal of treatment here. It doesn't mean that you need, in a patient like this, to bring them to normal. But offering them some treatment can bring them to a better situation that's greatly appreciated by the family and the patient.

I find it very challenging to discuss with families, during this very stressful time, very important concepts such as this is an emergency time in his brain. There has been brain death, there has been permanent damage. That dead brain, the core, I cannot bring that back, I'm sorry. However, there is still salvageable brain, and that's why I think we need to use something to intervene and prevent more devastation.

So we have come up with this analogy, that when a stroke strikes, it spreads like a fire in the brain. It starts small and burns a few trees, and over time it burns more and more of the forest. And our goal would be to limit the damage to a minimum in order to prevent this complete devastation.

What I find myself in my current practice, and my colleagues as well, is oftentimes you see a big fire with some salvageable brain, but the techniques that you couldn't have are not safe to be employed in a situation like this. So you can't offer the treatment and you can't go for this outcome, which is not a normal forest, not a normal brain, but a much better brain than something like this.

So I hope this analogy helps you understand why you need more tools in this patient population.

To conclude, I think the NeuroFlo device would be a very important complementary tool in the stroke armamentarium. I think the NeuroFlo device is a safer approach than many of the techniques that are used, including vasopressors to augment blood pressure, perhaps even thrombectomy, in patients with unfavorable anatomy, particularly the elderly.

And I think the SENTIS trial has shown very important things in terms of reduction in mortality and shifting patients to better outcomes and avoiding severe disability, which is the only thing that you can do at those

later time windows when too much of the forest has been burned.

I think the risk/benefit profile of this treatment has identified an untreated target population, that forest that I just showed you where there is a lot of fire, a lot has been burned, but there is some forest that I still can see; so in particular, the late-presenting patients where recanalization techniques are too risky due to the risk of reperfusion injury and hemorrhage; also patients with anatomic and medical exclusions through intravenous tPA or endovascular access of intracranial devices.

I believe the overall clinical evidence provides ample support for the use of the NeuroFlo system in the treatment of acute ischemic stroke, and that's why I believe NeuroFlo should be available for our clinical practice.

With that, I'll conclude and I'll pass it over to Dr. Alpert, who will wrap up our lecture.

Thank you.

DR. ALPERT: Thank you, Dr. Nogueira.

So we're here. Why are we here? What do we see in NeuroFlo? What do we see in SENTIS? And what do we hope we've shown to you?

First, NeuroFlo is technology that's in clinical use today. We understand it. Its risks are well understood, they're well controlled, and we've learned a lot about how to use the product.

Secondly, SENTIS has shown that NeuroFlo could be used in a

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large patient population that today is untreated. Not all of them. Not all of them will qualify. You heard the qualifications for patients that should be excluded even from NeuroFlo. There is a large unmet need in the stroke population, particularly late stroke patients who have no current alternatives, and NeuroFlo can provide that alternative.

The SENTIS study outcomes are in the right direction. There is clinical data that supports the use of NeuroFlo in the stroke patient, that it's been safe, that there's a mortality reduction, critically important and not seen in other trials, and that risk/benefit favors treatment over medical management.

CoAxia is seeking this labeling through the de novo population because safety has been established. There is a clinical benefit. There are good general controls for medical technologies and sufficient special controls that will allow FDA to maintain the safety and effectiveness of NeuroFlo and follow-on technologies for use in the ischemic stroke population.

Just to remind you, FDA has the tools. They have the flexibility to put this product in the market through de novo, looking at the magnitude and probability of the device impact, the impact it's had on patient management, improvements in quality of life, as you've heard, the reduction in the probability of death, which was seen in the SENTIS trial, and aiding in the improvement of patient function. Again, the sliding scale has shown that that this is a patient population with an unmet clinical need, where there are

no available therapies for many of these patients.

And not all the patients need to have all of the benefits of NeuroFlo in order for FDA to make a determination under their de novo process, that it's still appropriate to put this product in the market. They have the clinical data and they have the preclinical data that can help them appropriately label the product.

In conclusion, then, specific stroke labeling for NeuroFlo is needed. It's required so stroke patients can receive the benefit of the treatment, so physicians can receive training, instructions, and ongoing support to assure that the product will be used safely, appropriately, and in the right patients, and so that appropriate communication about how this product performs in stroke patients can be captured, shared, and utilized to maintain the safety and effectiveness of this product and others like it for this very important population.

With that, I thank you, and we look forward to your questions and your deliberations. And that concludes the Sponsor's presentation.

DR. HURST: I'd like to thank the CoAxia team for their presentation.

Does anyone on the Panel have any brief clarifying questions for CoAxia?

And I might also add that the CoAxia presenters, feel free to sit in those chairs in the front during this question session.

Yes, Dr. Hammon.

DR. HAMMON: I'd like to ask Dr. Nogueira. You showed some very good anecdotal data about the relationship between increasing collateral blood flow into the brain following a stroke using your device.

Do you have any evidence that the outcomes of those patients were improved? The clinical outcomes.

DR. NOGUEIRA: That was systematically studied in the SENTIS trial, so I can share with you some of our experience and the experience of my colleagues. But the trial is essentially the results where you saw -- it's the results that you have in terms of clinical outcomes.

DR. HAMMON: That was not my question. My question was, in those patients that you showed, were the clinical outcomes improved? The ones that you showed. We know about the SENTIS trial.

DR. NOGUEIRA: Oh, yes, yes. So if you want me to, I can talk about our individual cases. I think I showed you the cases of M1 occlusion, the 35-year-old patient. That patient had an NIH Stroke Scale of 2, which is extremely unusual for somebody who presents with an NIH Stroke Scale of 15 and an M1 occlusion, that it's not recanalized. I think that's a great example.

Moving on to my case of the intracranial stenosis, which again it's important to highlight. There is no other option for those patients. Once they fail medical treatment with antiplatelet therapy, intracranial stents do not appear to be a good solution for these patients. That patient I treated,

she was fluctuating with aphasia, hemiparesis. She stopped fluctuating and had a stable course.

Moving on to the patient with the large stroke, that had some suggestion of salvageable penumbra tissue on the CT perfusion scan, I think it clearly demonstrated that you could freeze this stroke, essentially prevent it from progressing, which is the only thing, again, that we can do in stroke patients. We cannot bring the dead brain back. You prevent just the spread of the fire in the forest. And if you look at the CT perfusion and the final scan, the dead brain you had on presentation is essentially what he had at the end. We prevented expansion of that stroke.

So I believe that, you know, in my experience and the experience of my close colleagues, I think we've seen enough of proof that this device works both in terms of the imaging profile and the clinical profile.

DR. HAMMON: And have you published any data regarding the outcomes of your patients that you've treated with this device?

DR. NOGUEIRA: The main reason for not having published it, it's the numbers are small. The numbers are small. The large numbers come from the trial. It's hard to keep treating these patients when you don't have reimbursement to do it. So the hospital gives you some, I would say, hard time about using the device, since it's not going to be reimbursed. It's also hard to do it when you can't train people, your technicians, your nurses, your colleagues, to know more about the device. So we haven't really used it in

enough scale to let me publish my own data. So the best, in terms of large data proof that you have, comes from SENTIS.

DR. HURST: Thanks.

Dr. Noonan.

Let me remind everyone, please state your name for the transcriptionist as you ask your question.

DR. NOONAN: Dr. Noonan.

Dr. Nogueira, a couple of questions. Regarding the animal models, why didn't you use a primate model? Swine have a rete mirabile, which is rather proximal, sort of like Circle of Willis. It's not really like the distal leptomeningeal collaterals. That's the first question.

Secondly, the study was controlled against the best medical therapy. What is the best medical therapy? Does it differ by region? Is the control a standardized control or are there different controls in different places?

DR. NOGUEIRA: I think those are two great questions. I think Dr. Saver will take the second question.

So the swine model preclinical data. I didn't participate in that particular study, but I did give input in the study design. I do a lot of experimental work in acute ischemic stroke, and it's very challenging to actually have a model where you can do endovascular therapy, as you know. Other than the primate, we use the swine, which is not a good stroke model,

and that's why that wasn't a stroke model. The goal there was just to show that partial occlusion with the device would lead to increased perfusion in different areas of the brain, and I think you have accomplished that task. I agree with you, the primate model would have been a better model.

Having said that, if you go back and search the literature, you're going to find very little data in primates and stroke, just because it's very challenging and costly and it's difficult to actually execute the study. I think the rat stroke model is well established, and that's why I chose using the second experiment.

DR. SAVER: And with regard to best medical therapy, in the SENTIS trial, sites were encouraged to follow the guidelines of the American Heart Association and American Stroke Association national guidelines for management of acute ischemic stroke patients. Key aspects of those are the use of aspirin in these patients who are not eligible for IV tPA or thrombectomy, but aspirin to deter clot propagation and early stroke recurrence; the provision of intravenous fluids in order to maintain euvolemia and help support collaterals; the control of temperature, normothermia, to avoid a fever and increased brain injury from that; the use of DVT prophylaxis to prevent DVT and pulmonary complications; the use of early institution of rehabilitation; the package of support of care, in general, that is provided in an acute stroke unit.

DR. NOONAN: One more question regarding in the patients

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who were treated. Were they sedated, or were they put under anesthesia?

DR. NOGUEIRA: So we just do conscious sedation. All of times MAC anesthesia or conscious sedation do not intubate these patients for these procedures. It's mostly related to the fact that, at least for thrombectomy, there has been a correlation between poor outcomes and general anesthesia. But it's not required for the procedure.

DR. NOONAN: And in the post-treatment period, the immediate post-treatment period, 5 hours or so, I assume you used a closure device in most of the groins. The patients were kept in an intensive care setting?

DR. NOGUEIRA: So in the SENTIS trial, none of the patients were tPA candidates. So for the first half of the study, the devices still required a 9 French access. For the second half, they developed a smaller device with a 7 French access. So it really varied across different sites where people used closure devices, I believe, mostly with the 7 French coming up later on, or manual compression.

DR. SAVER: And because this is a pretty simple procedure, most patients did not require intensive care unit management afterwards. We can provide you with the detailed data on the site of care after the procedure. But my vague recollection is that about 40% of patients were in ICU and that there was not a major difference in the proportion of patients in their sites of care, in the treatment arm and in the medical arm.

DR. HURST: Dr. Furie.

DR. FURIE: I have a question for Dr. Lutsep and Dr. Saver.

Dr. Saver, I wanted to ask you, just based on your experience, what percent of all stroke patients would meet the inclusion/exclusion criteria -- or the inclusion criteria, rather, for use of this device?

DR. SAVER: Well, just doing some back-of-the-envelope calculations, 10% of patients in the best centers may be getting tPA and another couple percent getting thrombectomy alone and without tPA. The 20% of patients who have lacunar strokes would not meet the entry criteria. We required cortical ischemia to be present. And about in this later time window, maybe 30% to 50% of the patients would have too minor a deficit to qualify. So I'd say maybe 30% to 40% of patients are potentially eligible, and a larger number of the more moderate to severe patients. But of all patients, maybe 30% to 40%.

DR. FURIE: Would you continue to limit it to patients with cortical involvement in the anterior circulation?

DR. SAVER: Initially I would. I think it's interesting to speculate whether this would be beneficial in patients with a lacunar stroke. The nature of collateral pathways in the penetrator territory is a matter of some speculation. Classically, those tend not to have collaterals, but some recent studies suggest that collaterals do develop when you have small vessel disease. So I think that would be an appropriate subject for further study.

I'm not sure that the posterior versus anterior circulation, per se, matters so much in my physiologic thinking. But small vessel disease, I think I would be hesitant about it until we have more information.

DR. FURIE: Dr. Lutsep, do you mind providing more detail about Slide 48, that talks about the causes of death and adjudication within the trial?

DR. LUTSEP: Sure. Can we get that up, please? In fact, I think that we may have a slide that provides even more information than Slide 48. Is that the one? Yeah.

DR. FURIE: I was particularly interested in how you defined stroke versus non-stroke related, how withdrawal of care was handled, and when in the course of the 90-day window these deaths occurred.

DR. LUTSEP: So the first definition, much of it had to do with the temporal relationship of an event to the stroke. So the systemic complications, I think, illustrates that probably the best. If a patient came in with renal insufficiency at day 89 which occurred and perhaps ended up dying as a result of multi-system failure, that would not be attributed to the stroke. But if a patient had the other example, such as pneumonia occurring around the time of the stroke and it appeared that the stroke perhaps contributed to that patient getting pneumonia, that was how that designation was made.

DR. FURIE: Did your committee use a standard definition for the time between the stroke and the event in order to classify it?

DR. LUTSEP: We tried to do so in the end. At the very end of the trial, in our in-person meeting, we tried to use times from the literature that have already been used as examples, such as the 24-hour hemorrhage rate; also for cerebral hemorrhage, 7 days. For renal events, you know, when do you expect the creatinine to bump after procedure. So it was not certainly one definition for every event, but we tried to apply them all consistently.

DR. HURST: Dr. Yang.

DR. YANG: So I have a question about the subgroups and given that that is what your contention about the effectiveness of this is. On Slide 61 you show the data for TFSO, less than 5 hours and less than 6 hours.

Do you also have the data for the rest of the time periods? Because the question arises whether or not this is a real trend or if this is just a bump in the data. In other words, on Slide 60 you're talking about a trend towards early presenters doing better with this.

DR. SAVER: I'm not sure if you're asking about the patients who are even earlier than this or patients who are later than this.

DR. YANG: Well, no, I'm talking about time -- your time period is between 4 and 18 hours, right? So less than 5 hours would be on one end of it. What I would like to know is whether or not your 6 to 7 hours, in other words, the early groups, do you really see a trend or is this just a bump in the data?

DR. SAVER: The patients in the earlier time period do respond

better, and the effect attenuates with later time. It's a curve that begins high and comes down over time.

DR. YANG: Right, that's what I'm looking for. So it is that, given that we're not shown the data, rather than just a peak and another peak later.

DR. SAVER: Right.

DR. YANG: Okay.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Yeah, a couple questions. One is do you have the physiologic measures that were done during the period of treatment in both the treatment patients and in the controls over that same period of time? Heart rate, blood pressure, respiratory rate, et cetera. Temperature.

DR. SAVER: We do have a set of data in the CRFs from the pressures achieved and other information during the procedure.

DR. GOLDSTEIN: Any differences? I mean, during those procedures, I know that the nurses are there recording things every 5, 10 minutes, and presumably the control patients, during that same period of time, are in an ICU or some other setting where their vital signs are being checked.

DR. HURST: Excuse me, let me just interrupt. If the Sponsor is not prepared to answer a specific question right now, you can collect that data and plan to answer it later in the afternoon.

DR. SAVER: Thank you, which was just what I was going to say. I do know that there were no concerns that we saw in the data that rose to a top-level attention. But to get you the detailed data, let us dig into that, and we'll get that back to you in the afternoon.

DR. GOLDSTEIN: Yeah, I'm just more interested in it from the standpoint of potential mechanisms. So if you have during the procedure, the patient's heart rate is changing and their blood pressure is going up and cerebral perfusion is changing, presumably, that might be things that might be noise, but it's systematic noise. In other words, that's happening in all the patients that are having interventions, compared to the ones that are in the control group.

The other question is -- and Dr. Caplan had mentioned this in his earlier presentation, that there are other ways of trying to augment cerebral blood flow, and one of which is making patients lie flat. And this has been studied fairly well. There have been at least a few publications about this, where cerebral blood flow does go up and go up significantly just by body positioning.

So were the controls at least similarly positioned during the same period of time that the patients were having the device put in?

DR. SAVER: The treatment of the control patients was, as mentioned, according to national guidelines for medical therapy. And I think that at most sites, that would include positioning of the patient with the head

of bed at 30 degrees or less. Some sites prefer to avoid aspiration and not have the head of bed flat. Some prefer to maximize perfusion with head of bed flat.

I don't think that we systematically recorded head of bed positioning in the control patients during this time frame, but my expectation is that patients would've been managed in a recumbent or semi-recumbent position.

DR. GOLDSTEIN: So, again, the point that I'm trying to get at is, you know, what is the additional added benefit of putting a device into patients, compared to just body positioning or just to changes in physiology? But we'll talk about it later.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Dr. Lutsep, thank you very much for your presentation.

You mentioned that the DSMB was not blinded when they reviewed safety data. Who is gathering the safety data, and were they blinded?

DR. LUTSEP: So the sites were the primary ones gathering the initial safety data and submitting it to CoAxia. I believe that CoAxia -- and they can speak to this, also -- when they monitored sites, probably picked up additional events. And then, once we had the medical record, more often than not we would also find events that had not been reported and we would

ask the site to report those as well as additional events.

DR. DORSEY: Were the site investigators blinded to treatment assignment?

DR. LUTSEP: No.

DR. DORSEY: How would, if the fact that no one was blinded, that safety assessments affected the safety results?

DR. LUTSEP: In my mind, I think it made us more aware of the potential safety issues, especially with the procedure and device arm, so that we were, if anything, at an elevated level of alertness, looking for any potential relationship that might be there.

DR. DORSEY: On objective measures like laboratory data, were there any trends, especially like on renal function, serum creatinine, and the like, between the two groups?

DR. LUTSEP: Again, I'd have to look at that in great detail. Nothing that popped out again, as I just said, at the higher level to alert us. But we would have to look at the exact numbers.

DR. DORSEY: Okay, that would be helpful to know if the device changed renal function, for example.

DR. LUTSEP: Um-hum.

DR. DORSEY: One final question. Dr. Saver and others identified subgroups that might benefit more from the device than others, among the subgroups who were older individuals, older than 70 and older

than 80.

Do you have safety data on those populations? Is the device more safe in those individuals?

DR. LUTSEP: We would have to pull those up for you.

DR. HURST: Dr. Zhou.

DR. ZHOU: So I have a few questions. So the first one is you actually discard the patients after randomization. I think that 26 have been excluded in the final analysis, and then 12 from the stroke mimics.

How different are those patients you discarded after randomization between intervention and control? Because what may happen is that, by discarding those patients, you might destroy your randomization, which is not the purpose of randomization. So usually we don't do the modified ITT population because that's kind of dangerous. You might destroy your randomization. So that's the first question.

The second one is, in your subgroup analysis, which is kind of a follow-up to one of the Panel members, have you done the regressions instead of the dichotomized, those covariates like the severity or the age? So you could do the regression and treat it as a continuous variable to see what's the trend of the treatment effect over the volume of those covariates.

The third one is for the safety data. Do you have an independent committee member to adjudicate whether you have side effects, severe side effects? Because that's usually done in practice. You

should have an independent committee which adjudicates whether you have severe adverse events or not.

So that's too many questions.

DR. SAVER: With regard to the first question about the primary trial analysis, the pre-specified analytic population was the modified intention-to-treat patient population. And I share with you concerns that it has a potential for introducing bias as compared to a true intention-to-treat analysis. Indeed, it did introduce bias in this study because the patients excluded from the treatment arm did better than patients in the medical arm. One of the reasons for exclusion was if you improved and it was hard to justify putting the device in.

So patients who improved in the device arm between randomization and treatment were excluded. Those patients, of course, are going to do well. Also patients with aortic pathology tended to be a little older and maybe had more atherosclerotic-origin strokes that were a little milder. They tended to do better.

So it turned out that the mITT, modified intention-to-treat analysis, is biased against the device. There's a slight trend to better effects when you look at a true ITT analysis.

DR. ZHOU: Excuse me. But do you have the data to show us?

DR. SAVER: Yes, we can produce that for you.

With regard to looking for regression for effects of age and

severity, I'm not sure if we have that, so I'll have to get back to you on that.

And for the DSMB question --

DR. LUTSEP: So I wasn't certain of whether you were referring to the evaluator who was evaluating the outcome of the patient or the safety of the patient.

DR. ZHOU: Safety of the patient.

DR. LUTSEP: Safety specifically.

DR. ZHOU: Adverse events, yeah.

DR. LUTSEP: Yes. So that I can answer quite readily. Our DSMB was entirely independent of the rest of the trial. You know, our protocol-specified analysis, even as we looked at that one glimpse of efficacy plus safety, was our own only. Our only instruction back was to continue to the trial at that point. The reviews were done completely independently of the investigators and everyone else.

DR. HURST: Dr. Ensrud.

DR. ENSRUD: For Dr. Saver. Was any sort of assessment possible in terms of the stroke volume between the entry CT and MRI and then the one that was done in all patients at 24 hours?

DR. SAVER: I'll have to get you the data on that. I don't remember, off hand, the results. I will say that 24-hour CTs, which were common in the trial, are difficult to read for infarct volume in a reliable way. You have the CT fogging effect and other aspects, so it's a very -- as imaging

biomarkers go, it's not the most informative. But I'll have to have that pulled for you.

DR. HURST: Dr. Hammon.

DR. HAMMON: John Hammon.

I know from some of the comments that were made before, that since the study is a de novo study, one of the things that you're really interested in is are you improving the quality of life of these patients that are treated, since many of them you can't really measure a huge -- the actual death rate in both the control and the treatment groups were relatively low. The only thing, in going through your data, that you can estimate quality of life is the mRS score, and that was not statistically significant. It was a little bit positive for your group.

Did you actually collect any quality of life data from some of the quality of life tables that are available that could support your contention?

DR. SAVER: We did, we collected that on the Stroke Impact Scale, which is one of the stroke-specific quality of life scales, and we'll get that data to show you.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

Another question for Dr. Lutsep. You said you saw efficacy data. Was that the interim analysis data that you saw? And is that this -- or

are those the same data that were published in the 2008 manuscript reporting interim results from the trial?

DR. LUTSEP: We did see the interim analysis and that, I believe, is at Patient 125. But to my knowledge, those were not published.

DR. SAVER: An unexpected moment in the history of this trial was that a site investigator, who received as a regular routine report an update on trial data, violated the agreement with the Sponsor to keep the results confidential and published the entire results, so far, under their own authorship without permission from the Sponsor or the other investigators. That publication, when this was pointed out to the journal, was withdrawn from the literature.

So that was not a published official publication of the trial and not an official publication at all. I can't quite remember whether it was the formal interim analysis look or a different look, but it was not anything that was an official action of the steering committee or the trialists and not something that affected trial management and course.

DR. FURIE: Did everyone in the trial receive the safety and efficacy data on a routine basis after the DSMB met?

DR. SAVER: At some of the investigator meetings, some of the safety and efficacy data were shared.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: My name is Alicia Toledano, and this is a

question for the DSMB.

We've heard about the importance of knowing the history of safety of this device, but not particularly in this population. And that's why we're here today, the labeling in this stroke population, ischemic stroke.

So as you went through and you were not blinded reviewing the AEs, reviewing the relatedness to the device and/or the procedure, you learned things, and at the end you took a whole bunch of AEs that were classified as unknown and ultimately reclassified their relatedness.

If you used an entirely new DSMB -- I'm not saying you have to, but if you could write down what you learned about whether an event is or is not related and used new people, how close do you think they would come?

DR. LUTSEP: It's an interesting question. We did actually publish our control population results in *Acta Neurologica Scandinavica*, partly because we thought that it might be helpful for other groups -- we weren't thinking of this trial, but for future trials -- to have some of that information because, you know, having defined many of these entities from the beginning and adjudicating them using the same definitions, I think, was extremely helpful.

So I think that most of the adjudication should be quite close. There weren't so many left at the end that made us have a real hard time. You know, certainly there are a couple that I think could go either way. But the great majority, I think we had a pretty good basis for it.

DR. HURST: Yes, Dr. Goldstein.

DR. GOLDSTEIN: Yeah, Dr. Goldstein.

I sort of lost track. How many statistical tests were actually done here? How many times have we looked and relooked and cut and sub-cut the data?

DR. SAVER: Well, if you look at the pre-specified statistical tests, there was 1 primary and 12 -- sorry -- 11 secondary pre-specified analyses. And of those 12, 9 of the 12, the point estimates favored treatment. If you look at the post hoc informative analyses that we undertook -- and that was a sub-study that was undertaking pre-specifying those four. Besides those, there have been many looks at the data, and there's not, that I know of, been a count of the number of those looks, but it is substantial.

DR. GOLDSTEIN: And we obviously don't have all of those other -- many, many other analyses. We just have the ones that were chosen to show us here now; is that right?

DR. SAVER: We actually have all the pre-specified analyses that are going in the right direction. You have this group of the informative analyses, and those are all the ones that we undertook in that study. And then you have some of the subgroup analyses that were undertaken, but there are lots of looks at the data that you don't have.

DR. GOLDSTEIN: Right.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: Thank you. Dr. Toledano. For Dr. Saver, just following up on Dr. Goldstein.

So if you pull up your Slide 62, where you show us the lovely graph of hypothetical SENTIS-like results and what would happen if there was nothing going on with the alpha control -- and you've just told us that there is a whole bunch of analyses that we didn't see. Any idea how many of them fall on the wrong side of the line?

DR. SAVER: Very few. Time and time again, when we cut this data, the point estimates fall on the right side of the line. There are some. For example, in the four components of the primary analysis, the Rankin, Barthel, and Glasgow, when adjusted, all fall on the correct side of the line, but the NIH Stroke Scale falls on the wrong side of the line. So you sometimes do see ones fall on the wrong side of the line.

But I think this -- you know, 75% of the pre-specified analyses fall on the correct side of the line. And in all the looks of the data, that's my sense, 75% to 85% of the looks are on the correct side of the line.

DR. TOLEDANO: Can you get those numbers?

DR. SAVER: If you look at Appendix J, we have information that shows that.

DR. TOLEDANO: Thank you.

DR. HURST: Dr. Zhou.

DR. ZHOU: Before I ask my question, I want to find out here.

This is Dr. Zhou.

How do you get these results? Did you generate data based on the hypothetical -- for the active side on the right side and then look at time point zero? So how did you get this graph?

DR. SAVER: This is not based on any model or actual data. This is just an illustrative schema to show what one might theoretically expect. But it's not any real data on this particular graph.

DR. ZHOU: So there could be other possibilities besides what you showed us?

DR. SAVER: Well, the --

DR. ZHOU: Because you are not based on any similar data based on real data.

DR. SAVER: Right, this is based on just a general normal distribution of results if you have a neutral result and that you would expect a normal distribution of multiple looks to fall on both sides of the graph. So just more statistical theory rather than any actual models.

DR. ZHOU: Yeah, because in order to produce the results, you have to assume what the true distribution of your outcome is, normal distribution, normal or chi-squared or whatever, in order to do that.

But the one you produce here is based on what assumptions? Or just hypothetically you think what it would look like.

DR. SAVER: Right. I guess the implicit assumptions of the graph on the left are that the true effect is neutral and the implicit assumption of the graph on the right is that the true effect is beneficial. And there are no strong assumptions made about normal or non-normal distribution. It's just that some of the looks -- that the looks will be equally distributed around the true biologic effect.

DR. ZHOU: Well, anyway, I think we can talk later.

But a question I have is, when you do the 12 time tests, have you adjusted for the multiple comparisons? I think if you adjust for the multiple comparisons, your p-value will be much bigger than what you show us here. So there may be cases not selected, then.

DR. SAVER: That's absolutely true; we did not do adjustment. Only your other adjustment for multiple looks. These are nominal p-values, not adjusted p-values.

DR. ZHOU: So the last one I want to ask is -- because you did show that mortality is significant, at least for the stroke-related mortalities. But when we look at the number of the deaths related to the stroke, it's actually small. It's 17 versus 37.

So when you calculated the p-value from the Kaplan-Meier or the log rank test, did you use an asymptotic look, chi-squared distribution or normal distribution? How did you do that more exact test for that?

MR. MULLIN: We don't have the exact test rate. We'll get you

that later today.

DR. HURST: We have time for one last question.

Dr. Sung.

DR. SUNG: Gene Sung.

Dr. Saver, I was wondering if you might speculate on the fact that the presumed benefit of NeuroFlo is increasing cerebral blood flow and perhaps collateral circulation. And that would supposedly be also the benefit of induced hypertension.

What do you think would be the relative benefit of one versus the other?

DR. SAVER: Well, to speculate, I think the distinctive advantage of the FloControl and NeuroFlo over-induced hypertension is that you avoid the side effects of pressor therapy in this ischemic stroke patient population who are older, average age 68 to 80, who have a high frequency of cardiac comorbidities and in whom pressor therapy, when undertaken, often has to be abandoned because of the development of side effects.

In terms of the degree of perfusion change induced, I don't have any data that speaks comparatively to the two. Due to absence of clear evidence for both approaches, it's hard for me to speculate. My guess is it may be fairly comparable, but that the NeuroFlo device permits it without the attendant side effects that complicate induced hypertension.

DR. SUNG: Just to follow up on that. So one thing that has

always been a little confusing about NeuroFlo is that -- and it is in regards to complications of these therapies -- is that if you do induce hypertension, you can always discontinue your therapy pretty simply, whereas the NeuroFlo device apparently has a continued effect some time even after the procedure; isn't that correct? And how long is that presumed to last?

DR. SAVER: Well, this is an observation that was seen in the animal models, and the physiology underlying this somewhat persistent effect is somewhat speculative. One hypothesis is that you pop open the capillaries with the increased cerebral perfusion pressure, and then it requires less pressure for them to stay open than to open in the first place, so that you recruit collateral channels with a one-time intervention that then stay open for hours thereafter. And that's a beneficial effect that will not have systemic adverse consequences but confer a prolonged benefit.

And I'll ask for Raul to comment on speculation about how long this effect lasts, but it does appear to last for at least a few hours.

DR. CAPLAN: The other issue about blood pressure is it needs to be titrated. And then there are variable blood pressures, some related to autoregulation. It may be very different if the blood pressure difference is between 150 to 170 or if it's 190, and for how long it's up.

So it's very difficult to give a single answer because it's not a uniform technique. It takes time and it takes titration. This is kind of a relatively short-lived treatment that then is over, so you don't have to

continue to monitor the patient's blood pressure.

DR. NOGUEIRA: I think it's just important to highlight the differences between pressure and flow, in terms of the potential impact to the distal territory, specifically through the ischemic core of that tissue. And I agree with Jeff that the current thought, this is more like a recruitment maneuver where you pop those micro-circulation channels open, and then the required pressure to keep them open is much smaller than the required pressure to actually recruit that. It's kind of a peep in the ventilator, if I may say.

DR. HURST: Thanks very much.

We'll now take a 15-minute break. Please remember that the Panel may also ask CoAxia questions during the Panel deliberations later this afternoon.

Let me just remind the Panel members not to discuss or contact anyone about the meeting topic during the break. This includes discussion amongst yourselves or with any members inside or outside the audience.

I'd also like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium.

We'll resume at 10:20.

(Off the record.)

(On the record.)

DR. HURST: I'm going to go ahead and call this meeting of the Neurological Devices Advisory Panel back to order.

And we'll now hear from the FDA.

DR. TOY: Good morning, distinguished Panel members, members of industry, and audience members. My name is Jeffrey Toy. I'm the team leader for the CoAxia NeuroFlo Catheter, the topic of today's FDA presentation.

This is an overview of the FDA Panel presentation. I will begin by stating the purpose of today's meeting and will provide you with a brief overview of the NeuroFlo regulatory history. Next, Dr. Natalie Getzoff will follow with a presentation of our preclinical and clinical analysis. Our clinical analysis will consist of an evaluation of the feasibility and SENTIS trials. Finally, Dr. Scott Miller will discuss the statistical issues with the SENTIS results.

The purpose of today's open public meeting is to solicit the Panel's input on the current knowledge of the safety and effectiveness of the NeuroFlo Catheter for use in patients with acute ischemic stroke within 14 hours of symptom onset.

Regulatory history.

FDA cleared the FloControl Catheter as a premarket notification, 510(k), for selectively stopping or controlling blood flow in the peripheral vasculature. Subsequently, the FloControl Catheter was cleared

with the addition of the phrase, "which includes the descending aorta."

The NeuroFlo Catheter is physically identical to the FloControl Catheter.

FDA approved the NeuroFlo Catheter Humanitarian Device Exemption, or HDE, for the "treatment of cerebral ischemia resulting from symptomatic vasospasms."

In 2005 the FDA approved Investigational Device Exemption, or IDE, to begin the SENTIS trial. The objective of the SENTIS trial was to demonstrate the safety and efficacy of the NeuroFlo treatment plus medical management relative to medical management alone in improving neurological outcomes in ischemic stroke patients. Dr. Getzoff will discuss this in greater detail.

In 2011 CoAxia requested 510(k) clearance for the NeuroFlo Catheter for the diversion of cardiac output via partial occlusion of the descending aorta, including in patients with acute ischemic stroke within 14 hours of symptom onset.

They cited the FloControl 510(k) as their predicate. We found the NeuroFlo indication to be not substantially equivalent, or NSE, to the predicate indication because the NeuroFlo indication alters the intended therapeutic effect or clinical benefit of a temporary intravascular occluding catheter.

Following our NSE decision, CoAxia filed a de novo petition for

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reclassification of the NeuroFlo into Class II. The de novo petition indication for use is provided on this slide.

Basically it states the NeuroFlo balloon inflation results in the diversion of cardiac output to the upper torso and core organs, like heart, spine, and brain. And NeuroFlo use increases cerebral blood flow in ischemic stroke patients and is intended for use up to 14 hours after symptom onset in patients who are ineligible for intravenous tPA or thrombectomy.

The NeuroFlo de novo petition is under review. Section 12.4 of your Executive Summary provides a high-level overview of the de novo process.

In addition to submitting a de novo petition, CoAxia requested supervisory review of the NeuroFlo NSE determination. The Center reviewed CoAxia's request and upheld the NSE determination. The Center offered to CoAxia to seek clinical and scientific input from the Neurological Devices Advisory Panel. Today we are here to seek your clinical and scientific input on the current knowledge of the safety and effectiveness of the NeuroFlo Catheter for use in patients with acute ischemic stroke within 14 hours of symptom onset.

The following FDA staff members were involved in the analysis of the CoAxia NeuroFlo SENTIS data. As you can see, it is a multidisciplinary team with diverse expertise.

I would like to now introduce Dr. Natalie Getzoff, who will

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provide FDA's preclinical and clinical analysis.

Thank you.

DR. GETZOFF: Good morning, Panel members, members of industry, and audience members. My name is Natalie Getzoff. I'm a neurologist and the clinical reviewer for the CoAxia NeuroFlo Catheter submissions and the SENTIS trial. I will be presenting a summary of preclinical and clinical data today. I will start with preclinical data.

The results of three animal studies included in the 2011 NeuroFlo 510(k) submission were discussed in detail in FDA's Executive Summary. These animal studies were conducted to assess safety and the physiological effect of partial aortic occlusion. I will focus on one of the swine studies, as that study was designed to assess the effect of short-term partial occlusion of the descending aorta on cerebral blood flow.

The objective of this study was to quantify cerebral blood flow changes caused by partial obstruction of the aorta in six healthy swine. The NeuroFlo Catheter was used in the study, and both suprarenal and infrarenal balloons were inflated. Different isotope-labeled microspheres were injected into the left atrium at different time points. Cerebral blood flow was indirectly measured by quantifying the deposition of the specific microspheres at pre-specified time points during the study, and microsphere deposition in several areas was assessed.

As you can see from this graph, cerebral blood flow was

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increased in all tested regions of the brain, beginning at suprarenal balloon inflation, which is the third group, and continuing through 90 minutes post-balloon deflation.

However, the only statistically significant increase in cerebral blood flow occurred during suprarenal balloon inflation in all measured brain areas. While other time points appeared to experience increased cerebral blood flow, none of these changes were statistically significantly greater than baseline, and the cerebral blood flow trended downward after the suprarenal balloon inflation.

Limitations of this study include the short-term time frame, cerebral blood flow assessments terminated in 90 minutes after balloon deflation, so there are no data to demonstrate if these observed findings are sustained.

A healthy animal model was used. It remains unclear if cerebral blood flow would be substantively changed in a stroke animal model or in humans in the setting of acute ischemic stroke, because cerebral autoregulation is often impaired and arterioles are often maximally dilated. Additionally, the impact of concomitant cardiovascular disease on effects of aortic occlusion are unknown.

Now I'll discuss the feasibility study data as they pertain to cerebral blood flow.

In the IDE submission, prior to expansion to the pivotal trial,

CoAxia provided a brief summary of a single-arm feasibility study which was intended to assess the safety and effectiveness of the NeuroFlo Catheter for augmented perfusion of the brain following acute ischemic stroke. Cerebral blood flow measurements were assessed during NeuroFlo in these subjects.

The feasibility data included results from two small prospective studies. The primary safety outcome was serious adverse events to 30 days post-procedure, and the primary efficacy endpoint was NIHSS score at 24 hours post-procedure, with success being at least a three-point decrease.

There were a total of 26 subjects in this feasibility dataset, which also included three compassionate use subjects. Seven out of 26 subjects experienced serious adverse events, two of which were device or procedure related. There were three deaths, none of which were adjudicated as treatment related.

Forty-one percent of Phase I subjects and 83% of Phase II subjects had at least a three-point decrease in the NIHSS score at 24 hours post-procedure. The greater success in the efficacy endpoint in Phase II was attributed to more subjects achieving the 70% aortic occlusion in that group.

For the cerebral blood flow analysis, data was collected prospectively from 17 subjects enrolled in the single-arm Phase I of the feasibility study. Cerebral blood flow was assessed with transcranial Doppler in 16 patients. Cerebral perfusion was assessed using a variety of measures,

seven subjects with angiography, two with SPECT, and one with a PET scan.

Cerebral blood flow increased more than 15% in 12 of these 16 subjects, with a mean increase of 25%. Perfusion was reported to have improved in three of six angiograms and in the PET and SPECT scans. Two subjects died of stroke progression during this feasibility trial.

This study has several limitations. Only a small population was studied. There was no untreated control group available for comparison. Correlation of clinical benefit to increased cerebral blood flow was not available as 90-day clinical outcomes were not assessed. And, lastly, this study does not address the potential impact that different assessment methods may have had on the study results.

CoAxia proposes the following indications for use for the NeuroFlo Catheter:

"The CoAxia NeuroFlo Catheter is intended for use in selectively stopping or controlling blood flow in the peripheral vasculature, which includes the descending aorta. When used in the descending aorta, balloon inflation results in diversion of cardiac output to the upper torso and core organs, e.g., cardiac, spinal, and cerebral vasculature. The NeuroFlo Catheter is intended to increase cerebral blood flow in patients with ischemic stroke and is intended for this use up to 14 hours after symptom onset, in patients who are ineligible for intravenous tPA or thrombectomy.

"In a randomized clinical investigation of stroke patients, use of

the NeuroFlo Catheter was demonstrated to be safe. The study did not demonstrate a statistically significant improvement in the 90-day 'return to normal' Global Outcome Score. Use of the catheter resulted in a reduction of overall mortality and stroke-related mortality."

Please discuss if the available data, including the SENTIS trial results and other NeuroFlo pre-clinical and clinical data, demonstrate effectiveness in increasing cerebral blood flow in patients with acute ischemic stroke within 14 hours of symptom onset.

You will also be asked to discuss several questions, on this slide and the next, regarding the role of cerebral blood flow as an endpoint in trials that assess effectiveness of device treatment for acute ischemic stroke.

Following the feasibility studies, CoAxia performed the Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke or SENTIS trial. I will start with a brief overview of the study design.

The SENTIS trial was designed "to demonstrate the safety and efficacy of the NeuroFlo treatment plus medical management relative to medical management alone in improving neurological outcome in ischemic stroke patients."

The SENTIS trial was a multi-center, randomized, controlled, prospective, assessor-blinded trial with 1:1 randomization to either NeuroFlo device plus standard post-acute stroke medical management or standard post-acute stroke medical management alone. The primary analysis

population was a modified intent-to-treat cohort, which included all randomized subjects, except for the NeuroFlo exclusions, who received a treatment and were analyzed according to the treatment randomized, not received.

Other important populations included the intent-to-treat cohort, which included all randomized subjects regardless of whether ultimately treated or not, and analyzed according to treatment randomized, as well as the modified as-treated cohort, which was all randomized subjects, except for the NeuroFlo exclusions, who received a treatment and were analyzed according treatment received, not randomized.

Key inclusion criteria were acute cerebral ischemia with hemispheric cortical dysfunction, a new focal neurological deficit of presumed vascular origin, a baseline NIHSS score of 5 to 18, and ability to start NeuroFlo procedure within 14 hours of symptom onset in patients.

Patients were excluded if they had significant pre-morbid disability, massive stroke, new intracranial bleeding, rapid neurological improvement, or concurrent use of thrombolytic agents or neurothrombectomy devices, among other reasons.

For subjects who were randomized to the NeuroFlo group, further angiographic exclusions were applied, specifically aortic diameters outside the device-defined limits, evidence of aortic aneurysm, or high-grade iliac stenosis or tortuosity.

The primary safety endpoint of the SENTIS trial was to compare the incidence of serious adverse events, as adjudicated by a data safety monitoring board, from the time of enrollment through 90 days of follow-up between the NeuroFlo and control groups.

The four secondary safety endpoints were comparison between NeuroFlo and control groups in 90-day mortality and survival, new intracranial hemorrhage, symptomatic intracerebral hemorrhage, and index stroke-related serious adverse events.

In the IDE supplement requesting addition of these secondary endpoints, CoAxia did not modify the protocol to include a statistical analysis of these secondary endpoints, stating that “as labeling for secondary objectives is not requested, hypothesis testing will not be performed on these.”

The objective of the SENTIS trial was to estimate the effect of NeuroFlo treatment plus standard of care medical treatment as compared to standard medical treatment alone on the proportion of patients showing a favorable outcome at 90 days using the global test comprised of four outcome measures.

Components for the global test measurement were the National Institutes of Health Stroke Scale, modified Rankin Scale, Barthel Index, and Glasgow Outcome Scale. Favorable responses for each component were NIHSS of 0 or 1, mRS of 0 or 1, Barthel Index of 95 to 100, and a GOS

of 5.

Result of the global test is an overall odds ratio. The odds ratio assesses the association between treatment and a favorable outcome at 90 days. Odds ratios greater than 1 favor treatment and an odds ratio of less than 1 favors the control.

Dr. Miller will discuss the primary endpoint from a statistical perspective later in this presentation.

There were eight pre-specified secondary effectiveness endpoints in the SENTIS protocol. These were primary efficacy endpoint component analysis; acute improvement in NIHSS, defined as change in NIHSS greater than or equal to three points or an NIHSS score of less than or equal to 2, measured at 24 hours post-procedure; the Stroke Impact Scale as collected at 30 and 90 days; hospital length of stay; mRS shift analysis; dichotomized mRS 0 to 2 versus 3 to 6; entry severity responder analysis; and subject disposition upon discharge.

As with the secondary safety endpoints, CoAxia did not modify the statistical plan, stating that “hypothesis testing would not be performed, as labeling for these objectives were not being requested.”

The SENTIS trial did not include any endpoint evaluating efficacy of the device in increasing cerebral blood flow.

Five hundred and fifteen subjects were enrolled at 72 sites. Of the enrolled subjects, 257 were randomized to the control group and 258 to

the NeuroFlo group. Twenty-eight subjects were excluded after randomization to the NeuroFlo group due to protocol-specified exclusions. Of these, 25 subjects were excluded due to anatomical ineligibility via angiography and three due to rapid neurological improvement. There was no statistically significant difference between NeuroFlo exclusion, NeuroFlo control groups, and demographics, mortality, and endpoints. The final NeuroFlo sample was 230.

I will now talk about the safety results in the SENTIS trial. I'll discuss the safety endpoints and the adverse events.

The primary safety endpoint of the SENTIS trial was met. There was no statistically significant difference in serious adverse event rate between the NeuroFlo and control groups.

While the serious adverse event rate did not differ statistically between NeuroFlo and control groups, this finding should be interpreted in light of the following:

The overall SAE rate does not differentiate between random events unassociated with the device or procedure and those which can be reasonably associated with the device or procedure. And an overall SAE rate weights all SAEs equally, but physicians and patients may not attach equal weight to all SAEs.

I will now discuss the adverse events in the SENTIS trial.

This table shows the serious adverse events by treatment

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group. There were no significant differences between groups when all serious adverse events were categorized by organ system.

Although there was no statistically significant difference between NeuroFlo and control groups in the rate of serious adverse events, several clinically significant device and/or procedure-related serious adverse events occurred in the SENTIS trial. Specifically, there were eight serious adverse events adjudicated by the DSMB to be related to NeuroFlo treatment, or 3.4%.

One subject experienced a fatal procedure-related serious adverse event. This was a new stroke with hemorrhage and cerebral edema. The new stroke symptoms began during the period that the NeuroFlo balloon was inflated, and the subject died on post-enrollment day seven.

The other treatment-related serious adverse event of note occurred in a subject with peripheral artery disease, who developed femoral artery occlusion with associated limb ischemia and required an above-the-knee amputation.

There were no significant differences between groups when all adverse events were categorized by organ system.

There were 36 non-serious NeuroFlo treatment-related adverse events in 35 subjects, for a total 15.2% rate of non-serious treatment-related adverse events. The great majority of these adverse events were vascular, the most common being hematomas and anticipated sequelae in a procedure

requiring puncture of the femoral artery.

The SENTIS trial met its primary safety endpoint of no statistically significant elevation in the rate of serious adverse events in the NeuroFlo-treated group relative to the control group. Specifically, there were 174 SAEs in 43.9% of NeuroFlo subjects and 177 SAEs in 42.8% of control subjects. However, there were SAEs not seen in the control group that were adjudicated as related to the NeuroFlo treatment.

In light of all of the available safety data, please discuss the safety of the NeuroFlo device in the SENTIS population (patients with acute ischemic stroke treatable within 14 hours from symptom onset, with baseline NIHSS score of 5 to 18, and without evidence of massive infarct or hemorrhage).

Please discuss any additional measures that may reduce the risk of these SAEs associated with use of the NeuroFlo device in the SENTIS population.

I will now present the results of the pre-specified secondary safety endpoint analyses.

There was no statistically significant difference between groups at 90 days for all-cause mortality or for survival using a Kaplan-Meier analysis. There is a slight difference between the all-cause mortality and survival estimate comparisons. Mortality was assessed by comparing the rate of 90-day mortality in the two groups by a Cochran-Mantel-Haenszel test.

Ninety-day survival was assessed by a log rank test. This compares not only the rate at 90 days but the timing of the events over time.

The estimates at 90 days do not directly compare, because the log rank test accounts for censored subjects, that is, subjects who discontinued from the trial prior to 90 days. Additionally, two subjects died more than 90 days post-procedure but were within the pre-specified 90-day evaluation window and were included in the 90-day visit and in the mortality analysis. These subjects, however, were not included in the 90-day survival analysis.

The 90-day survival analysis demonstrated no statistically significant difference between groups. And here are the Kaplan-Meier curves for reference. The shaded areas are the confidence intervals.

The SENTIS trial resulted in a 90-day all-cause mortality rate of 11.3% in the NeuroFlo group versus 16.3% in the control group. Survival at 90 days by Kaplan-Meier was 88.5% and 84.2% in the NeuroFlo and Control groups, respectively.

Please discuss the clinical significance of these findings.

There was no statistically significant difference between NeuroFlo and control in new intracranial hemorrhage.

There was no statistically significant difference between NeuroFlo and control in symptomatic intracranial hemorrhage at 24 hours post-procedure.

There was no statistically significant difference between groups in stroke-related serious adverse events at 90 days.

Next, I will discuss the post hoc secondary safety analysis.

Stroke-related mortality was a safety endpoint not pre-specified in the SENTIS protocol. It was defined by CoAxia as deaths adjudicated by the DSMB as due to stroke, systemic complications associated with stroke, and/or new stroke. The stroke-related mortality rate in the NeuroFlo group was 7.4% and 14.4% in the control group, with a nominal p-value of 0.011.

The 90-day stroke-related survival analysis demonstrated a nominal difference between groups. And here are the Kaplan-Meier curves with confidence intervals for reference.

As with the all-cause mortality analysis, there is a slight difference between the stroke-related mortality and survival estimate comparisons. Mortality was assessed by comparing the rate of 90-day mortality in the two groups by a Cochran-Mantel-Haenszel test, and 90-day survival was assessed by a log rank test. This compares not only the rate at 90 days but the timing of events over time. The estimates at 90 days do not directly compare, because the log rank test accounts for censored subjects.

Interpretation of the stroke-related mortality endpoint is challenging for several reasons. First, this analysis was performed in the absence of a statistically significant primary effectiveness analysis. Second, it

was a post hoc analysis. And, lastly, the 90-day all-cause mortality did not have a corresponding statistically significant decrease.

Dr. Miller will discuss the challenges in interpretation of this endpoint from a statistical perspective later in FDA's presentation.

CoAxia conducted a post hoc analysis of multiple effectiveness and safety endpoints using SENTIS results and found stroke-related mortality to be decreased for NeuroFlo-treated subjects. For the purpose of this analysis, stroke-related mortality is defined as deaths that were adjudicated to have been due to stroke, systemic complications associated with stroke, or new stroke.

Post hoc analyses are challenging to interpret, especially if conducted in the setting of a non-significant primary endpoint. You will be asked to discuss the clinical significance of this post hoc analysis finding.

Now I will discuss the effectiveness results from the SENTIS trial.

As I mentioned earlier, the primary effectiveness endpoint of the SENTIS trial was an estimation of the effect of NeuroFlo treatment as compared to control using the global test outcome at 90 days.

The SENTIS trial failed to show a significant difference between the treatment and control groups for the pre-specified primary effectiveness endpoint, with an odds ratio for improved outcome of 1.17 and a p-value of 0.407. This analysis was performed on an agreed-upon modified intent-to-

treat dataset. Results were similar for the intent-to-treat and modified as-treated datasets. This finding is supported by a lack of difference between the NeuroFlo and control groups when the four components of the global test were analyzed separately, as I'll show in a moment.

The SENTIS trial used a global test-type endpoint with multiple components to assess effectiveness. Please discuss your interpretation of this global endpoint in evaluating clinical outcomes in subjects enrolled in SENTIS.

I'll now discuss the results of the pre-specified secondary effectiveness endpoint analyses.

This table shows each of the components of the global test analyzed separately. None of these components were statistically significantly different between groups.

Dr. Miller will discuss the primary efficacy endpoint component analysis in greater detail later in FDA's presentation.

There was no statistically significant difference between groups in acute improvement in NIHSS score.

There was no statistically significant difference between NeuroFlo and control groups in the distribution of the full range of mRS scores.

When the mRS score was dichotomized into good, 0 to 2, and poor, 3 to 6, outcomes, there was no statistically significant difference

between the NeuroFlo and control groups.

The entry severity responder analysis is a sliding dichotomy mRS analysis, in which good outcome, defined by mRS score at 90 days, is based on the baseline NIHSS score. There was no statistically significant difference in entry severity responder analysis between the NeuroFlo and control groups.

There was no statistically significant difference in the mean Stroke Impact Scale scores between NeuroFlo and control groups at 30 or 90 days.

There were no statistically significant differences between the NeuroFlo and control groups in hospital length of stay. Due to differences in standard of care, hospital length of stay was also analyzed separately by region. There was no statistically significant difference between the groups when hospital stay by region was examined separately.

Subject disposition upon discharge was assessed only on subjects in the United States. There was no difference between groups in disposition after discharge from the hospital.

Please discuss any relevant treatment effect identified in the data from the SENTIS trial and if any effects are clinically meaningful.

CoAxia identified several subpopulations with potential clinical benefit from the use of the NeuroFlo Catheter. Numerous analyses were performed, and none of these analyses were pre-specified in the protocol.

Here are results of some of the subgroup analyses provided by CoAxia, as presented earlier. These analyses were performed on subsets of the predefined modified as-treated -- I'm sorry -- the predefined, yeah, modified as-treated cohort. None of these analyses were pre-specified in the protocol. Some have nominal p-values less than 0.05 and some do not, depending on the subgroup and/or metric analyzed.

Keep in mind, the overall odds ratio of the mRS 0 to 2 versus 3 to 6 outcome was 1.34, but was not statistically significant. Therefore, for subjects with larger effects favoring NeuroFlo, such as some of the ones on this table, there may be corresponding subgroups which would favor the control.

Here are results of several other post hoc subgroup analyses provided by CoAxia. These analyses were performed on a unique population significantly different from the analysis population as pre-specified in the SENTIS protocol. In these analyses, the NeuroFlo exclusion subjects were included in the NeuroFlo group, although they did not receive NeuroFlo treatment. And subjects were excluded if they had missing data or were considered to have been stroke mimics after the NeuroFlo procedure was performed.

Subjects who were enrolled in SENTIS and fulfilled the eligibility criteria, including the clinical diagnosis of stroke, were enrolled appropriately. Identification of other causes of neurological dysfunction, such as stroke

mimics after treatment, has been delivered, and exclusion of these subjects from the analysis dataset is not good clinical trial practice. This may lead to study bias, skewed results, and inappropriate conclusions. Because of the post hoc nature of these analyses and the modifications to the population analyzed, including reallocation of treatment assignment, we consider these findings exploratory in nature at best.

Please discuss whether the benefits from use of the NeuroFlo device outweigh the risks of its use in the patient population enrolled in the SENTIS trial. Please discuss these benefits and risks in the context of alternative treatments, including non-device therapies, approved or cleared for the intended condition and patient population, as this is a component of FDA's final regulatory decision with respect to benefit/risk determination.

After failing to meet any pre-specified primary and secondary effectiveness endpoints, CoAxia conducted multiple post hoc analyses and identified several subgroups in whom they state the NeuroFlo device shows larger treatment effect; for example, subjects greater than 70 years or subjects with a baseline NIHSS score between 8 and 14. FDA has concerns that due to the post hoc nature of these subgroup analyses, the results may represent false positive findings. Taking these concerns into consideration, please discuss the benefits and risks in the identified subgroups.

Dr. Miller will now discuss the statistical issues.

DR. MILLER: Good morning. My name is Scott Miller, and I'm

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the statistical reviewer for the CoAxia NeuroFlo submission.

I'll be discussing two main statistical issues regarding this submission. The first is a brief discussion regarding the nature of the global outcome test, which was the pre-specified primary effectiveness endpoint for the SENTIS trial. I'll then address the concern regarding the overall Type I error inflation present in this submission and its implications for the conclusions which can be drawn from the SENTIS trial.

As previously discussed by both CoAxia and Dr. Getzoff, the pre-specified primary effectiveness outcome was a global test consisting of four component outcome scales: the NIH Stroke Scale, mRS, BI, and GOS. Global tests have been in use for some time, although their use in the acute ischemic stroke arena stems primarily from the 1996 NINDS rt-PA stroke study.

In a global test, each of the components is classified as either favorable or unfavorable, and the model then calculates an overall odds ratio for the effect of treatment. In the case of the SENTIS trial, an odds ratio greater than 1 indicates a positive association between treatment and outcome.

An underlying assumption of the global test approach is that the odds ratio for treatment is roughly similar for each of the component scales. In other words, the more consistently the treatment improves all of the components, the more powerful the global test approach will be.

Note that the global test approach is not a simple composite or combination of the components, as I'll explain in the next slides.

To illustrate, consider that we're given a hypothetical subject with each of their four component scales classified as either favorable or unfavorable, as shown here. As there are four components in total, there are five possible permutations of the total number of favorable outcomes, ranging from four unfavorable through to all four favorable.

For a composite outcome, only a subject with all four components classified as favorable would be considered a success. That would be corresponding to the bottom-most row of this table. With the global test, subjects are not classified as favorable or unfavorable. Rather, each of the components is included in the model, which accounts for the fact that the components are correlated by subject.

The global test takes advantage of the correlation between these outcomes in order to gain power relative to either a composite approach or assessing each component outcome separately. The result is a single overall odds ratio for the association between treatment and then overall favorable disposition at 90 days.

The model effectively starts with an odds ratio treatment at 1, which corresponds to no effective treatment. The more favorable components a given subject has, the stronger that subject pulls, in essence, the odds ratio for treatment higher than 1. If a subject has more unfavorable

outcomes, then the model would pull the odds ratio below 1. By combining all of the subjects, the global test arrives at a single summary odds ratio for treatment.

As an example, consider a treated subject or a control subject with the same demographics had two favorable components at 90 days. If the treated subject had two favorable components, corresponding to the middle row, the global odds ratio would be pulled to 1. If the treated subject had more than two favorable outcomes, the odds ratio would be pulled greater than 1.

Conversely, if the treated subject had less than two outcomes classified as favorable, the odds ratio would be pulled to less than 1, and the strength of that pull would correspond to the agreement of the individual components for that subject.

This slide shows the predefined primary effectiveness endpoint, the global test. The overall odds ratio for the effect of treatment is 1.17. The 95% confidence interval is shown below, with a p-value of 0.407. And for reference, recall from the protocol that the trial was powered to detect an odds ratio of 1.7.

This result is based on the covariate-adjusted analysis using the modified intent-to-treat population. The results were similar if conducted without adjusting for covariates as well as for the modified as-treated and strict ITT populations. An odds ratio of 1.17 suggests that, on average,

NeuroFlo-treated subjects would be expected to have a 17% increased likelihood of a favorable response at 90 days, relative to a control-treated subject.

Note, however, that the 95% confidence interval suggests that this effect could range anywhere from 19% worse likelihood of treatment to a 67% increased likelihood of improvement. And as the interval contains 1, the treatment is not statistically significant.

This table shows each of the component outcome scales of the global test analyzed separately. As seen, the covariate-adjusted proportion of subjects with a favorable component numerically favors the control group for three of the four components when covariate adjusted. However, none of these analyses were statistically significant when analyzed separately.

Looking at the effect of treatment, the column highlighted in yellow here, the odds ratios are roughly the same direction in magnitude; approximately 1 or slightly above for all four outcomes. This provides evidence that the underlying assumption of the global test, that the odds ratios for each component are similar, is not violated.

From this table, it appears that this difference is driven primarily by the Barthel Index component, as that is the largest difference in favor of treatment.

So to summarize from these slides, the overall odds ratio is 1.17, although not statistically significant, and it appears to be driven largely

by an increased number of NeuroFlo-treated subjects with one favorable component, and that is likely the Barthel Index.

To explore that slightly further, when the number of favorable components is examined by subject, there's a numerically higher percentage of NeuroFlo-treated subjects with one favorable component relative to control-treated subjects. That's the row highlighted in yellow.

Examining the table further, these subjects appear to be coming equally from the adjacent 0 and 2 favorable component categories, the rows just above and just below it. And this appears to be the main driving factor of the overall odds ratio exceeding 1.

Please consider this information when addressing the Panel question. The SENTIS trial used a global test-type endpoint with multiple components to assess effectiveness. Please discuss your interpretation of this global endpoint in evaluating clinical outcomes in subjects enrolled in SENTIS.

The previous slides have demonstrated that the SENTIS trial failed to achieve statistical significance for the predefined primary effectiveness endpoint. This holds true regardless of whether the analysis was adjusted or unadjusted for clinical covariates as well as for several analysis populations.

CoAxia has highlighted several comparisons with nominal p-values of less than 0.05. However, it should be noted that these are a

subset of the post hoc analyses.

There are two types of analyses presented beyond the primary. Those are secondary and the post hoc. The statistical implications of each of these will be discussed separately.

Interpreting a secondary analysis is difficult in the absence of a statistically significant overall analysis, as well as the absence of a multiplicity adjustment to control the overall Type I error rate.

Post hoc analyses are generally not recommended but if conducted are typically considered hypothesis generating, requiring independent confirmatory data external to the original study.

Note that while there are methods to control the overall Type I error rate, they are only valid if pre-specified, for example, for secondary analyses but not for post hoc analyses.

So we've talked a bit about Type I error rates, so this slide is to discuss what that is. The Type I error is the statistical term which refers to the likelihood of concluding that a difference is statistically significant when it is not, i.e., the false positive rate. There are a number of statistically accepted methods which can be pre-specified and used to control the overall Type I error rate of a clinical trial. But the SENTIS trial did not utilize any of them for the secondary or post hoc analyses.

As Dr. Getzoff has previously mentioned, the protocol states that "no hypothesis tests will be performed for the secondary outcomes

because there are no plans to make labeling claims for these."

Assume we conduct 10 independent statistical tests, each at 5% significance level, and that there's truly no effect. The probability of at least one significant difference, i.e., a p-value of less than 0.05, is not 5%; it is approximately 40%. When increasing the number of independent statistical tests to 20, the probability correspondingly increases to approximately 64% and similarly increases further if conducting 30 or 40 independent tests.

Note that this does assume that the tests are independent. If they are not independent, then the Type I error remains inflated relative to the 0.05 level, but the exact value is complicated to calculate. And this Type I error concern would apply to both the secondary and subgroup analyses that CoAxia has presented earlier this morning.

The pre-specified primary and secondary safety outcomes are listed on this slide. The role of these analyses was to attempt to rule out that NeuroFlo intervention increases the risk of certain adverse events, relative to control.

So I've shown that there's a theoretical risk of a significant increase in the risk of a false positive finding when conducting multiple hypothesis tests. How might that impact the SENTIS trial results you've already seen through the course of this morning's presentations?

Let's look at the number of outcomes examined, that is, the number of statistical tests conducted. The trial had a primary safety outcome

as well as several pre-specified secondary safety outcomes.

Moving to the effectiveness outcomes, the primary effectiveness outcome was the global test. Note that the global test was conducted twice, once adjusted for covariates and again unadjusted.

This trial shows that the trial also had a number of pre-specified secondary effectiveness outcomes in addition to the primary effectiveness analysis.

Additionally, CoAxia conducted a number of post hoc analyses, including stroke-related mortality; baseline NIH stroke score between 8 and 14; age, using a cut point of 70 years and again using a cut point of 80 years; time from symptom onset using a cut point of 5 hours or 6 hours, as well as several categorizations of the modified Rankin score using different cut points.

Further, as Dr. Getzoff presented previously, CoAxia also conducted a number of analyses on a non-pre-specified subset of the data, which excluded stroke mimics.

As shown on the previous slides, CoAxia conducted multiple statistical analyses, primary, secondary, and post hoc, for both effectiveness and safety. Given the statistical concerns discussed, you will be asked to discuss the clinical significance of the post hoc stroke-related mortality analysis finding in this question.

In conclusion, the SENTIS trial failed to achieve statistical

significance on its pre-specified primary effectiveness outcome as well as all pre-specified secondary outcomes. A trend for effectiveness in the global test appears largely driven by the Barthel Index component.

And the trial analyzed a number of post hoc outcomes, some of which have nominal p-values less than 0.05; for example, stroke-related mortality. However, we are concerned that these may be false positive findings due to the number of tests conducted, and thus, the overall Type I error rate of the SENTIS trial is uncontrolled and unknown. Thus, reference to a 0.05 threshold for p-values is not appropriate.

I will now turn to Ms. Quynh Hoang for our closing summary statement.

MS. HOANG: Panel members, colleagues, ladies and gentlemen, I'm Quynh Hoang, Chief of the Neurodiagnostic and Neurosurgical Devices Branch.

You have heard from Dr. Toy the regulatory history of the NeuroFlo Catheter. Drs. Getzoff and Miller, respectively, discussed the clinical results and statistical issues associated with the SENTIS trial.

To briefly summarize, the SENTIS trial objective was to demonstrate the safety and efficacy of the NeuroFlo treatment plus medical management relative to medical management alone in improving neurological outcome in ischemic stroke patients. The SENTIS study did not assess cerebral blood flow.

Its outcomes include achieving its primary safety endpoint of no significant difference in the serious adverse event rate between NeuroFlo group versus the control group.

The SENTIS trial, however, failed to achieve statistical significance on its primary effectiveness endpoint and all pre-specified secondary effectiveness endpoints.

Post hoc. The Sponsor conducted numerous analyses and identified several that were statistically significant. As with all post hoc analyses, there are limitations, such as how to interpret the multiple secondary analyses in the absence of significant primary analysis and without multiplicity adjustment, given that both could increase the overall Type I, that is, false positive error.

Given the increased chance of false positive findings, we are here to seek the Panel's input on how to best interpret the SENTIS trial results.

This concludes the FDA's presentation.

DR. HURST: I'd like to thank the FDA team for their presentation.

Does anyone on the Panel have any brief clarifying questions for the FDA? Please remember that the Panel can also ask FDA questions at the deliberations this afternoon.

Yes, Dr. Zhou.

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DR. ZHOU: So I have a question on the global test. From the package, we see that they use logistic regressions to perform the global test, is that right?

DR. MILLER: Yes. This is Scott Miller. They implemented it with the GEE logistic regression.

DR. ZHOU: GEE?

DR. MILLER: Yes.

DR. ZHOU: But if you look at the logistic regressions, if it's just for covariates, the odds ratio is actually a conditional odds ratio, not the global odds ratio. I don't know how you can derive the global odds ratios from the logistic regressions if it's conditional covariates. The beta is an odds ratio given the covariate X. It's not the odds ratio over the whole population. I don't think you can derive easily the global odds ratio.

From your understanding, how did they derive that?

DR. MILLER: So this was a population averaged as opposed to a subject-specific GEE, so the difference would be that one, as you mentioned, would apply to basically everyone, as opposed to estimating a separate odds ratio and sort of averaging those.

In terms of the question regarding how did they calculate an overall odds ratio --

DR. ZHOU: Because the logistic regression is conditional. If you look at even GEE, it is the population conditioned on the covariates, so

there's not the subgroup-specific covariates effect. So the beta itself is not over the whole population, if you look at it. I did a pre-calculation and actually you cannot -- it's not easy to convert the covariate-specific odds ratio to the whole population odds ratio because of the log-linear models. If you use a linear model, it's easy.

So maybe I have a question as to how actually you can get the overall odds ratio. It's not clear to me from the condition of logistic regression, even using the GEE approach.

DR. MILLER: So the Sponsor could discuss it possibly later on, on their side.

Basically, they did conduct an unadjusted as well as the adjusted. The adjusted included those covariates in the model and then took the beta parameter from the effect of treatment to calculate the odds ratio.

DR. ZHOU: So when these are adjusted, how they did it, still using logistic regression?

DR. MILLER: It was just the GEE, the same model, but excluding the covariate terms.

DR. ZHOU: So still a logistic regression?

DR. MILLER: Yes, still a logistic regression with the GEE approach.

DR. ZHOU: Okay, that clarified it to me.

DR. HURST: Dr. Layton.

DR. LAYTON: Yes, Terry Layton.

I have several questions. The first one relates to the '03 and the '09 510(k)s. What were the indications? I thought the '09 was some additional clinical indications, and I thought one of them was cerebral blood flow.

My second question relates to the differences between 510(k) and the de novo. Is there a slide? This is the first time I've sat with a de novo, and I imagine it's the same with everybody else here. What about the requirement? I mean, what's the difference between the requirements for the de novo and a classical 510(k) versus a Class III premarket approval?

And the third question relates to the statement of no evidence of cerebral blood flow increase. I thought we saw some of that and, I thought, on your slides. But what did you want then for evidence of cerebral blood flow?

DR. EYDELMAN: Hi, this is Dr. Eydelman. I'll try to address your questions.

If you turn to our Slide Number 4, under regulatory history, the indications for the 510(k)s cleared in 2003 and 2009 are summarized. Specifically, it was to selectively stop or controlling blood flow in the peripheral vasculature, which includes the descending aorta. So the newer indication was not part of either of the 510(k)s.

Regarding your question --

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DR. LAYTON: Why the '09, then? What was added in the '09?

DR. EYDELMAN: So I believe '09 added the descending aorta.

DR. LAYTON: Okay.

DR. TOY: Yes, that's correct, the '09 added the phrase "descending aorta." It's a little bit more descriptive.

DR. EYDELMAN: In regard to your question about the de novo, if you open to our Executive Summary, Section 12.4, we provided a summary, which I'll just read for the record.

We have a section saying, "What is an Evaluation of Automatic Class III Designation (de novo) petition?" And we provided the following explanation.

"Initially, devices submitted for 510(k) clearance for which no suitable predicate was identified were automatically classified as Class III. The FDA Modernization Act of 1997 (FDAMA) created the de novo pathway to allow for moderate risk devices without a suitable predicate to be reclassified to Class II or Class I, providing adequate special controls can be developed. The FDA Safety and Innovation Act of 2012 (FDASIA) made this premarket pathway available to low to moderate risk devices without predicates regardless of whether FDA determined them to be Not Substantially Equivalent."

Having said that, I would like to redirect the Panel's attention to the clinical data before them so that they can provide their

recommendation on the SENTIS trial and its outcome to us.

Thank you.

I'm sorry. Can you restate your question number three?

DR. LAYTON: Question number three was about no evidence of cerebral blood flow improvement. The statement read, the "study did not assess cerebral blood flow."

MS. HOANG: That is the case with the SENTIS trial. That trial did not assess cerebral blood flow. There were no outcome measures included in the SENTIS trial to assess cerebral blood flow.

DR. HURST: Dr. Posner.

DR. POSNER: I have a follow-on question regarding that.

DR. NOONAN: Yes. I'm sorry, go ahead.

DR. HURST: Go ahead, Dr. Posner.

DR. POSNER: A question on de novo. We received all the data for the SENTIS trial, but there was a huge number of clinical exclusions from patients that are included in the SENTIS trial: heart disease, renal disease, hypertension, anticoagulants, et cetera.

And the question that I have, when we make a decision for use of this, when a patient comes in with stroke, is the ability to assess these exclusions for the value of using this device something that we should consider? Because some of those exclusions are not that easy to assess on an emergency basis, particularly when they took their subgroups of 80-year-olds

and 70-year-olds.

DR. EYDELMAN: So we would like to seek your input on the data provided, i.e., the data that was collected, and then we'll utilize that to further decide on how we're going to proceed. As you know, any approval or clearance has a particular indication which can limit the patient population. So we're seeking the Panel's input on the benefit and safety of the population studied.

DR. HURST: Dr. Noonan.

DR. NOONAN: Regarding Slide Number 23, Panel question, if cerebral blood flow changes are used as an endpoint, discuss the following. And cerebral blood flow was not measured. I think, on some of the initial Phase I studies, there were some angiographic images, and I have some problems using angiography. For example, when we inject contrast in a vessel, we add a certain volume to that vessel. And if I inject less, I see less vessels. If I inject more or faster, I see more vessels. So that's one potential problem with measurement of cerebral blood flow at the time the procedure is done.

Any comments?

DR. EYDELMAN: I was wondering if you have a specific question for us. I think this time is reserved for clarifications regarding our presentation.

DR. NOONAN: Very well.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: Thank you. It's Alicia Toledano, and I do have a specific question for you.

So CoAxia told us -- the Sponsor told us that they initially proposed including the cerebral blood flow as an endpoint, and they were told by the FDA that that would not fly. You reviewed the pre-IDE, you reviewed the IDE, and you approved the IDE.

So how does that happen without cerebral blood flow as part of the protocol?

DR. GETZOFF: Now, I was not on the team at the time, so I can go by history. From what I understand, the proposed eventual indication was for treatment of stroke, and it was felt that clinical endpoints were much more appropriate if the eventual indication for the device was to be for treatment of stroke as opposed to something more consistent with a physiological effect.

DR. TOLEDANO: So Dr. Toledano following up.

You knew that they came in with the cerebral blood flow endpoint. You knew that they were putting it into the IFU. You asked them for clinical. That's great. Or the people on the FDA review team at the time asked for clinical, and that's good.

But where did the cerebral blood flow endpoint go? Why in the entire time that things have been under review did that never come back in?

DR. EYDELMAN: So let me try to attempt to answer this.

The IFUs for IDE, the SENTIS trial, versus the de novo, as you know, are a bit different. So what Dr. Getzoff is addressing are the endpoints that were felt to be appropriate for an IDE study that supported the SENTIS, which was a stroke indication.

DR. TOLEDANO: Thank you for the clarification.

DR. GETZOFF: We can bring up Slide 25, which clarifies what the objective of the SENTIS trial was, and that's sort of where it came from.

DR. HURST: Dr. Yang.

DR. YANG: Linda Yang.

To branch off from what Dr. Posner said, given the data that we're seeing here, it seems to me that if this were approved, it would be for a certain population, like the 70-year-olds, and a certain time period, et cetera.

Should we not be looking at just the safety profile for those patients?

DR. EYDELMAN: So we are asking you specific questions regarding the indications and we would -- but should you want to provide additional data, we are always eager to listen to it.

DR. YANG: I think the reason I asked that is because there is the question -- there's always the question of risk/benefit. And if we're talking about risk versus safety and if we're talking about the safety of the entire group, but we're only talking about effectiveness for a particular group,

then that makes it very difficult for us to make that assessment.

DR. EYDELMAN: So, again, we're asking about the indication that is currently being proposed by the Sponsor.

Having said that, if you believe that the data supports something different, once again, we would love to hear your opinion about that.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Ray Dorsey.

Could either the FDA or Sponsor discuss the use and the safety of the FloControl Catheter in practice to date, like how many times it's been used? Any safety issues with it to date?

DR. EYDELMAN: Can you repeat your question?

DR. DORSEY: Sure. My understanding is that the FloControl Catheter is currently on the market and cleared. I was wondering if you could discuss its use and safety to date, or if lots of adverse events have been reported with it. Is it used?

DR. GETZOFF: So I can answer in respect to medical device reports to us at FDA, specifically for the NeuroFlo Catheter, which is HDE approved for vasospasm in subarachnoid hemorrhage, and FloControl, which has the more general indication for use. It's not the specific population that would be indicated in this submission, and there were no adverse events tagged for this particular device.

DR. EYDELMAN: I believe his question was about the 510(k) indication.

DR. GETZOFF: Right. So we did an --

DR. EYDELMAN: The MDRs.

DR. GETZOFF: -- MDR search for both the NeuroFlo HDE and for the FloControl, and we found none.

DR. DORSEY: How commonly is it used? Is it once a year, 100 times a year? I mean, how many times a year?

DR. EYDELMAN: I believe that's a question better asked from the Sponsor.

DR. HURST: So just to clarify my understanding of that. So you do collect the data that are reported on your database, regarding the ones that are currently available under the HDE or the 510(k), and you have not received much in the way of safety reports or issues on that; is that correct?

DR. GETZOFF: So we don't seek it. We don't go out and collect it.

DR. HURST: Yes, correct. Right, right.

DR. GETZOFF: These are reported by --

DR. HURST: Yes.

DR. GETZOFF: -- clinicians or patients or other healthcare professionals.

DR. HURST: Although there's a mandate for the companies to

report that, when they receive it.

DR. GETZOFF: And then the companies provide it, as well.

DR. HURST: Okay.

DR. GETZOFF: So that's the information that I'm --

DR. HURST: Okay, thank you.

Dr. Goldstein.

DR. GOLDSTEIN: Yeah, just one point of clarification first. The indication is 14 hours, but I keep hearing people say 18 hours. Where is the 18 hours coming from?

DR. EYDELMAN: So we can only talk about the indication as it currently is in our slide, which is the current indication proposed by the Sponsor, which is 14 hours. I would suggest that you ask that question of the Sponsor.

DR. GOLDSTEIN: Okay, we can just remember that for later.

The second question is there was one quality of life measure, the Stroke Impact Scale, and we saw the 30 and 90 days. Did the FDA do any other analyses looking at quality of life outcomes with that data?

DR. GETZOFF: No, we didn't.

DR. HURST: Other questions?

Yes, Dr. Toledano.

DR. TOLEDANO: Thank you. So this is Dr. Toledano. I have a question for Dr. Miller.

At what point did you make CoAxia aware of your issues with the global outcome for effectiveness?

DR. MILLER: In terms of the use of the global test or in terms of the failure to achieve statistical significance after the fact?

DR. TOLEDANO: In terms of use of the global test as an endpoint.

DR. MILLER: That's something I'd have to check the review history of. I was not the statistical reviewer at the time. Typically, unless there's a significant concern, if the Sponsor proposes a primary effectiveness endpoint, it's up to them to take the risk if it's an appropriate endpoint or not, if they proposed it. If we had a significant concern with it, we might raise it. But if it's something that they feel strongly about, we can sometimes say well, that might not be a good endpoint. In this case, I don't believe that the endpoint was inappropriate. It simply didn't meet what they expected it to.

DR. TOLEDANO: Thank you for clarification.

DR. HURST: Dr. Hammon.

DR. HAMMON: John Hammon.

Since this study appears to me -- and this is a personal opinion -- to be biased toward a less robust outcome result because of the time in which these patients were studied, up to 14 hours, do you believe that this particular study should be held to the same statistical rigor that a study that was more acute and more apt to show any kind of good result from an

intervention?

DR. MILLER: So I guess I would answer that by saying that we would expect to see some evidence of effectiveness, regardless of the time period. Certainly, the Sponsor has argued that the long-term outcome through 14 hours should mitigate the magnitude, perhaps, of the estimated treatment effect. Nevertheless, I think that we still would like to see some evidence of effectiveness.

DR. EYDELMAN: If I just might add. The data is what the data is. We're here to present it to you, and we're actually looking for your input on whether you believe there's something else in the time frame that is not being evaluated by the statistical.

DR. HAMMON: Well, I would like to say that, in order for us to make that kind of a decision, we need to know some of the background information. And so the information that I would want is did the FDA insist on the 14 hours, or was that the Sponsor?

DR. EYDELMAN: We can get back to you on that. Oh.

DR. GETZOFF: Yeah, that was a modification to the protocol provided by the company, the 14-hour cutoff.

DR. HURST: Other questions?

Sorry, Dr. Goldstein.

DR. GOLDSTEIN: Yeah, Dr. Goldstein.

Just a point for clarification. In the FDA report that we got for

the time-to-treatment analysis, it said that there was no significant -- a statistically significant difference in the pre-specified analysis model, 0.817, and when it was divided between less than or greater than 5 hours, that there was no -- that there was also no difference. And it's on page -- it's under 10.2.1 in your document. But then, from the Sponsor, it looked like that there was some difference with this five-hour cutoff.

I'm just trying to understand, you know, what's different between the two analyses of this time-to-treatment effect.

DR. MILLER: So, effectively, what the first approach is, is looking at the -- if we take the Sponsor's GEE model, the covariate adjusted, and then add in the time from symptom onset as a covariate in that model, that's the p-value you get. It's not independently statistically significant after adjusting for the other covariates.

With respect to breaking it down by 5 and 6 hours, that's looking at, effectively, whether there's a significant interaction in terms of effectively saying, if you took an odds ratio for less than 5 and greater than 5 after you account for the 95% confidence intervals, those do not differ or diverge enough that they are significantly different. If you wanted specifics, I'd have to refer back to the Executive Summary and bring them up.

DR. GOLDSTEIN: Right. So I'm just putting these two things together, then. On their Slide 61, that's looking at a subgroup also with a different outcome, not the pre-specified full outcome, right? Because this is

their Slide 61. There's mRS 0 to 2 in these time-based subgroups. Your analysis is looking at the entire spectrum of their primary outcome for those two subgroups. Am I getting that right?

DR. MILLER: Yes, that's correct. So this is based on the global test. Slide 61 is based on the modified Rankin Scale 0 to 2.

DR. GOLDSTEIN: Okay, I got it. Thanks.

DR. HURST: No other questions from the Panel?

(No response.)

DR. HURST: All right, we'll now break for lunch. Panel members, please do not discuss or contact anyone at the meeting about the meeting topic during the break. This includes discussion amongst yourselves or with any members inside or outside of the audience. We'll reconvene at 1:00.

Thank you.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)

DR. HURST: We'll reconvene this meeting of the Neurological Devices Panel at this time. And we'll now proceed with the Open Public Hearing portion of the meeting.

Public attendees are given the opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda. Ms. Facey will now read the Open Public Hearing disclosure process statement.

MS. FACEY: 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.

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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. HURST: All Panel members have also been provided with written comments received prior to the meeting and have had the opportunity to review them.

There has been a request to speak by three people, the following: Richard Klucznik, M.D., representative for the Society of NeuroInterventional Surgery; Diana Zuckerman, Ph.D., President of the National Research Center for Women and Families; as well as one other individual.

Each speaker will be given approximately 10 minutes to address the Panel. Once you have been asked to approach the podium, please be sure to state your name, company, and any affiliation that you might have with the entities presenting today. At the completion of your 10 minutes, you will be directed to discontinue. Please adhere to this request.

And we can start with Dr. Klucznik.

DR. KLUCZNIK: Good afternoon. I'm here on behalf of the Society of NeuroInterventional Surgery, and I'm actually on the board of directors at the time, and I have no conflict of interest.

First, I was going to read the letter that we have in support of CoAxia.

On behalf of the Society of NeuroInterventional Surgery, I'm

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writing to you in regards to the upcoming Neurological Devices Panel meeting for the CoAxia NeuroFlo Catheter and its use in the treatment of patients with ischemic stroke.

SNIS is a scientific and education association with over 600 members worldwide and is dedicated to the advancement of neurointerventional surgery. Our membership draws from three subspecialties: interventional neuroradiology, endovascular neurosurgery, and interventional neurology. The unparalleled experience of our society is a driving force behind our desire for continued stroke treatment options.

Treatment options for the most common type of stroke, known as ischemic stroke, are limited, and very few patients have access to the key treatment. Left untreated, strokes are often debilitating and devastating for the affected patients and their families.

Currently, the only FDA-approved therapies include IV tPA and intravascular clot removal. Sadly, these devices are typically only available at highly specialized centers or comprehensive stroke centers. SNIS fully supports the development of additional safe treatment options for acute stroke with a device that allows flow augmentation as a reasonable adjunct treatment.

Several of our members, including me, have experience with the CoAxia NeuroFlo Catheter and have participated in the SENTIS study. The device is safe and easy to use, making it available to many more patients. The

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consensus of SNIS is that the authors of the study are correct in their assessment that the NeuroFlo Catheter appears to be safe and offers potential benefit in selected patients suffering from acute stroke.

It is important that the device be labeled for use in stroke specifically, so education can commence to hospital staff, referring physicians, and emergency personnel.

Thank you for your time and allowing our comments.

And on behalf of SNIS and myself, I really wanted to just show a couple cases, too.

We were in the trial that showed -- for the subarachnoid hemorrhage, and this is a patient that we treated. This coil is present. So this patient is in vasospasm. We were on the vasospasm trial. So you're wondering about does the device work. A picture is worth a thousand words at times. So this is extremely narrow, these blood vessels are narrow. On the left is the pre and on the right is the post.

So, clearly, there is a benefit to using this device. It does augment flow, and this is something visual that we see. You don't see it all the time in patients, but this is something you can see. There's no change in anything other than just the AP, and diameter are both the same. We store those so the pre and post match exactly and you can see that it does augment flow.

Here's what we're really talking about. This patient is visiting

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from Canada; an acute onset of hemiparesis. This is a carotid T lesion. This is a devastating lesion. The clot is at the top of the internal carotid artery. That's the pre. We go up and we try to restore flow. But not only do we restore flow, we use the FloControl, we use the NeuroFlo, because this patient has been at this -- when we got the patient, it was close to 6 hours already. So the time limit was running, and the patient's ready to have a devastating stroke.

Well, this is what it's all about. Three months later, this patient is able to mow his lawn. He's back in Canada, and we get a note that comes back to us from Canada saying thank you. This patient is doing well. And here's what he does. His son has a boat, and there he is out on the lake 3 months after an almost potentially devastating stroke. It is both.

It's not just able to get the clot, but it's able to retrieve -- I mean, to get that and restore flow.

And the last thing I'll tell you is just a case from this Thursday -- I mean this Friday afternoon. At 12:20 I took a phone call of a patient having an acute stroke. He's been waxing and waning. By 1:00 I've done the angiogram, and his carotid is occluded down below at the bifurcation. He doesn't have much collateral flow, he doesn't have a good ACOM and doesn't have a good PCOM. And he has flow that's not so good up in the parietal region on the left.

Well, what do we do? I can't get at it. There's no clot to go

after. He doesn't have much collaterals. So we used the NeuroFlo. His NIH stroke score was 9 on Friday afternoon, and this morning it was 3, and he got out of bed and he walked to the bathroom.

So to me, as a person, I call myself the plumber. I'm the one who goes and does it and gets these things out and uses these devices. The NeuroFlo is easy, and we don't want to lose this device. It's something that we use as an adjunctive treatment. Our stroke neurologists are in tune to this device. They ask us almost every single time that we have an acute stroke whether we want to use it.

Someone asked how many times do we use this a year. We use about three to four a month, actually, now at our institution. So to give you an answer, just at our stroke center, we were one of the first ones that got the comprehensive stroke center designation in the United States, and our stroke neurologists are in tune to it, and we want to use it, and it helps and benefits our patients.

Thank you.

DR. HURST: Thank you, Dr. Klucznik.

Dr. Zuckerman.

DR. YTTRI: Actually, I am Dr. Jennifer Yttri, and I'm pleased to speak here on behalf of myself and Dr. Diana Zuckerman, who was unable to attend. And I am representing the National Research Center for Women and Families, and we do not have any conflict of interest in this case.

Our nonprofit research center analyzes and reviews research on a range of health issues and provides objective, understandable information to patients and providers.

My doctorate is from Washington University in St. Louis, and Dr. Zuckerman's perspective is as a former faculty member at Vassar and Yale and a research director at Harvard. Dr. Zuckerman was trained in epidemiology at Yale Medical School.

Our center is an active member of CUE, Consumers United for Evidence-based Healthcare, which is part of the U.S. Cochrane Center at Johns Hopkins School of Medicine.

Our perspective is to focus on meaningful data, scientific evidence of real benefits and risks. And we urge you to do the same at today's meeting, focusing on the outcome measures that mean the most to patients: survival and quality of life.

The primary safety endpoint for the clinical trial presented today was a comparison between the treatment and control groups in the incidence of serious adverse events from the time of enrollment through 90 days of follow-up. The SENTIS study did achieve its primary safety endpoint by demonstrating no statistically significant difference in the number of SAEs between the NeuroFlo and control groups.

However, the FDA scientists stated in their summary that serious and non-serious adverse events, including, but not limited to, new

fatal stroke with hemorrhage, limb ischemia necessitating amputation, aortic injury, and hematoma, were determined to be device or procedure related by an independent DSMB. The SENTIS study did not have a significant benefit to patients with the primary or secondary efficacy endpoints, including faster and better recovery or survival.

From the scientific perspective, the results are not surprising. The NeuroFlo device works to create a block in blood flow and allow blood to be diverted into the upper body and potentially the brain. The only way this NeuroFlo device could have had a measurable change would have been to see an increase in cerebral blood flow, something that was not measured in the SENTIS trial but easily could have been, as we have seen data today.

But let's think about the device's utility from a theoretical standpoint.

In the best-case scenario, the device would change blood flow in the brain with or without any confirmed benefit to stroke patients, at least in the data presented to the FDA. At worst, the device would cause vessel rupture, potential brain hemorrhage, another stroke, and potential failure of lower body organs such as the liver and kidneys, adverse events that were reported with the SENTIS trial. Thus, the clinical utility of the NeuroFlo device for the SENTIS subject population should be carefully assessed, considering both the lack of benefits and increased risks with an unnecessary procedure.

The goal here should be a better outcome, not an outcome that

is not significantly worse, but where there are very serious risks that might be significantly worse in a larger sample. Today's meeting is especially important because it will set a precedent for other decisions that the FDA makes. Lives are at stake.

The law requires that the FDA have two different pathways to approval for medical devices, which we've heard about today. The PMA pathway is similar to the one for prescription drugs and requires scientific evidence of safety and efficacy. Only high-risk devices, those that are implantable, life-sustaining, or potentially lifesaving, are reviewed through the PMA process.

The 510(k) process is different. Those devices must be substantially equivalent to other medical devices on the market, which are called predicates.

As the FDA has explained, medical devices submitted for 510(k) clearance for which no suitable predicate was identified can be reviewed through a third pathway, the de novo review, which, to quote the FDA, "allows moderate-risk devices without a suitable predicate to be reviewed with adequate special controls."

We don't believe that this device, used for the treatment of acute ischemic stroke within 14 hours of symptom onset, is a moderate-risk device. Since people's lives are at stake, we believe it is a high-risk device and therefore should not be approved through a de novo review. And given the

ambiguity of the research results, we believe this potentially lifesaving or life-threatening device absolutely needs to be held to the higher standard of a PMA review.

I'd like to mention that our center's president is on the board of directors of two nonprofit organizations that are dedicated to providing needed resources to the FDA, the Alliance for a Stronger FDA and the Reagan-Udall Foundation, which was created by Congress to provide support to the FDA.

We are dedicated to ensuring that the FDA has the resources it needs to do its job to make sure that all medical products are safe and effective.

Allowing a lifesaving device that is not eligible for 510(k) review to go through a de novo review process sets a dangerous precedent under any circumstances, it is even more worrisome when the data do not clearly indicate that the device is beneficial in saving the lives or improving quality of life in the target population.

If this Advisory Committee supports a de novo review for this product, and if it determines that these ambiguous research results are not great but good enough to recommend approval, patients will be harmed. The harm is because of the potential risks, such as new fatal stroke, but also because of the cost of approving a device despite the lack of evidence of any benefit to the lives of patients.

Your task today is to determine the risks and benefits based on the research that is available. More than that, the FDA has asked you to determine if the existing data is sufficient to support a de novo application. And that decision will have implications for FDA's use of de novo reviews for hundreds of other devices in the years to come.

Based on the data, not on subjective opinions or even limited clinical experience but on the actual data itself, it is clear that more research is needed. This device should not be approved for acute ischemic stroke during the first 14 hours until research clearly shows a benefit to patients' lives. It therefore requires PMA review with better safeguards to save these patients.

Thank you.

DR. HURST: Thank you, Dr. Yttri.

Dr. Jovin from the Society of Vascular and Interventional Neurology.

DR. JOVIN: Thank you for allowing me to speak. My name is Tudor Jovin. I represent the Society of Vascular and Interventional Neurology, whose vice president I serve as, and I have no conflicts to disclose.

This is a letter that we have submitted, and as per the request of the FDA, we are asked to read here today.

I am writing on behalf of the Society of Vascular and Interventional Neurology, a medical society with more than 200 members

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dedicated to the treatment of neurovascular disease, regarding the upcoming Neurological Devices Panel meeting for the CoAxia NeuroFlo Catheter and its use in the treatment of patients with ischemic stroke.

SVIN is a medical society dedicated to the advancement of treatment of neurovascular diseases, which include ischemic stroke. Our membership is largely comprised of stroke neurologists, who are subsequently fellowship trained as neurovascular interventionalists. We share a basic background in vascular neurology, with a strong desire to improve long-term outcomes through acute interventions and treatment of stroke-related conditions. We are focused on medical evidence but recognize the need for new innovative treatments.

Ischemic stroke is a condition for which few treatment options exist. Fewer than 5% of ischemic strokes receive thrombolytic therapy, and there are limited options for patients who often have disabling and devastating outcomes.

Restoration and augmentation of cerebral blood flow is the primary acute treatment for ischemic stroke patients. It stops the spread of the infarction and saves brain. IV tPA and intravascular clot removal provide revascularization and have made a great impact but, to date, only reach 2% to 5% of patients. Therefore, different methods are needed to augment cerebral blood flow as those that are currently available have associated complications that severely limit their use.

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In our view, the CoAxia NeuroFlo device represents an important new technique for augmenting cerebral blood flow in ischemic stroke patients. Many of our SVIN members, including myself, participated in the SENTIS study, based on their interest in the technique and their support for the randomized trial design. A number of SVIN members are included in the SENTIS steering and publication committees. We are thus familiar with both the safety and outcome results from the SENTIS study.

The board of the SVIN believes that the SENTIS trial was well run and that the trial results support the use of NeuroFlo in select patients with ischemic stroke. The board believes that the NeuroFlo device does lead to flow augmentation, based on the available data, without significant risk to patients. To this end, it may be a reasonable option for some patients suffering from stroke, and its availability for clinical use is warranted.

Thank you for your time and for allowing our comments. We look forward to hearing the FDA's decision based on the upcoming Panel meeting.

And I'd like to give some personal perspective to this. I am a stroke neurologist and interventionalist. I am an associate professor at the University of Pittsburgh, where I direct the stroke center, which is one of the largest stroke centers in the country. We admit about 2,000 patients with stroke every year, and for the last 12 years I've dedicated my practice to treatment of stroke patients, not only from a medical standpoint, but also

from an interventionalist standpoint. I consider myself, first and foremost, a stroke neurologist and then a neurointerventionalist.

And over the years, it's been very clear to me that there are a lot of patients out there with stroke, whose natural history, whose outcomes on currently available treatment methods are poor, who are in need of treatment alternatives. Most of these treatment alternatives involve augmentation of blood flow to the brain. And yes, we have tPA, and yes, we have endovascular recanalization techniques, but we need other options, because even when patients present to the hospital in due time, many times these treatment options are just not available or indicated.

More importantly, in the absence of these new techniques, we resort to treatments that are unproven to be beneficial but proven to have significant side effects, such as pressor therapy, for which really there's not much proven benefit. And this is, right now, the only alternative we have to flow augmentation techniques.

I think that the SENTIS trial data is compelling in terms of safety. There are strong signals, in my opinion as a stroke neurologist and academic neurologist, that there are stroke signals in there that this device works, and it would be important for our patients to be able to offer them this novel treatment.

I respectfully urge the FDA Panel to give this treatment method a favorable consideration.

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Thank you.

DR. HURST: Thank you, Dr. Jovin.

And I've been asked by the FDA to emphasize that the comments that Dr. Jovin presented were presented in written form, that the only way they could have been read was to have someone come and read them; i.e., the FDA did not request that they be read. They were submitted in written form.

Thank you.

Does anyone else wish to address the Panel at this time?

(No response.)

DR. HURST: Okay. Does the Panel have any questions for the Open Public Hearing speakers?

(No response.)

DR. HURST: Very good. I now pronounce the Open Public Hearing to be officially closed, and we'll proceed with today's agenda.

We'll now begin the Panel deliberations structured around the FDA questions. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair.

First, I'd like to address the issue of questions to the FDA or to the Sponsor, from the Panel, some of which were at least present this morning and we didn't get a chance to address.

Do any of the Panel members have questions?

Dr. Eydelman.

DR. EYDELMAN: I believe the Sponsor is ready to address the questions which were left over from this morning.

DR. HURST: Would the Sponsor like to go ahead and address that now, please?

MS. KVISTAD: Thank you, Panel.

Before we begin, I'm going to actually issue some clarifications for maybe some misconceptions or misinterpretations that happened earlier.

During Dr. Saver's presentation, he incorrectly stated that time to enrollment in the study was 18 hours. It was 14 hours.

There was also a question regarding our interim analysis and if that information had been provided to anyone outside of the company or to investigators. The answer is no, the interim analysis that was conducted was provided only to FDA and to the reviewing DSMB. However, according to FDA regulations, we do provide all participating sites with routine updates on safety. So they did receive those safety updates, but no effectiveness updates for that interim analysis.

And also just as a clarification for Mr. Layton. You had asked a question about cerebral blood flow in our labeling, and I'll actually help with that. Our current FloControl labeling, which is our 510(k)-cleared device, the indication statement for that device states that the FloControl Catheter is

intended for use in selectively stopping or controlling blood flow in the peripheral vasculature, which includes the descending aorta.

When the descending aorta description was added in 2009, at that time, that label was also modified in the device description, not in the indication section, but in the device description, to add that when used in the descending aorta, balloon inflation results in the diversion of cardiac output to the upper torso and core organs, for example, cardiac, spinal, and cerebral vasculature.

So this specific statement is not part of our indications, but it all plays into the device's intended use.

That's the end of the clarifications, and I will turn it over to --

DR. SAVER: Thank you.

So we have some of the data that was requested, that we said we'd come back with in the afternoon.

One question was the results of the intention-to-treat analyses in the pure intention-to-treatment population versus the modified intention-to-treat population. And here's that data. And it's probably too small to see, but it shows that the results were the same. In general, the results in all three populations, intention to treat, modified intention to treat, and modified as treated, were consistent with one another.

As mentioned, the odds ratio point estimates are slightly more favorable to NeuroFlo, in general, in these pure intention-to-treat analyses

because excluded patients tended to do better than the patients in the control group. But, overall, they did not differ in a significant way from the included patients in the modified intention-to-treat analysis.

This also speaks to the number of additional analyses submitted, which we were asked about, and the general direction of those analyses, about 70% to 80% in favor of the NeuroFlo device.

Here's the results for safety, in addition to the results for effectiveness in the ITT group.

Another question was with regard to the pattern of the time from onset to treatment effect, was that it only magnified at the beginning of the time window or where there were bumps along the way. And here's a Forest plot showing that it was a pattern of magnification in the earliest time periods, and the effect was attenuated along the way, still remaining favorable. But there were not subsequent bumps. It was left shifted.

We were also asked about quality of life data, and as mentioned, the Stroke Impact Scale was an outcome measure in this study. Here's the data for the Stroke Impact Scale, the point estimate of 2. This is on a 0 to 100 scale, looking at physical functioning domains of hand function, strength, activities of daily living and self-care as quality of life measures, 0 being no useful quality of life, 100, full quality of life. And the point estimate slightly favored treatment, but was nowhere near statistically significant.

But it's important to point out that this analysis that you have did not include the patients who died. They were censored from this analysis. Over the lunch period, we added those patients in using the convention of assigning the worst possible score, 0, to the patients who were not alive for quality of life, and here you can see, at 90 days, a median score of 70 with treatment versus 62.5 with control. And that's a p-value of 0.06 for the difference between the two groups.

Now we're going to bring Chris up to speak about the statistical aspects.

MR. MULLIN: Hi, I'm Chris Mullin, a statistician and paid consultant to CoAxia. I have no financial interest in the company.

One question that came up was on the difference of methodology and tests for mortality. So there were tests based on the log rank statistic. We also did tests over lunch for Fisher's exact test. You can see all-cause mortality, a p-value of 0.12. I think that compares with the 0.08 or 0.09 from the log rank test. Stroke-related mortality, we had a p-value of 0.01; essentially the same from the prior analysis. This test helps to address potentially smaller sample sizes.

Covariate analysis. There was a question on age as a continuous outcome. I apologize; this is a little hard to read. So in the material submitted to the FDA, there was some multi-variable modeling performed. And you'll see that the second row of this model has age as a

continuous parameter with a point estimate and odds ratio of slightly less than 1. So the interpretation is, as age increases, the odds of success decrease. But this is as part of an overall adjusted model. Here you see the treatment effect, 1.17, in favor of NeuroFlo.

Some other covariates included in this model were baseline NIHSS, glucose at presentation, gender, and time from symptom onset.

Now I'd like to turn it over to Dr. Helmi.

DR. LUTSEP: Another question revolved around the creatinines themselves, rather than just the serious adverse events involving them. And the values are shown first for the baseline presentation. You can see that they were the same in the treatment and control groups, both creatinines of 1. At 24 hours, they were also no different. The mean creatinine was 0.9 in each group.

We also had a slide for BUNs, as well, which may have escaped. There it goes. Again, there's no difference in the treatment and control groups here as well, the 24-hour period.

And then there were questions regarding safety, specifically in the older populations. So, first, here are the serious adverse events in those subjects that were 70 years of age or older. In the top line you can see the summary of any serious adverse event. These did not differ in the treatment and control groups, and then likewise in the patients that were 80 years of age or older. If anything, there was a trend toward fewer serious adverse

events in this older population. The general theme was similar to that that we showed in the study as a whole.

And I will now turn this over.

DR. POSNER: This is Dr. Posner.

Your pulmonary events, what were they? You list events as pulmonary events, but what were the events? Were they pulmonary edema?

DR. LUTSEP: So the main serious adverse event was flash pulmonary edema, and it occurred twice in the same patient while she was on the table. She was later found to have a reduced ejection fraction, which was unknown at the time that she was enrolled.

DR. HURST: Sorry, go ahead.

DR. NOGUEIRA: That timely brings us to the next topic, which was a question about any hemodynamic change in blood pressure, heart rate, changes related to the treatment.

First, just going over that swine model that was presented, those swine subjects were studied with cardiac output measurements via thermodilution as well as pulmonary capillary wedge pressures. And you can see here, there are actually no significant changes throughout the course of the treatment.

In terms of the blood pressure in the swine model, again, you don't see any significant changes throughout the course of the treatment. This is the pressure in the infrarenal balloon and the pressure in the

suprarenal balloon; a little bump, but nothing significant. And that's exactly what you saw actually in the SENTIS dataset.

What you have here is the analysis of the first 71 patients. We can provide the whole cohort at a later time. We couldn't have the analysis, but that shouldn't be any different.

So you can see here both suprarenal and infrarenal pressures at baseline. Infrarenal/suprarenal balloon inflation. You can see that, essentially, the systolic pressure was maintained in these patients. Actually, these are maps throughout the course of the treatment.

We also have data comparing baseline, 6 hours post-treatment, 24 hours post-treatment, comparing the treatment versus the control. You see here mean, median, and range are pretty compatible between the two groups at baseline, 6, and 24 hours, in terms of heart rate, systolic blood pressure, and finally diastolic blood pressure.

So we do not feel that there are any significant changes in terms of blood pressure or cardiac work with the NeuroFlo device profile, a very favorable hemodynamic profile.

I think this is importantly -- it's specifically important to acknowledge facing the other alternatives you have to turn to. If this device is no longer available to us, we can't just watch a patient with a progressing stroke, an evolving stroke, losing neurons in front of us. So if you don't have NeuroFlo, you have to turn to intravenous phenylephrine and induced

hypertension, which has significant pulmonary and cardiac side effects, as we all know.

Thank you.

DR. HURST: Thank you.

Do any of the Panel members have questions for CoAxia?

Yes, Dr. Zhou.

DR. ZHOU: Well, just to be on the record because my questions, I think, have not been answered on the rates, which is very important about interpretation of your beta treatment parameters, you know, logistic regression, which is on your statistical analysis plan.

On page 16, you defined beta treatment as a log odds ratio. So I take that as the beta treatment is a population odds ratio. So if that's the case, I don't think you can derive that based on the condition of the logistic regressions you give on the page 15. So on the page 15 you have logistic regression, but you ask for covariates. So if you have a covariate in your logistic regressions, the beta treatment is conditional odds ratios, conditional on the covariates. So that will not give you the overall odds ratios.

So actually the results you show us don't have the overall odds ratios. I want you to comment on that because that's very important for the results.

MR. MULLIN: Chris Mullin, statistician. I'll do my best to answer your question, but I think it's a rather complicated one.

So we used the GEE model logistic regression. So that fit with an iterative process where you have a working correlation structure, compound symmetric for this case, and it's iteratively fit with primary estimates. So there's a beta term for treatment group, and that's produced with this iterative method, the GEE. When that converges, we get a point estimate, and we can use that as an estimate of the odds ratio. My understanding, tenuous as it is, is that it's a marginal interpretation.

DR. ZHOU: Well, it's marginal, it's a population average, it's still conditional. So the marginal is a contrast to the random effect. So that's what marginal means for the GEE approach. But it still is a conditional average. In other words, it's conditional of the covariates you have.

So, for example, if the covariate is a male. So the beta is the expression of odds ratio among the male or female. So they don't give you the overall odds ratios.

MR. MULLIN: Okay.

DR. ZHOU: So marginalizing, I mean, there may be some -- the marginal here in the GEE approach is the subgroup population average. So instead of the random effect, more of the people have to be used to deal with the correlated data.

So I think, in order to get the overall odds ratio, you have to integrate out the conditional odds ratio for all the possible values of the covariates, which you can do it, but I don't think you show it here in the

results.

MR. MULLIN: So just maybe a little more comment. I think both FDA and CoAxia, I think, had an agreement on the method. Practically speaking, the estimate comes out of the software that we use. So the odds --

DR. ZHOU: I understand. But the software don't give you the model interpretations.

MR. MULLIN: Correct. In terms of marginal versus conditional.

DR. ZHOU: Exactly. And I mentioned that today, also.

MR. MULLIN: Yeah. We do have, you know, a great many supportive analyses not using the GEE model; for example, mRS. There were two of sliding dichotomy. There are another whole set of analyses, and those odds ratios are all consistent with the overall primary global endpoints.

DR. ZHOU: So when you do the alternative analysis, what model did you use?

MR. MULLIN: So those would've been just logistic regressions themselves.

DR. ZHOU: Yeah, if you use a logistic regression as the -- as long as you use a logistic regression with covariate adjustment. If you don't have a covariate adjustment, it's okay. But if you put a covariate adjustment into the logistic regression, the beta for treatment won't have a conditional odds ratio interpretation.

MR. MULLIN: Okay. So we also have presented unadjusted

odds ratios. Those are slightly more attenuated to the null.

DR. ZHOU: Yeah. So if you don't have a covariate adjustment, then you can interpret the beta treatment as an overall odds ratio.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Yeah, Dr. Goldstein.

Helmi, could you tell us what the renal SAEs were? Because you showed us that there was no difference, overall, in the entire group in BUN or creatinine. But what constituted a renal SAE? Because they were about -- it was significant, but they were about double, at least numerically.

DR. LUTSEP: Yeah. So the renal SAEs occurred often much later in the time course. Many of these patients were readmitted, therefore creating the SAE by itself. So things like dehydration, you know, failure to thrive, used loosely, would cause these patients to come in and develop that diagnosis. So I think that was probably the most common cause. We also had one with the urosepsis and another ill one, but I can't remember the details of it. But those were the kinds of things, but usually later, not in those first few days.

DR. GOLDSTEIN: And the other question about the -- thank you for showing the data on the physiologic monitoring. What I was asking about, though, is during the period of the procedure, not before and 6 hours afterwards.

DR. NOGUEIRA: So the initial part that we demonstrate,

actually this is intra-procedural measurement, so going from baseline throughout the whole procedure until balloon deflation. So as you can see, there is no meaningful change in the mean arterial pressure above the balloon, which is a good reflection of what you get from, for instance, a radial A-line. I actually have correlated both in other patients.

So I hope that answers the question.

Thank you.

DR. SUNG: And I'm sorry. Why were there only 71 subjects?

DR. NOGUEIRA: So that's the analysis that you could put together in the one-hour break that you had. We'll be glad to provide the complete analysis. We don't expect it would be any different than this. Oftentimes this is what you see when you treat these patients. We don't really see any big variations in the map.

DR. SUNG: And then can we go to the next slide?

DR. NOGUEIRA: Sure.

DR. SUNG: So, actually, I guess I missed this when I read the paper, too, is that the range of the blood pressures is quite significant. The diastolic is as low as 33 and as high as 169.

DR. NOGUEIRA: So this is heart rate. So let me go to -- do you want systolic or diastolic blood pressure?

DR. SUNG: Oh, I see.

DR. NOGUEIRA: This was heart rate.

DR. SUNG: The diastolic. Yeah, 33 to 169. So patients whose diastolics were 33 were treated? And as high as 169?

DR. NOGUEIRA: Exactly. Those are like baseline. One would expect that a lot of these patients probably had divergent blood pressures from chronic hypertension, so stiff atherosclerotic vessels giving divergent blood pressure, I expect, because the criteria was based on mapping systolic. So we didn't hold treatment for somebody with a low diastolic if they had a good map. And you can see it's kind of compatible with both groups. And those are, of course, the outliers.

DR. GOLDSTEIN: You really had patients with diastolics at 169?

DR. SAVER: I suspect that these are baseline readings that separated with some point in time from the moment of randomization and certainly a lot of time from the moment of treatment. And there were a few outliers that you're seeing at the extreme ends of the range. But if you look at the means of standard deviations, the great majority of the population was about where you'd expect them.

DR. SUNG: It's probably too late now, but it would be, I think, important to know how many patients were at the far ends of these, of the range for these, even though admittedly there seems to be equal distribution between the control and the treatment groups. But those are pretty extreme ranges.

DR. HURST: Dr. Posner.

DR. POSNER: Dr. Posner.

I was also under the impression that you excluded people that had hypertension and blood pressure issues from the study. I thought that was one of your exclusionary factors.

DR. SAVER: I think we excluded patients with a systolic blood pressure exceeding 220, but I don't recall that we had a diastolic blood pressure exclusionary criterion.

DR. POSNER: It's hard to imagine a diastolic of 170 and a systolic much --

DR. SAVER: I concur. That's why I would not put too much weight on that single outlying value.

DR. HURST: Dr. Furie.

DR. FURIE: Can you also go back to the slide on renal function? So, again, it looks like -- is it correct that patients with creatinines up at 8 or 9 were in?

DR. LUTSEP: That's a good point. They were supposed to be excluded with renal insufficiency, which I believe was two times the lab normal. Uh-huh. So I can only hope that those were converted appropriately. We did have some European patients with different units.

DR. FURIE: Thank you.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: Thank you.

If someone from CoAxia could please give me the relationship between output among output, pressure, and flow. And think while I read these two pieces from your device description K090970.

"When used in the descending aorta, balloon inflation results in diversion of cardiac output to the upper torso and co-organs, e.g., cardiac, spinal, and cerebral vasculature."

So you've got output going to the cerebral vascular -- vasculature. Sorry. And your IFU, your proposed IFU, wants to say that you increase cerebral blood flow.

So please tell me about output, pressure, and flow.

DR. NOGUEIRA: That's a great question. Oftentimes we hear about that.

So, essentially, the device does not increase cardiac output or cardiac work. What it does, it simply -- it redistributes the blood flow from the lower body to the upper body. And essentially what you have in the upper body is a bunch of high-resistance systems. You know, your muscles are high resistance. The lower-resistance system in the upper body is the brain, so most of the blood would be diverted to the brain. And that happens at no increase in systolic blood pressure, mean arterial pressure. So it's essentially no increase in cardiac output and a shift of that cardiac output from the lower body to the low-resistance system in the brain.

DR. TOLEDANO: And how do you know -- sorry. Dr. Toledano

again. How do you know that it actually flows once it gets there?

DR. NOGUEIRA: So I hope you could show all of those imaging studies. I have to tell you, I've been doing this for some time, angiography and TCD measurements. We do this in the ICU. When you do induced hypertension, when you do other therapies, it's very hard -- and I think I'm sure there are members in the Panel that have similar experience -- to actually see that type of effect that you have shown with a twofold increase in the mean and peak systolic velocity by simply inflating a device in the descending aorta. So I think that's quite dramatic.

The other point that I would like to make, I think Dr. Noonan made that point, in terms of the angiographic aspects, in terms of how hard you inject. So I can't talk about the first angiogram. I don't know if that was a machine injection. But the second angiogram was actually a machine injection from the aorta, doing a parenchymogram. So there should be no variation in terms of the angiographic technique between the baseline and the post-procedure example.

DR. HURST: Dr. Posner.

DR. POSNER: This is Dr. Posner again.

What you're doing by inflating the balloon is basically causing a coarctation of the aorta. And when you say mean arterial pressure, where are you measuring it? It's going to be different above the balloon and below the balloon.

When you say there's no change in work of the heart, there's definitely change in work of the heart because it's pumping against a higher resistance, which is the balloon, unless you're measuring a reduced resistance of the brain and the upper musculature. You also aren't taking into account what's happening to the heart rate, the stretch receptors in the ventricle, the receptors in the carotid sinus.

So unless you've measured these things -- and I'm not saying what did happen or what didn't, but you have to have measurements to say there's no change in work of the ventricle. You don't know that. Intuitively, there should be an increase in work in the ventricle because that's what you get in coarctation of the aorta and that's why you fix coarctation of the aorta.

DR. NOGUEIRA: I think probably there is a difference between something that's transient, like a procedure like this, where again the idea here is to do a recruitment maneuver of the collapsed micro-circulation collateral channels versus somebody who has an aortic coarctation. I think that's the first point.

The second point is I can only answer the cardiac work question by showing what's the thermal dilution cardiac output data on the swine. Unfortunately, for ethical reasons, Swan-Ganz didn't really go into these patients.

One thing I can tell you, because I have done this several times,

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is the suprarenal balloon pressure correlates with the radial A-line perfectly. It's like the exact same map with minor variations, if any. So I do believe that reflects your mean arterial pressure very well. That's the infra --

DR. POSNER: I'm sorry. It should, because that's upper body.

DR. NOGUEIRA: Exactly.

DR. POSNER: What goes down into the arm is above the balloon, so that's going to be what you're getting there. But the pressure below the balloon is going to be way down.

DR. NOGUEIRA: Oh, so that's actually measured as well, and that's this pressure here. And the whole premise of the balloon -- and I'm sorry if I didn't make that clear -- is to aim for the pressure gradient of 10 mm/Hg to 15 mm/Hg between the upper measurement and the infra measurement. That's how you titrate the effect. That's how you know you have enough of a blockage to shunt blood. Your question makes perfect sense to me, and I hope what I said answers it.

DR. POSNER: Yes, thank you, the titration.

DR. NOGUEIRA: Exactly.

DR. POSNER: Thank you.

DR. NOGUEIRA: You're absolutely right. Infra is lower, upper is higher, and that's how you titrate the effect, a 10 mm to 15 mm difference.

DR. HURST: Other Panel members?

Dr. Furie.

DR. FURIE: Just to follow up on the previous question about blood flow. If you have either extracranial or intracranial large vessel stenosis, would you consider that still a low-resistance system and see the same effects on flow, or would that confound the effects of augmenting the perfusion pressure?

DR. NOGUEIRA: So that's a great question. I think, at the site of stenosis, yes, you'd have a high-resistance focal lesion. But these patients, actually they exhaust their autoregulations distally, right, by vasodilation to the maximum extent that they can possibly do. If anything, I would think it's even a lower-resistance system, distal to the site of occlusion, which is typically a focal site.

So I think, globally, it's more like a distal in a low-resistance system and you're attacking it through the periphery, coming kind of bypassing the occlusion, so coming more like in a centripetal way in relation to the ischemic tissue.

DR. FURIE: This is Karen Furie again.

Do you have any data on the actual vascular pathology in the study?

DR. NOGUEIRA: I believe you do have -- do you have TOAST in some of these patients? You know, we do have atrial fibrillation and the incidence. They all had cortical findings. We have cardioembolic versus atherothrombotic strokes. But I would like to confirm that with other people

that were more knowledgeable about it.

DR. HURST: Dr. Noonan.

DR. NOONAN: I'd like to rephrase that question, if I could. Do you have actual data of which vessels in the brain were occluded or stenosed or thrombosed?

DR. SAVER: On that we do not. As mentioned, only a non-contrast CT was required for imaging before study entry. And the procedure itself required only the manipulation of the aorta. There was no requirement for a diagnostic catheter angiogram to be performed. So we do not have systematically collected data on the site of occlusion intracranially.

DR. NOONAN: And you don't have any data on whether flow to the head actually increased, by imaging?

DR. SAVER: We do not have systematically collected and analyzed data. We did collect some studies on an opportunistic basis at some sites. We also have shown some of those individual cases, but we don't have systematic data on the changes in cerebral blood flow.

DR. HURST: Dr. Layton.

DR. LAYTON: Just a point of clarification to Alicia.

To a biomedical engineer, or myself, cardiac output is flow rate. It's flow. It isn't pressure.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: Kris Mattivi, the Consumer Representative.

I'm just wondering if in your analyses you looked at outcomes by gender or race.

DR. SAVER: We did, and there were not important interactions of gender or race or ethnicity with outcome.

DR. HURST: Other Panel members, questions for CoAxia?

Yes, Dr. Toledano.

DR. TOLEDANO: So thank you. It's Dr. Toledano. I have one question that wasn't answered, and Chris would be the one.

I asked you for the number of analyses that you did for all of these post hoc things, and you pointed me to Appendix J, which lists the results of various subgroup analyses. There's no one number that says we did 20, 40, 100, 27 million post hoc subgroup analyses.

How many?

MR. MULLIN: Chris Mullin.

I don't know how many. We didn't have someone with a clipboard writing down each analysis that was done. I know it wasn't 27 million. There was the analysis that was done in the protocol. We did the pre-specified analyses, and that included a number of sensitivity analyses that I think are standard for clinical trials, including analysis of different populations, analysis of subgroups. And when I referred to Appendix J, I was referring to the larger clinical report. So I think that gives you a sense of how many.

And I think our point in all of this is that the overall results are not as high as we had hoped, in terms of favorable treatment effect. But overall trends on the order of 70% to 80%, the odds ratios of treatment effects favoring NeuroFlo.

There is an issue, I think, with how to control the Type I error, and there are some complexities. A lot of that is due to the lack of independence of tests, because you have multiple populations with a lot of overlaps, and there's a lot of correlation. That doesn't inflate the Type I error as much as it would if you had, for example, 27 million independent tests.

So I don't have an answer to the question exactly, but we've provided, I think, our sense of the data. And I think the clinical motivation was really the rationale for a lot of what was included in the slides. The slides were also high level, so we didn't mean to sub-select the most extreme results in the presentation and mislead the Panel in that way.

DR. TOLEDANO: Thank you.

DR. HURST: Yes, Dr. Posner.

DR. POSNER: Just one more question, and it's another definition as opposed to flow perfusion.

In coronaries, when you have an increase in perfusion, it's a reperfusion event. So when we blow up a balloon in a coronary and then we let it go down, there's reperfusion, and there's a lot of stuff washed downstream. And I wonder if you saw any adverse events within the first 1 to

15 or 20 minutes, such as some seizures or other things that might've been from potassium or things being flushed downstream.

DR. LUTSEP: I don't know. We've got lists of this. I don't recall particular things like that. It is muddied a little bit by the fact that some of the patients did receive sedation as part of the procedure. So I do recall that there were some patients that were either a little bit confused or a little bit nauseous, but I think we ascribed that more to the medications and didn't suspect the procedure.

DR. HURST: Yes, Dr. Hammon.

DR. NOGUEIRA: I would think that a lot of the mechanical effects of the balloon inflation/deflation are reflected in the distal bed, so the lower body as opposed to the cerebral vasculature. I just wanted to mention that.

Thank you.

DR. HAMMON: John Hammon.

This morning I asked about quality of life, and you said you were going to see if you could find some. Any luck?

DR. SAVER: Yes, I showed two slides on that. We can go back and show them again. It went by very quickly at the beginning, when we first sat down.

So here, the quality of life measure was the Stroke Impact Scale, the SIS-16. It looks at physical functioning quality of life items,

strength, hand function, ADL, and self-care as reported by the patient. Here are the 30- and 90-day outcomes; no differences between the groups among survivors. The scale is from 0 to 100, 100 being high optimal quality of life, 0, no quality of life, a 2-point difference not reaching statistical difference in favor of treatment.

When you assign to the patients who died a quality of life score of 0, that convention for handling the deaths, then the median score at 3 months was 70 in the treatment group and 62.5 in the control group, and that was a difference nominally significant at the 0.06 level.

DR. HAMMON: And just for a point of clarification, this is something that the patient told you or filled a form out or whatever?

DR. SAVER: Yes, this is patient-reported outcomes. If the patient was aphasic, otherwise unable to themselves report, then a proxy reports who knows them well.

DR. HURST: Yes, Dr. Zhou.

DR. ZHOU: So I have hopefully a final question.

You have missing data in this dataset, your analysis, and I noticed you are using a technique called a last observation carried forward. As we know, in the statistical literature, this is bad method for deal with missing data. There are much better methods available there, like multiple imputation, weighted GEE.

Have you tried more appropriate statistical methods to handle

missing data and then are you going to get the different results?

DR. SAVER: Let me make a comment about the last observation carried forward. In general, it's a technique for stroke trials. And then Chris can speak to whether we did multiple imputation or other approaches.

But in acute stroke trials, the last observation carried forward remains not a great technique, but the directional effect is different than in usual clinical trials. In usual clinical trials, patients get worse over time, and last observation carried forward imputes a better outcome to patients than they actually have.

In acute stroke trials, patients are worse when they have the stroke, and over the 3 months of observation, they tend to get better, so last observation carried forward is a very conservative approach in an acute stroke trial, and it imputes poorer outcomes to most patients than they're likely to have.

That said, it's clearly not the best approach; multiple imputation would be better, and Chris can speak to whether we undertook that or not.

DR. ZHOU: Actually, can I say that that's actually not true; only true if you are assuming that effect over time, then you can treat them in a control group. If the effect of the treatment over time is different between the control and the intervention, then the direction of the last observation carried forward will not clear because one situation you can imagine that, in

your intervention group, the effect of time is more dramatic than in the control group. Dramatic, going faster.

DR. SAVER: In general, with acute stroke, patients survive their acute period and then improve through 3 months and are physiologically seen -- it's absolutely true, statistically, but the physiologic expectation is if they survive with a little better brain, that's going to have the greatest impact; as they improve, they'll make use of that recovered brain and do better over time.

So you would expect, from physiologic principles, last observation carried forward is going to attenuate treatment differences rather than magnify them in an acute stroke trial. But, again, I'm not defending it as the best approach.

DR. HURST: So the question is for CoAxia?

DR. ZHOU: I think he has answered the questions. Do you have an alternative approach, though?

MR. MULLIN: Well, no. Chris Mullin.

The only missing data analysis we did was the one discussed with FDA, the pre-specified last observation carried forward, so we did not do multiple imputation.

DR. HURST: All right, if no other questions for the CoAxia people, any questions for the FDA from the Panel members?

(No response.)

DR. HURST: No. Very good. All right.

At this time, we'll focus our attention on the FDA questions, and copies of those questions are in your folders. I want to remind the Panel that this is a deliberation period among Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations we heard this morning, and the expertise around the table.

With that said, I would ask that each Panel member identify him or herself each time he speaks to facilitate transcription.

And with respect to commenting on the questions, what I'd like to do is, I'd like to start first with Dr. Hammon and work around the table so that everyone gets an opportunity to comment. With the next question, I'll start with the next person, Dr. Dorsey, and work around so Dr. Hammon is not first every time.

And I think we are ready to look at the first question, please.

DR. TOY: Thank you.

The first question: The SENTIS trial met its primary safety endpoint of no statistically significant elevation in the rate of serious adverse events (SAEs) in the NeuroFlo-treated group relative to the Control group. Specifically, there were 174 SAEs (43.9%) in NeuroFlo subjects and 177 SAEs (42.8%) in Control subjects. However, there were SAEs not seen in the Control group that were adjudicated as related to the NeuroFlo treatment. In light of all of the available safety data..." It's not advancing.

DR. HURST: We're almost at the question.

(Laughter.)

DR. EYDELMAN: Why don't you read the question while IT issues are being addressed?

DR. TOY: Oh, okay.

DR. EYDELMAN: I'll read the question:

- a. Please discuss the safety of the NeuroFlo device in the SENTIS population (patients with acute ischemic stroke treatable within 14 hours from symptom onset, with baseline NIHSS score of 5-18, and without evidence of massive infarct or hemorrhage).
- b. Please discuss any additional measures that may reduce the risk of these SAEs associated with use of the NeuroFlo device in the SENTIS population.

And as soon as we figure out the IT issue, this will be projected.

DR. HURST: Dr. Hammon, comments?

DR. HAMMON: Okay, John Hammon.

First of all, I do believe that the industry study did answer the question that there were no SAEs that were not to be expected. And let me explain that.

If you take a group of patients and treat them like you normally would after a stroke, they don't have a balloon in their abdominal aorta; and

if you have a balloon in your abdominal aorta, there is going to be -- you would have to expect a small number of complications, which was true in this group, and so I am not surprised nor do I think it is a "something" that is out of bounds of reason.

If I were going to do the study again, I would screen these patients with ultrasound or Doppler, or preoperatively, to determine the efficacy or determine the patency of their iliofemoral systems before I actually put a catheter in there because the ones that have significant atherosclerosis both above and below -- or would be expected to have complications such as the patient that had to have the amputation.

DR. HURST: Thank you, Dr. Hammon.

Dr. Dorsey, comments on 1a or 1b?

DR. DORSEY: Sure. So I think it's pretty clear that intervention has risks; it's not riskless. Three percent of the research participants randomized to the intervention arm had an intervention-related serious adverse event, and 15% had a non-serious adverse event related to the intervention.

The investigators did a nice job in terms of having a blinded independent rater for assessing efficacy, but there was no blinded assessment of safety at any level, which was actually kind of surprising and can lead to a measurement bias which would likely under-report safety concerns related to the intervention.

DR. HURST: Thank you.

Dr. Goldstein.

DR. GOLDSTEIN: Yeah. I think, based on the way the protocol was written, the primary safety endpoint was met. There weren't excess numbers of SAEs in the NeuroFlo group compared to the control group. So I think that part is pretty straightforward.

I think, as was said, though, there were adverse events that happened that were unique to the NeuroFlo subjects, and one would wonder whether there might be ways of trying to avoid those, although it seems like these were pretty much scattered in things that one would expect from putting catheters into people with atherosclerotic disease, the lower extremity ischemia, and et cetera.

So the problem always is, in open-label studies, is attributing these types of things to a specific intervention when the people doing it and the people recording the adverse events also clearly know which groups the patients are in. I don't see any way around that. At least on a study design like this.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

An acute stroke population is going to have a high rate of adverse events, and that's certainly what we saw in this trial. I agree that the risk appears moderate, and I guess the numbers that stand out to me are an

18.6% rate of serious adverse events related to the catheter versus 0% in the control population.

And in terms of interventions to reduce adverse events using this technique, it's unclear to what extent technical ability may have contributed to some of the complications at the insertion site, and it may be that with greater proficiency, then the safety of the device would be enhanced.

DR. HURST: Thank you.

Dr. Toledano.

DR. TOLEDANO: So thank you.

I'm just going to do a little bit of math. So on the SAEs, it's 3.4% and on the non-serious AEs, that's where the other 15.2 come from. So when we talk about rates of serious of the SAEs, that's 3.4%, and they are expected. And I would hope that there would be ways to better select patients and monitor their progress through the treatment with labeling and instructions, so just -- it's 3.4 for the SAEs.

Thanks.

DR. HURST: Thank you.

Dr. Noonan.

DR. NOONAN: Dr. Noonan.

I agree with Dr. Hammon. One thing I would add, that by decreasing the French size from 9 to 7, that's probably a very positive step. If

it could be smaller, that would be even better.

DR. HURST: Dr. Yang.

DR. YANG: I do think that the data, as presented, showed that the primary safety endpoint was met. However, as others have pointed out, the device-related ones are the ones that are worrisome and, of course, for me, it's always justifying that against the potential effectiveness or non-effectiveness.

DR. HURST: Thank you.

Dr. Ensrud.

DR. ENSRUD: Erik Ensrud.

I felt like the primary safety endpoint was met. The 3.4% is not out of what would be expected for an interventional procedure. I do agree with the earlier comment that possible ultrasound screening at the time of the procedure may be helpful reducing that further.

DR. HURST: Thanks.

Dr. Sung.

DR. SUNG: Yeah. So I agree. I think that any time a device is used, you would expect more complications related to the device, and I think that's what we see. Overall, it seems to be balanced by the overall adverse events in the control arm to negate that, extra added adverse events, but really the proof is in balancing risk and benefit. So that will be, I think, the entire question.

I do agree that there should be some -- hopefully, some more detailed analysis to determine if there is any site-specific or training-specific or practice-specific issues that are related to these serious adverse events.

DR. HURST: Thank you.

Dr. Zhou.

DR. ZHOU: I agree with others. I think the primary safety endpoint has been met to show there are no statistic significance between the two groups.

So I do have a comment about as a definition of SAE. Given this is actually the international study, you have lot of centers, including the center oversea, so the definition of SAE and the reporting by each center may not be uniform. So there may be more uniform training on the hospitals across this study, make data more uniform, more reliable, that might be better results.

DR. HURST: Thank you.

Dr. Posner.

DR. POSNER: Yeah, I agree with everything that's said and to go along with that, on several of the studies I've been involved in, when we've had overseas participants, the numbers have been quite different depending upon where they were based, upon how things are reported. But the other point to be made on this, that the numbers are what I would expect for intra-aortic balloon catheter. It goes in, we do a lot of them in the heart.

But one of the things that would be important in having approval of this is training for people that don't do this all the time as opposed to having it used as an off-label item, because the people that did this are trained, they know what they're doing, and they had really good exclusionary criteria, whereas if that's not made available and it's out there and someone decides to use it off-label, they may not know what the exclusionary criteria is.

So there is a safety issue that will come in one of the later questions that we talk about, but other than that, I agree with everything that's been said.

DR. HURST: Thanks.

Ms. Mattivi.

MS. MATTIVI: Again, I agree with everything that's been said about the primary safety endpoint having been met. I do think that there seems to be some confusion about things like the ranges of the diastolic pressure and the systolic pressures and that maybe there are some reporting things that could be investigated a little further. And if there's a treatment effect based on subpopulations, that maybe some of the SAEs may also -- be some subpopulations influences.

DR. HURST: Dr. Layton.

DR. LAYTON: I don't have anything new to add about the primary safety endpoints, but I do want to make one comment about the

device, also. It's also safe, and FDA did also point out that some of their adverse events and the MDR analysts didn't find anything necessarily different from the FloControl device and what they had here.

DR. HURST: Thank you.

Dr. Eydelman, then, my sense is that the Panel generally believes that the safety endpoints were met, there were very few unexpected SAEs; however, blinded safety evaluation might be better.

Possibility exists to decrease potential problems by ultrasound evaluation of lower extremity vessels prior to angio and, certainly, the decrease in the French size that happened during the study, I'm sure, contributed to a lowering of problems.

DR. EYDELMAN: Thank you, Dr. Hurst.

Question Number 2, please.

DR. TOY: It's now working. I'll read it out.

Please discuss any additional measures that may reduce the risk of these SAEs associated with the use of the NeuroFlo device in the SENTIS population.

DR. HURST: Wait a minute. I think we're on Question 2.

DR. TOY: Okay.

DR. EYDELMAN: Yes.

DR. TOY: The SENTIS trial did not achieve its primary effectiveness endpoint or any of the pre-specified secondary endpoints. The

SENTIS trial used a global test for the primary effectiveness measure, which is comprised of four components (NIH Stroke Scale, Modified Rankin Scale, Barthel's Index, and Glasgow Outcome Scale) to assess the effectiveness of the NeuroFlo device in treating patients with acute ischemic stroke within 14 hours of symptom onset.

- a. CoAxia conducted a post hoc analysis of multiple effectiveness and safety endpoints using SENTIS results, and found stroke-related mortality to be decreased for NeuroFlo-treated subjects (90-day stroke-related mortality: NeuroFlo 7.4%, Control 14.4%, nominal $p = 0.011$). Survivorship at 90 days by Kaplan-Meier was 92.4% (88.1%, 95.2%) in the NeuroFlo group and 85.3% (80.3%, 89.2%) in the Control Group ($p = 0.0146$ using log-rank test). For the purpose of this analysis, stroke-related mortality is defined as deaths that were adjudicated to have been due to stroke, systemic complications associated with stroke, or new stroke. Post hoc analyses are challenging to interpret, especially if conducted in the setting of a non-significant primary endpoint. Please discuss the clinical significance of this post hoc analysis finding.

DR. HURST: All right, Dr. Dorsey, any comments on 2a?

DR. HAMMON: Okay. Do you want me to comment?

DR. HURST: Oh, I'm sorry. I thought we'd start with -- you can start, if you want to, Dr. Hammon.

DR. HAMMON: I don't care.

DR. HURST: Let's start with Dr. Dorsey and go around. So you don't have to be first every time. All right. You can be last this time.

DR. DORSEY: We're just doing 2a? Dr. Hurst, just 2a?

DR. HURST: Just 2a, yes.

DR. DORSEY: Sure. So Ray Dorsey.

Okay. So mortality, for stroke-related mortality, the fact that the overall mortality did not differ significantly between the two groups and the fact this was a post hoc analysis, I think, greatly limits any conclusions that can be drawn from this. Had there been an overall mortality benefit and a stroke-related mortality benefit, I think it would be worthy of more consideration.

DR. HURST: Thanks, Dr. Dorsey.

DR. GOLDSTEIN: Dr. Goldstein.

So the first thing is that this wasn't a pre-specified efficacy measure, right. This was part of the -- safeness was one component of safety, and I think the conclusion there is that there was certainly no excess mortality in the group that got the device. But, again, there is no statistically significant difference between the two groups. I think that's part of the safety analysis. It was not, again, one of the -- either the primary or any of

the secondary efficacy analyses.

DR. HURST: Thank you, Dr. Goldstein.

Dr. Furie.

DR. FURIE: Karen Furie.

I agree with the other speakers that, as a post hoc analysis and one of many analyses, it's a Type I error and therefore should be deemed hypothesis generating, not definitive.

I also believe that the definition of stroke mortality was somewhat unconventional. It was developed by the event adjudication committee and DSMB, who were somewhat hindered by wearing multiple hats and being unblinded to the data. And so a more objective, standardized definition might have been more reassuring, as well.

DR. HURST: Thank you.

Dr. Toledano.

DR. TOLEDANO: Well, now I'm just going to agree totally with Dr. Furie. Next.

DR. NOONAN: I have no additional comments.

DR. HURST: Dr. Yang.

DR. YANG: I do not think there's any significance to that finding.

DR. ENSRUD: Being that the overall mortality is not different, I also feel there's not a significance to the finding.

DR. SUNG: Gene Sung.

I also agree. This is very, very hard to interpret, and it would be difficult. I guess I would also be interested in all-mortality studies, to know how many of these cases were actually withdrawal of care as opposed to just expiring from medical causes with full care and if there is a bias toward the treated groups or not.

DR. HURST: Dr. Zhou.

DR. ZHOU: So I just -- three point.

When you move away from all-cause mortality, when you do survival analysis, the technique is much more complicated. So that will involve competing risk. In other words, people can die from other causes. So those people will die not due to a stroke-related mortality is not censoring anymore, so we call it a competing risk. So the methods who analyze competing risk is different from a standard method like Cox model or the Kaplan-Maier. So whether this result will be the same or not if you use a more appropriate statistic method need to be seen. So that's first comment.

Second is for any post hoc analysis, you will have danger of the false positive, so is better to do another confirmatory analysis if you do believe the statistical significant issue here is a true statistic significance, so I have to wait to see to make a judgment whether it's clinically significant.

DR. HURST: Dr. Posner.

DR. POSNER: I agree with the statisticians.

(Laughter.)

DR. HURST: Ms. Mattivi.

MS. MATTIVI: As do I.

DR. LAYTON: Terry Layton.

I have nothing to add.

DR. HAMMON: John Hammon.

Ditto.

DR. HURST: Dr. Goldstein, did you have more to say?

DR. GOLDSTEIN: Yeah, I just wanted to rephrase one of the things that I said just for clarity.

I think that the overall mortality is pretty straightforward, that there was no difference, and this is a safety measure. I think looking at stroke-related mortality is interesting just from the standpoint of trying to understand the data. From the standpoint of patients, I don't think they give a hoot. I mean, dead is dead, right, so it's the total number that matters.

DR. HURST: So, Dr. Eydelman, my sense is that the Panel feels that the conclusions are very severely limited by the post hoc analysis, that confirmatory analysis would be best, that there is a potential for a considerable post-Type I error generation from using this kind of data.

DR. EYDELMAN: Thank you very much.

And 2b is actually projected this time.

DR. TOY: Yes. The SENTIS trial resulted in a 90-day all-cause

mortality rate of 11.3% in the NeuroFlo group vs. 16.30% in the Control group ($p = 0.087$ using Cochran-Mantel-Haenszel test). Survival at 90 days by Kaplan-Meier was 88.5% and 84.2% in the NeuroFlo and Control groups, respectively. Please discuss the clinical significance of these findings.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

They're not significant, and I don't have any other comment.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: So we're rotating, okay.

So in terms of clinical significance, I can't say very much to that, I'm a statistician. In terms of statistical significance, if you have a difference, you can, in theory, always do a big enough trial to get your p-value low enough. So I know that you all underwent a huge global effort four years, four-plus years, on this trial, getting these 515 patients. But I don't know, really, what I would say here. I would say you could report it; I wouldn't say you could claim it.

DR. HURST: Dr. Noonan.

DR. NOONAN: Dr. Noonan.

I concur. I have no additional comment.

DR. HURST: Dr. Yang.

DR. YANG: I think it's difficult to discuss the clinical significance if you don't think there is a significant difference.

DR. HURST: Dr. Ensrud.

DR. ENSRUD: I really wish that it were significant, but the data are not.

DR. SUNG: Gene Sung.

Again, difficult to interpret. No real differences. And, again, the plea for all clinical trials is to determine if there was active withdrawal of care in these cases or not. And, again, I think that there would be a natural tendency to work harder on the patients who are treated versus those who are not, but that's just conjecture.

DR. HURST: Dr. Zhou.

DR. ZHOU: So I agree there's no statistical significance either method. But I do want to comment on the reported -- both the 90-day all-cause mortality as well as survival use two different technique. One is the Cochran-Mantel-Haenszel test; one is a Kaplan-Meier one. Because we know the Cochran-Mantel-Haenszel test does not able to adjust for the censoring.

So I think the first method may not be right, but so the better just reporting the second results because with survival, you can copy what mortality is with survival rate. So you could convert from survival to mortality rate instead of report the 90-day all-cause mortality rate, use the method which are not able to adjust for the censoring.

DR. HURST: Dr. Posner.

DR. POSNER: Once again, I have to agree with the statisticians

and the clinicians that it has to be statistically significant to be clinically significant, and it needs more work to do that.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: I have nothing further.

DR. HURST: Dr. Layton.

DR. LAYTON: Terry Layton.

Nothing further.

DR. HAMMON: I don't have anything to add. I agree that the data are not significant. On the other hand, I'll have an aside here, and that is I'm not surprised, given a study where you have a 14-hour window study in an acute ischemic event, you really don't know if it's a big vessel that's occluded or a small vessel or multiple small vessels. I think it's going to be very difficult to get some sort of unified confirmatory statement about efficacy.

DR. DORSEY: Ray Dorsey.

Nothing to add.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Yeah, Larry Goldstein.

Yeah, again, I think the clinical interpretation of this is that there is not increased mortality with the device, that this was -- again, this was a safety measure, not an efficacy measure.

DR. HURST: Thank you.

Dr. Eydelman, the sense of the Panel seems to be there is no statistical significance. Clinical significance is quite difficult to evaluate, although certainly not identical to statistical significance. And I think that point needs to be kept in mind when we look at this, that those are not identical.

And I think that pretty much sums it up.

DR. EYDELMAN: Thank you. 2c.

DR. TOY: The SENTIS trial used a global test-type endpoint with multiple components to assess effectiveness. Please discuss your interpretation of this global endpoint in evaluating clinical outcomes in subjects enrolled in SENTIS.

DR. HURST: Let's start with Dr. Toledano.

DR. TOLEDANO: So it's Dr. Toledano.

And I kind of understand why they did it. It was the only precedent, and it's what was discussed with FDA, and it's what you hoped would work out. I don't know how to interpret it, I don't know what it means in real life, I don't know if it's appropriate to patients who have had stroke up to 14 hours before they come in to the ED. I just don't know what to do with it or how to interpret it when it's all mushed together like that.

DR. HURST: Dr. Noonan.

DR. NOONAN: Dr. Noonan.

I concur.

DR. HURST: Dr. Yang.

DR. YANG: I think, as a neurosurgeon, I would have to defer some of this to my neurology colleagues, my stroke colleagues, but from what I understand, you cannot equate, sort of, a blood flow to outcomes after stroke. So if we are looking at a device and we do not have any other precedent measures to use, then outcomes is not an unreasonable thing to go for; although as I think someone else mentioned, this is a very wide spread of patients to try to achieve with a global outcome measure.

DR. ENSRUD: I also felt that the desired endpoint wasn't reached and other -- until we broke down into a multiple subgroup, their post hoc analyses, we didn't find a significant effect.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

So I agree with what was said before, which is that you followed the instructions. But I think, unfortunately, the instructions may not have been the best in this regard and that certainly it would have been highly useful to have some kind of marker of blood flow, which, I think, was the main intention of this catheter, and then perhaps some other different clinical endpoints. But you, again, did what you were told, so can't fault you for that.

DR. HURST: Dr. Zhou.

DR. ZHOU: Well, I think this is actually an interesting question

from a statistic point of view because in the clinical trial we have -- often have a lot of outcomes. So the question is how do you test treatment effect when you have a lot of outcomes? I mean, they do have some methods there. This is the first time I saw this kind of way to do -- use a GEE approach. I don't know if it's the best way to do that, because what has been done is actually you make assumptions to try to deal with the multiple outcomes.

They are assuming, which FDA also pointed out, that you assume treatment effect the same for each component, which is not true, by the way, from the data you show. So I feel like the better approach would be -- is to jointly, actually, model those outcomes using joint modelings in a joint test.

Or another way you can do it is to combine the four components into the global measure based on the importance, clinical importance, of each component. If you believe one of the scales, like quality of life is the most important, you maybe should give more weight to that when you do analysis, compared with other components in your analysis. So that might be more reflected to the clinical outcome, so that's -- probably should use a clinical weight to combine those four components into overall components and then compare that between the two groups.

DR. HURST: Dr. Posner.

DR. POSNER: That's a tough thing to do looking at global tests based upon the wide population of plasticity and reserve in the population.

And the only thing you can really measure for effectiveness is if you could measure blood flow or the size of the infarct area and the area at risk, because those are things you can actually measure with MRI and with tracers. But as far as global function, there are so many differences in individuals as to reserve and plasticity that it's almost impossible to do.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: It may be impossible to do, but as the Consumer Rep, I am thrilled to see some functional outcomes as endpoints, especially for a stroke study. I think, you know, weighting these outcomes by importance would also be a difficult thing to do because so much of it would be personal preference on the part of the patient or the patient's family and their ability to care for the patient depending on the outcome, so I think it's a very difficult thing to do.

I think the global testing, that it incorporated several different scales looking at several different types of functional outcomes was a great start, and unfortunately, it didn't turn out the way everybody had hoped it would. But, again, as a consumer, as a physical therapist, as the daughter of a stroke victim, I think that the functional -- it's all about the function, in the end. Like dead is dead, you know, function is function.

DR. HURST: Dr. Layton.

DR. LAYTON: Yes, I agree with the Panel, that global testing with multiple endpoints is very difficult.

DR. HURST: Dr. Hammon.

DR. HAMMON: I have nothing to add.

DR. HURST: Go ahead, Dr. Dorsey.

DR. DORSEY: Ray Dorsey.

I think the absence of a significant effect on the global measures or any of its components or any of the 11 pre-specified secondary outcome measures all, unfortunately, speak to the lack of efficacy of the intervention.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Dr. Goldstein.

Yeah, I was going to make the same comment and I guess, you know, I understand the rationale for using this measure when you have an intervention that has potential risk, that has potential high cost, that's an intervention that may change the types of therapies a patient may get. You set the bar high, and the bar was set high here, and unfortunately, it just didn't work out.

But as I said, you know, even if the global measure failed, none of the components and none of the pre-specified secondary measures were positive either so that, if anything, it supports the global test as being the primary measure for the study.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

I have nothing to add.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: I think I started it, so I don't --

(Laughter.)

DR. HURST: Sorry.

All right. So my sense is that the Panel felt that while this was the only precedent at the time that the study was initiated about eight years ago, that these endpoint measures are difficult to interpret, that there is a lack of significance that was reported over the time that the study was undertaken. However, there seems to have been some evolution or development in understanding of the validity of different endpoints for acute stroke versus strokes that appear a little bit later on. And I think we may be seeing some effect of that, as well.

The comment was also made that blood flow markers, as an endpoint, would be a good thing. The comment was also made, on the other hand, that clinical endpoints are also a very good thing. And we certainly heard that excessively heavy reliance on "surrogate" endpoints is not always a good thing, as well. So while certainly blood flow would be of interest here, and I think many people feel that it would be, we don't want to lose the clinical endpoint, either.

DR. EYDELMAN: Thank you very much. 2d.

DR. TOY: CoAxia proposes the following indications for use for

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the NeuroFlo Catheter:

The CoAxia NeuroFlo Catheter is intended for use in selectively stopping or controlling blood flow in the peripheral vasculature, which includes the descending aorta. When used in the descending aorta, balloon inflation results in diversion of cardiac output to the upper torso and core organs, e.g., cardiac, spinal, and cerebral vasculature. The NeuroFlo Catheter is intended to increase cerebral blood flow in patients with ischemic stroke and is intended for this use up to 14 hours after symptom onset in patients who are ineligible for intravenous tPA or thrombectomy.

In a randomized clinical investigation of stroke patients, use of the NeuroFlo Catheter was demonstrated to be safe. The study did not demonstrate a statistically significant improvement in the 90 day 'return to normal' Global Outcome Score. Use of the catheter resulted in a reduction of overall mortality and stroke-related mortality.

Please discuss if the available data (including the SENTIS trial results and other NeuroFlo pre-clinical and clinical data) demonstrate effectiveness in increasing cerebral blood flow in patients with acute ischemic stroke within 14 hours of symptom onset.

DR. HURST: Dr. Noonan, why don't we start with you?

DR. NOONAN: Dr. Noonan.

This is basic, the indication for the device, and let's go step by step.

The first sentence, intended to be used in selectively stopping or controlling blood flow, that's probably certainly true. There was pressure drop, and if they had measured pressures in the legs, they probably would have been diminished.

When redirecting flow, I'm not sure that's been entirely proven. It's been redirected to the head, there were the animal studies, and I think I have some problems with that. There was a porcine model rather than a primate model.

Only a few of the patients, I think 14 or 16 patients in the Phase 1 trial and the imaging seemed to be different, and in this trial there were no imaging, no vascular imaging, so we don't know what vessels were particularly occluded, proximal distal, so forth. So that's missing.

With regard to redirecting flow to the cerebral vasculature, that's still uncertain in my mind.

With regard to redirecting flow to the spinal vasculature, there is the artery of lumbar enlargement which may arise in the aorta below the level of the balloon. So presumably, in patients in which it does arise in the aorta below the levels of balloons, the spinal vascular supply would be diminished, the flow in the spinal arteries would be diminished. So that's probably not always true.

And regarding the time at which patients are treated, certainly treating them earlier, they will do better. It seems to be most studies proving

that. I have no additional comments.

DR. HURST: Thank you.

Dr. Yang.

DR. YANG: As I recall, I do not think there is any direct and consistent data collected about cerebral blood flow; therefore, I have to say that the available data does not significantly demonstrate the effectiveness in this.

DR. HURST: Thank you.

Dr. Ensrud.

DR. ENSRUD: Erik Ensrud.

The available data that was shown today was anecdotal and didn't clearly demonstrate effectiveness in humans.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

I agree. These reports were of nine or so patients, using a variety of different measures, including TCD and PET scan and angiography for blood flow and certainly no uniformity in the data collection and too few numbers; so really no, essentially no, meaningful data in this regard.

DR. HURST: Dr. Zhou.

DR. ZHOU: Yeah, I agree. From the data available to us, I don't see that it has been demonstrated that this intervention is effective in reducing the overall mortality or the stroke-related mortality. I didn't see

that from the data.

DR. HURST: Dr. Posner.

DR. POSNER: I agree about the blood flow, but I'd also make a comment that for any future studies that are done, the question should be perfusion of the ischemic area because even if this did increase cerebral blood flow, we don't know if that blood is going to the right place, so I agree with everything said. We don't know if it increased cerebral blood flow, but even if it did, we don't know if it did anything because we don't know what happened to the ischemic area.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: I agree with everything the Panel has said.

DR. HURST: Dr. Layton.

DR. LAYTON: Yes. As you know, from my earlier questions, I have a little problem with some of this, and this goes back to the '09 510(k) where there is the clearance, the FDA approved or cleared, where it states in the device description that it results in a diversion outflow, i.e., cerebral vasculature. So the FDA has ruled on that one other time. But I also would have liked to have seen flow data. I mean, I agree with that also. But, I mean, here you have an extension of a device, and it has been looked at from that standpoint where it does divert flow.

DR. HURST: Dr. Hammon.

DR. HAMMON: Yes, I agree, and I think that's a very good

point. And I think Dr. Posner's point is very good, about "is the blood flow going to the right place," and we had some beautiful pictures today showing that in some patients, it was. And I would challenge the people that presented that data to keep doing that and keep records. It doesn't cost any money to write something down on a piece of paper.

The other thing I would say is that nobody in their right mind would stop the blood flow in the abdominal aorta for more than about 5 or 10 minutes, and if I was going to rewrite this, I'd take "stopping" out.

DR. HURST: Dr. Dorsey.

DR. DORSEY: I generally agree with the assessments of the data.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Dr. Goldstein.

Two points: One is, again, the preclinical studies that showed diversion of flow were predominantly in a normal porcine model, and the data from this trial, obviously -- and we've talked about this -- didn't include that, so I'm concerned about that portion of it.

The other portion is "increased." Increased compared to what?

I mentioned a couple of things to think about, at least. Just the positioning of the control patients might also augment their cerebral blood flow for a similar period of time and that, itself, may potentially affect outcome.

And we talked about no comparative medical therapy, but as was said, we do a number of things now, pharmacologically, to try to augment cerebral blood flow in patients, and that might also be inappropriate for a control population to really try to address this question, try to nail it down, whether this adds anything to those other measures.

The other portion of this that sort of slipped through here, and maybe I misunderstood it, it said, "Use of the" -- in the double star at the bottom, it said, "Use of the catheter resulted in a reduction of overall mortality," and I thought we said, from the pre-specified safety analysis, that there was no significant effect on mortality. There was a trend, but there was no significant effect on overall mortality, so I'm not sure what the basis of that statement is.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

Because stroke is such a heterogeneous disorder, I think this is a very challenging problem, and the human data, to date, are limited to the small pilot that used multiple modalities to assess blood flow. The comment was made earlier that it's important to correlate the blood flow changes with some clinical improvement -- and I do think that that is very important.

For instance, we saw increases in peak systolic velocity on transcranial Doppler studies, but it's unclear what impact increasing TCD velocities within the normal range, even if they're doubled from, let's say, 50

to 100, would actually have on preservation of ischemic tissue in functional outcomes.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: So I'm going to pick up on where Dr. Layton started, with the K090970, and if we just take this proposed IFU, the first sentence is the old IFU, and the second sentence already occurs in the device description, so we've already got those two pieces.

But then we start with that truly new bit of increasing cerebral blood flow in this group of patients, and that's where we just don't have or -- I, personally, just don't see enough data in these patients. And, yes, we see it's safe, and yes, I think if you are making any claims, you have to say that you didn't meet your primary efficacy.

And I totally agree with Dr. Goldstein, that you can't have that last sentence in there because those are all post hoc and they're just not proved. They may be hypothesis generating, but they're just not proved.

DR. HURST: Thank you.

Dr. Eydelman, my sense is that the Panel feels there was no systemic, or a systematic data collection to demonstrate increase in cerebral blood flow; that the possibility exists that a control population using pharmacologically elevated blood pressure might serve to evaluate a population using this device to look at cerebral blood flow.

Again, there were concerns and questions about the use of the

post hoc conclusions, but the comment was also made that the FDA should pay attention to the previous approval of this device when looking at it going forward, as well, that it was approved for some other indications.

DR. EYDELMAN: Before we proceed, I just want to clarify that we did read in the record the indication for use for 510(k), and the indication for use did not have cerebral blood flow in the IFU.

DR. HURST: Correct.

DR. EYDELMAN: Was that -- 2e, please.

DR. TOLEDANO: It's in the device description.

It's Dr. Toledano.

Just repeating from Dr. Layton, the second sentence is in the device description. It is not in the IFU.

DR. NOONAN: Dr. Noonan.

I have a problem with the spinal blood flow, increasing spinal blood flow. I think I mentioned that. The artery of lumbar enlargement could arise as low as L2 or even lower, and the balloons seem to be placed above that level.

DR. TOY: Question 2e: Please discuss any other relevant treatment effect identified in the data from the SENTIS trial and if any identified effects are clinically meaningful.

DR. YANG: Unfortunately, I do not think there are any other meaningful effects that can be gleaned from the data as presented.

DR. ENSRUD: I don't have any specific comments.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

I agree that everything that was seen was post hoc analysis and not particularly meaningful.

DR. ZHOU: I agree. I think that more analysis needs to be done to confirm some of those preliminary results.

DR. POSNER: Dr. Posner.

I agree.

MS. MATTIVI: I think there were some very clinically interesting ideas presented, but not clinically meaningful.

DR. HURST: Dr. Layton.

DR. LAYTON: I don't have any additions.

DR. HURST: Dr. Hammon.

DR. HAMMON: I think the one thing that came to me about this is, you can blow up two balloons in the abdominal aorta for 45 minutes, and it's really reasonably safe with just a very small number of complications.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Ray Dorsey.

I think the analyses that were done many times were post hoc, and on multiple levels in terms of the defined subpopulation, was defined post hoc, that outcome measures defined were done post hoc. I mean, even

those outcome measures were dichotomized at post hoc, so I put very little value in those analyses.

DR. GOLDSTEIN: Dr. Goldstein.

Yeah, I think from a trial conclusion standpoint, I totally agree that we can't take much home. I think that these exploratory analyses are enticing, there are a lot of possibilities here, but I think we need more work and more data to be able to prove any of them. If we had done the same type of thing for many of the pharmacologic neuroprotective agents, we'd have 50 of them approved by now because many of them had very enticing data in subgroups in very similar patient populations. That then went on to larger trials looking at subgroups and found that they, in fact, could not demonstrate that effect. So, again, I think looking at the data this way is perfectly reasonable. It provides hypotheses, but hypotheses are not proof.

DR. FURIE: Karen Furie.

I agree with the earlier comments.

DR. TOLEDANO: It's Alicia Toledano.

I agree. And I would just urge you, please don't give up, because there are so many stroke patients like my mom and Ms. Mattivi's mom and other patients who are going to get these strokes and not get into the hospital in time for the tPA, so don't give up. Just learn and don't give up.

DR. HURST: Dr. Noonan.

DR. NOONAN: I have no additional comments.

DR. HURST: Thank you.

The Panel's sense seem to be that there was little or no relevant treatment effect identified. However, a considerable number of clinically interesting findings that were presented, at this point, seem to be exploratory and need more data.

DR. EYDELMAN: Thank you.

Question Number 3.

DR. TOY: Question 3: Please discuss whether the benefits from use of the NeuroFlo device outweigh the risks of its use in the patient population enrolled in the SENTIS trial. Please discuss these benefits and risks in the context of alternative treatments (including non-device therapies) approved or cleared for the intended condition and patient population as this is a component of FDA's final regulatory decision with respect to benefit-risk determination.

DR. ENSRUD: Hi, Erik Ensrud.

I certainly agree with all that's been said today about the great need for further therapies in this group of patients. However, I don't feel that the benefits that were found from the NeuroFlo device outweigh the risks because we do have a 3.4% risk of SAE and we haven't unequivocally proven a benefit in the patient population.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

So I think that, in summary, there seems to be a clear trend for increased adverse events with the device and a trend for increased benefits, neither of which are really statistically significant. Whether or not this meets the de novo classification for new devices is, I think, the crux of the matter. And, certainly, there is a consideration of, again, induced hypertension, maybe meeting some of the goals or flow increases of NeuroFlo. But we don't have any, certainly, hard evidence comparing the two or even something as simple as head positioning which is -- unfortunately, that was not even captured for the control patients. So it seems to be a unique methodology. The data, I'd have to say, isn't particularly clear of any new benefit, really.

DR. HURST: Dr. Zhou.

DR. ZHOU: Yeah, I agree with what has been said, that technology does seem to make some sense, but the data presented to us does not compare with the control group and there is the great -- the efficacy and also have a much safer, the outcomes. So I just agree with what has been said.

DR. HURST: Dr. Posner.

DR. POSNER: Yeah. Based on the information we've had, if this were a compassionate use and there was nothing else available to use, then I think it reasonable.

One of the things that hasn't been mentioned that's really

benign is an old EMT or pressure pants, where you can do an extravascular compression of the lower body, which is even more effective than laying your head down in bed, to get the blood flow up to the brain. And the body, itself, by a cushioning mechanism, will get the blood up to the brain by constricting it. So based on normal physiology and EMT, I think there are other things that are less risky.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: As great as it would be to have an alternative therapy for this population of patients, the data do not support that this is it.

DR. HURST: Dr. Layton.

DR. LAYTON: Yes, I think I did see the benefits versus the control, but I do acknowledge that the statistical significance wasn't there. The other thing is, I don't think the risks were that burdensome.

DR. HURST: Dr. Hammon.

DR. HAMMON: Yeah. A study like this in a large number of patients showing low risk and unfortunately low benefit is a cry in the wilderness for better study design, increased use of new technology to measure cerebral blood flow, and I'll bet you'll show something.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Ray Dorsey.

Unfortunately, the evidence does not suggest that the benefits outweigh the risks.

DR. GOLDSTEIN: Yeah, issues with controls aside, there was no benefit for the primary or any of the 12 secondary pre-specified measures. There was also safety overall, which we said didn't seem to be an issue, although there are some issues related to, at least, some of the patients that had a device placed, so I don't see any risk/benefit ratio here.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

I'll just add that, with regard to the primary endpoint, although the point estimate was 1.17, the confidence interval did allow that there was potential harm associated with the use of the device. And so I think that the comment was made earlier that there was no risk and potential benefit, but I think that we can't say that with confidence.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: I agree with my colleagues.

DR. HURST: Dr. Noonan.

DR. NOONAN: Dr. Noonan.

In the best of hands, there was only a minimal benefit for some patients, but certainly not all patients. There were some people with risks, groin issues, losing a limb, renal function, and in the end, I don't think the benefits outweigh the risks because it's going to be given to everybody to use and then we'll see.

DR. HURST: Dr. Yang.

DR. YANG: When you look at a risk/benefit ratio, if there's no demonstrable benefit and the denominator is zero, then any risk that's demonstrated today would be too hard to swallow for me.

DR. HURST: So it seems that the sense of the Panel is that there was no significant benefit shown. A clear trend for benefit, but also some degree of a trend for SAEs, both without significance. Although the risks seem quite low with this device, there exists at least the potential for some harm.

DR. EYDELMAN: Thank you.

Question 4.

DR. TOY: Question 4. After failing to meet any pre-specified primary and secondary effectiveness endpoints, CoAxia conducted multiple post hoc analyses and identified several subgroups in whom they state that the NeuroFlo device shows greater treatment effect (e.g., subjects >70 years or subjects with baseline NIHSS score between 8 and 14). FDA has concerns that, due to the post hoc nature of these subgroup analyses, the results may represent false positive findings. Taking these concerns into consideration, please discuss the benefits and risks in the identified subgroups.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

So, of course, any post hoc analysis must be considered carefully. However, it certainly is interesting and maybe hopeful that there

seem to be some benefit in older patients since older patients, in general, tend to do worse with most of our current aggressive therapies for stroke care.

It was, actually, a little disappointing to see, in the review of the after-break data, that the benefit in the patients remained in the earlier treated category, so the posed time window for the therapy of up to 14 hours may not be valid after all, since most of the benefits seem to be treated, seem to be in the early category of patients.

DR. HURST: Dr. Zhou.

DR. ZHOU: Well, yeah. I can see the value of the post hoc analysis. To answer one of the FDA's questions, sometimes the overall may not be statistically significant, but you still can identify subgroup, which is worse. That's actually one of the hot topics current today, is called personalized medicine, so that means you try to find the individual treatment for individual patients. But in order to do that, feel like you need to do more globally, not just choose arbitrary cutoff points.

So what they can do is actually to look at what is treatment effect as a function of the age, what is treatment as a function of the NIHSS as a continuous score, now the individual cutoff point. So you can see how the treatment changes over the changes of the NIHSS score and also change over time. And then you find best cutoff point instead of the cutoff point of the choose 70 here.

But I do see the place for the post hoc, but have to be careful with follow-up confirmation study to verify this, indeed, is true results.

DR. POSNER: Yeah, I have to agree that the post hoc study should be a hypothesis that needs to be tested.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: They pose more questions than answers.

DR. HURST: Dr. Layton.

DR. LAYTON: I think subgroups are important, but it's also difficult for me to specify which types they should -- or what they should be.

DR. HURST: Dr. Hammon.

DR. HAMMON: Yeah, logical findings are eminently hypothesis generating.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Ray Dorsey.

Nothing new to add.

DR. GOLDSTEIN: Dr. Goldstein.

Yeah, so I think we've talked about this, that the subgroups are important for hypothesis generating. If you're going to do them, the usual first pass is to do a subgroup by treatment group interaction for the study's primary endpoint, and I didn't see those types of things for the subgroups. The FDA ran some of them, and those weren't significant, so I'm questioning even how to interpret these subgroup analyses using altered endpoints as

well. It's just completely hypothesis generating, I feel, at this point.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

I think we've discussed the questionable benefits already, and although it was wonderful that the investigators were able to crunch numbers over the lunch hour to try and present some information on risks, the fact that some of the numbers on the slides didn't appear to be quite accurate suggests that more needs to be done in that regard.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: Keep looking. It's hypothesis generating.

DR. HURST: Dr. Noonan.

DR. NOONAN: I have no additional comments.

DR. HURST: Dr. Yang.

DR. YANG: I have nothing to add.

DR. ENSRUD: I have no additional comments.

DR. HURST: Thank you.

My sense is that the Panel feels that while subgroup analysis is important, the results of the post hoc analysis currently available are primarily useful for hypothesis generation.

At this point, I think we want to take a 15-minute break, and we'll return to the room in 15 minutes. Thank you.

(Off the record.)

(On the record.)

DR. HURST: Let's go ahead and reconvene at this time. And we'll move on with the FDA panel questions. We're currently on Question Number 5.

DR. TOY: Question 5: In addition to the questions above, FDA is seeking the Panel's input on the advantages and disadvantages of endpoints assessing cerebral blood flow for future device trials intended to evaluate safety and effectiveness in acute ischemic stroke patients.

The following questions pertain to the assessment of cerebral blood flow in acute ischemic stroke trials:

- a. Please discuss the role of increased cerebral blood flow as a complement to or surrogate for the primary effectiveness endpoint to assess effectiveness of device treatment for acute ischemic stroke.

DR. HURST: I'd like to start back over here with Dr. Hammon again, please.

DR. HAMMON: I think that we've sort of skirted around this issue in our previous questions, and I think Dr. Posner said it the best. Increased blood flow is one of the components of effectiveness. The other component is decreased size of damage.

We're sort of at the stage we were 15 years ago in looking at myocardial infarct size, where you not only had to have increased blood flow,

but you had to have some measure of myocardial infarct size, which took years to do. And now we have the technology to look at the infarct size in the brain pretty easily. It's expensive, but it's easy to do.

So I would have to say, yes, increased cerebral blood flow is a surrogate for the primary effectiveness endpoint if you add infarct size.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Building off the earlier comments, those of Dr. Posner, I think it can be useful as a complement or a supplement, but certainly not as a surrogate or a substitute. There are lots of questions to be asked and answered, including where the blood flow is increased to, when it is increased, by how much, for how long, and at what cost.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Yeah, I think the value is to try to better understand how an intervention may be working. I think it's quite hazardous to use that as a surrogate endpoint or even as -- and certainly not as a substitute for a clinical endpoint. We've seen this over and over again in clinical stroke trials.

One of the most recent examples was the EC/IC bypass trial for complete carotid occlusion. The study was designed with the notion that the procedure would increase cerebral blood flow to the hemisphere at risk defined by PET and, in fact, from a physiologic standpoint, it did just that and it did it quite successfully. However, it did not improve clinical outcomes. If

anything, they did worse. So our preconceived notions about pathophysiology, especially in the brain, have to be taken very, very carefully.

The other point that was made about improving infarct size, yes, in general, that's true. However, there's a fairly large literature now showing that sometimes making the hole smaller is not necessarily the best thing for people because a dysfunctional brain may actually be more disadvantageous to surviving a maladaptive brain. And many of the therapies that we might use to try to decrease infarct size may actually end up making patients worse.

And I think it's a critically important thing, especially where you think the physiology is to increase cerebral blood flow, to be able to show that; but that in no way substitutes for clinical outcomes. Did we make patients better is the question.

DR. HURST: Dr. Furie.

DR. FURIE: Karen Furie.

I also feel that it contributes more as a complement than a surrogate measure, and we just raised the issue of using imaging as a primary endpoint, such as infarct volume. Given the broad window for this intervention, it may -- some thought would at least have to be given to whether you would expect changes in infarct volume once the core had adequately evolved.

DR. HURST: Thank you.

Dr. Toledano.

DR. TOLEDANO: I agree with the last three panelists.

DR. HURST: Dr. Noonan.

DR. NOONAN: I agree. I've seen increase in blood flow with certain interventions in certain patients, but it made no difference whatsoever. We have to know the size of the infarct. If the intervention may decrease the infarct size, maybe that's good, but maybe, as prior panelists said, maybe not in all cases.

DR. HURST: Dr. Yang.

DR. YANG: I think use of it as a surrogate would be dangerous. I think a complement along with size of the ischemic area is reasonable, perhaps a biosemi specialty, but in certain patients, I think ICP is also an additional point of notice.

DR. HURST: Dr. Ensrud.

DR. ENSRUD: I think the use of it as a surrogate would be interesting, but not nearly as important as functional or quality of life outcome measures.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

I agree that the cerebral blood flow measures would be a very interesting and probably important complement to any clinical outcome.

DR. HURST: Dr. Zhou.

DR. ZHOU: This is an interesting question. And I think this study need to be done, try to figure out what the pathway, the cerebral blood flow play from treatment to the clinical outcomes. Is this a mediator or this is, we call it direct effect or indirect effect. So is mediated through -- suppose we see the treatment has impact on the clinical outcome, so we sort of figure out is this treatment effect through increased cerebral blood flow or through other mechanisms actually affect the clinical outcome.

If we can figure that mechanism, and then we can decide whether the cerebral blood flow can be used as a surrogate or not, because they're in the pathway between the treatment and the clinical outcome. I think you could use as a surrogate -- pathway and something else, to make better use of that complement. I think we can do some study to figure out whether this should be used as a surrogate or not.

DR. HURST: Dr. Posner.

DR. POSNER: Everybody said the right thing: It's good physiology.

You know, I think what blood flow is going to do for you is it may salvage the ischemic zone, but you don't know what it does functionally.

I'll be a patient now: I have MS. If you looked at my MRI and you saw the scarring I've got in my brain, you'd figure I'm lying there in the middle of the floor and I couldn't speak, but I've got enough reserve and plasticity and the rest of it that I'm functional. And so to get to your point,

function, clinical function, is the most important thing. But when you're doing things, you have to take care of the ischemic zone, if you want to salvage tissue.

MS. MATTIVI: Obviously, it's an important piece, but not the whole pie.

DR. HURST: Dr. Layton.

DR. LAYTON: This is an excellent question, not only for the Panel on this device today, but FDA, looking for future devices. Yes, flow is an important endpoint.

DR. HURST: So my sense is that the Panel generally believes that the role of measuring and evaluating cerebral blood flow is one component, but should complement other potential endpoints such as ICP, or understanding between the cerebral blood flow and the relationship to many of the interventions is really very imperfect at the present time, and it should certainly not be used as a substitute for a clinical endpoint.

DR. EYDELMAN: Thank you. 5b.

DR. TOY: Question 5b: If increased cerebral blood flow is used as an endpoint in an acute ischemic stroke trial, please discuss the advantages and disadvantages of the following assessment measures:

- i. Increase in overall cerebral blood flow;
- ii. Increase in regional or local cerebral blood flow; or
- iii. Increase in collateral blood flow.

DR. HURST: Let's start with Dr. Dorsey, please.

DR. DORSEY: Ray Dorsey.

I think this would have to be determined in the setting of a clinical trial or a clinical study, which would associate clinical outcome measures with the differences in each of these different blood flows. My colleagues may have more insights.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Yeah. So if we're considering trying to treat the penumbra and, you know, the penumbra we never really defined it. The penumbra is an area of ischemic electrically quiescent brain that's potentially salvageable. What you want to know is did the blood flow -- if you're going to use this again as a physiologic marker, did the blood flow to that area of brain increase or not; I guess that's what you'd be trying to assess physiologically. But, again, without having that tied closely to a functional outcome, it's explanatory but certainly not sufficient.

DR. HURST: Dr. Furie.

DR. FURIE: Of the different assessment measures, the ones that seem most important would be increase in regional or local cerebral blood flow and particularly increase in collateral flow. There's been sort of a surge in a number of publications identifying collateral flow as a critical feature in predicting outcome from stroke, and so if there were a way to capture that, I think it would be an important contribution.

I think this is complicated, especially in a population that might have multifocal cerebral vascular disease, and certainly, the still phenomenon of shifting blood from one part of the brain to another could potentially cause infarcts in other unrelated areas, so I think this is an important question.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: I agree that this is an important question to study further before we can finalize what would be the best way to measure blood flow and where we would measure it, and it has to be tied to a clinical outcome.

DR. HURST: Dr. Noonan.

DR. NOONAN: With regard to the three statements, I think the first one, techniques probably already exist. Xenon. Studies can be done. I'm not sure xenon is approved. Oh, sorry.

I concur with previous guests.

DR. HURST: Dr. Yang.

DR. YANG: I think this is a whole topic unto itself. I don't have anything relevant to add to the conversation here.

DR. HURST: Dr. Ensrud.

DR. ENSRUD: I have nothing to add to this point.

DR. HURST: Dr. Sung.

DR. SUNG: Yeah, I just would reinforce it. I think cerebral blood flow will be critical in the treatment of acute stroke, and hopefully, this

can help both in the research as well as perhaps treatment of stroke.

DR. HURST: Dr. Zhou.

DR. ZHOU: Yeah, I just want to emphasize, I think before we can actually answer this question, probably need to have to do some study to look at how each of those related to clinical outcomes, particularly functional outcomes. So which one actually strongly predict the functional outcome, that's the one probably should be used.

DR. POSNER: I agree with what everybody has said, and I say to my neuroscience associates, since I went from cardiology to neuroscience, take a look at what they've done in the heart because a lot of the baseline work has been done on ischemia infarction recovery, reperfusion, et cetera, et cetera. And I think you can learn a lot of things as to what's going to be important as far as increasing blood flow, and the clinical measures are the most important, though, for the end result.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: I have nothing further to add.

DR. HURST: Dr. Layton.

DR. LAYTON: I have nothing to add.

DR. HURST: Dr. Hammon.

DR. HAMMON: Well, I think obviously the goal is to increase regional or local cerebral blood flow whether you do it by antegrade flow or collateral flow, and the only way to do that is to increase overall cerebral

blood flow.

DR. HURST: Thank you.

It seems that the sense of the Panel is that we really don't have quite enough information to definitively answer the advantages and disadvantages of these three techniques. Certainly an increase in overall blood flow might be a good thing but under some circumstances could actually cause harm, for example, to uninvolved areas of brain.

In most of the large vessel or local ischemic strokes, we're most interested in an increase in a regional or local cerebral blood flow to the penumbra, and certainly, there's plenty of data suggesting that increases in collateral flow seem to be very important or, at least, the presence of collateral flow seems to be important in outcome from stroke.

Having said all that, I don't think that anybody wants to replace any of these measurements with a clinical endpoint.

DR. EYDELMAN: Thank you for your input.

DR. TOY: Question 5c: If cerebral blood flow changes are used as an endpoint in an acute ischemic stroke trial, please discuss the following:

- i. Appropriate measurement technique(s) to assess cerebral blood flow or collateral flow;
- ii. The amount of blood flow change that is clinically relevant; and
- iii. The duration of blood flow change necessary to be

considered clinically relevant.

DR. HURST: And let's start with Dr. Furie, please.

DR. FURIE: Karen Furie.

I think this is the toughest question that's been posed. There aren't great answers to any of these.

There are multiple measures or techniques, rather, that can be used to look at blood flow and perfusion. I think the decision about which one was the most sensitive technique to gauge a response to augmented flow is unclear at this time. There are advantages and disadvantages to all of them in the acute ischemic stroke setting. I think, currently, MR might be the easiest modality for most acute stroke centers, but you said that there's probably -- there would be debate as to whether that was true over CT.

The amount of blood flow change that's relevant has not been established definitively, and it's probably related to patient-specific factors in many cases, as well as to the actual pathophysiology of the stroke.

And the duration of blood flow changes necessary, again, is an unknown, and obviously, any extension of the duration of occlusion is going to be mitigated by the safety concerns of inducing ischemia. So I would imagine that the 45 minutes was determined based on preliminary data performed by the company, and it's already been suggested by someone on our panel that even a briefer duration might increase safety. So I would say that question remains unclear, at least to me.

DR. HURST: Dr. Toledano.

DR. TOLEDANO: So I agree with Dr. Furie about the little "i," which is, I guess, the little Roman I, that there are a variety of techniques out there, and we won't really know which one is the best and it might vary on a patient-by-patient basis.

As we look at items ii and iii, there has been some work done on estimating minimally important change and minimally clinically important change related to clinical outcome in epidemiological literature, and some of the work that the FDA has done on patient-reported outcomes and to ROC curve methods, which would include methods to identify optimal operating points and tradeoffs in consequences of false negatives and false positives. So we do not exactly have cardiology to go to, but some nice literature to go to as we go forth in this exercise to determine the minimal important clinical change.

DR. HURST: Dr. Noonan.

DR. NOONAN: One thing I would say regarding appropriate measurements, whatever is used, the measure should not perturb the system so much that it is really causing some of the effect you see. We do angiography, inject contrast, high volumes or whatever volume, and it's somewhat stressful sitting for the patient, even if they're having a stroke. That may change what we see as far as flow goes.

Perhaps the best, I think, speed -- the least invasive and the

easiest to obtain: MR, certainly, in many patients; CT for those patients who can't get an MR, those are good techniques. Xenon, as I was going to mention. It might be a good technique; I'm not sure that's approved.

The other two issues, I'm not sure we have the answers to those, so maybe if we decide on some good techniques, we could have the answers.

DR. HURST: Dr. Yang.

DR. YANG: In answer to the question, anecdotally, we have, of course, used everything from bedside monitors to xenon CT. However, I don't believe there's any literature out there that definitively states how you should do this, nor is there anything to say the amount or the duration that's going to change anything.

DR. HURST: Dr. Ensrud.

DR. ENSRUD: I have no comment on this particular question.

DR. HURST: Dr. Sung.

DR. SUNG: Gene Sung.

So I agree. I think this is the most interesting and difficult question of all with the least amount of data, even not just regards this particular project but just in general, in this field of stroke.

In relation to this study particularly, probably you'd stay away from CT perfusion because of the dye load, because of the renal complications we've already seen to have. But, certainly, a consistent

measure would be a great utility, I think. And, again, the other questions, too, are wide open to speculation.

DR. HURST: Dr. Zhou.

DR. ZHOU: So comment I have is for the measurement technique; they're different type. One is more accurate but might be very invasive; other one is the less accurate but less invasive, so have to balance between invasive measurement versus non-invasive but as good as invasive. So I think that's really the issue about -- for the blood flow, what's the gold standard for the blood flow. So if you want to measure that, would have to figure out what to choose about it in order to find the appropriate measurement, which is the good accuracy but also non-invasive. So I'm just thinking maybe have to consider bad as opposed to accuracy and non-invasiveness.

DR. HURST: Dr. Posner.

DR. POSNER: The need for accuracy is going to be variable because every patient is different. If you have a sudden stroke due to a spasm or a thrombus, it's going to be different from somebody that's had coronary vascular disease for a long period of time and it's come on slowly. If you go to the coronaries, you have things that are called preconditioning. So the preconditioning people can tolerate a lower flow for a longer period of time, whereas the ones that have a sudden infarct, a sudden thrombus, or a sudden -- is more difficult. And so everybody's going to be different.

And we get back to our clinical signs again in determining what we're doing, one of the things that can be done to modulate the amount of flow that's needed is temperature, cooling. If you cool the area, you cool the brain, the metabolic rate goes down, there's less demand for oxygen, there's less waste products produced, and so you can get more work done with lower increase in low flow. So I think there's no absolute how much blood flow you need; what duration you need for it depends on the individual patient, and that should be done based on the history of that patient plus on clinical signs.

DR. HURST: Ms. Mattivi.

MS. MATTIVI: I think I'm going to go get an ice pack for my head, thank you.

(Laughter.)

DR. HURST: Dr. Nelson. Dr. Nelson.

DR. LAYTON: Oh, yeah.

DR. HURST: I'm sorry, Layton.

DR. LAYTON: Relative to appropriate measurement, yes, there are methods there, and one aspect was of altering or have an impact on the hemodynamics of the patient and the stress level. But the other thing that I always want to look at for appropriate measurement is a technique that isn't at risk to the patient.

Relative to the next two -- and this is why I said earlier that this was such a great question -- I meant nothing has come up that's available

that's relevant relative to blood flow change or duration, which is going to be the same issue with the FDA with the next devices that come in. And that's why it's necessary to get some research and understanding of this flow rate and the potential changes and the duration that are necessary.

DR. HURST: Dr. Hammon.

DR. HAMMON: Well, you just about reached the limit of a surgeon's knowledge, but the one thing that I would say based on some studies that we've been doing is that you can have an area of the brain that undergoes changes that you would relate to as ischemic, and then you do some intervention and that area of the brain by CT scan comes back. In other words, it appears that you have rescued that area of the brain.

If you do an MRI study on that same patient, that area of the brain is not normal; if you do SPECT studies, it doesn't metabolize at a normal rate. And so you'd have to have multiple elements to measure to understand if the intervention that you've done has actually helped the patient. And I think that may go along with Dr. Goldstein's idea that you have a decrease in the size of the infarct by CT scan, but yet the patient still doesn't function well, and maybe that's one of the reasons for it.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Ray Dorsey.

I have nothing to add.

DR. HURST: Dr. Goldstein.

DR. GOLDSTEIN: Yeah, I think that these questions are probably at best, at least initially, addressed in animal models with gyrencephalic animals. I think there are too many degrees of freedom in trying to understand this non-systematically in people, at least to begin with.

One of the slides that were shown early on by Dr. Caplan was one of these classic experiments looking at the interface between penumbra and infarction, and it's a function of both a degree of ischemia and the duration of ischemia with pretty wide confidence intervals around that differentiation. But I think exploring that in animals first might be the best way to go.

DR. HURST: So, Dr. Eydelman, I think that there is at least unanimity among the Panel that this is a very confusing question or a group of confusing questions, the answers of which are, at present, somewhat unclear. There certainly seem to be advantages and disadvantages of the various imaging techniques, CT versus MR.

MR, of course, is going to be very problematic in some of these sick stroke patients. CT, there are a number of parameters with some degree of disagreement as to which one is the most important one to really reflect the status of the underlying brain parenchyma. In addition, the amount of blood flow changes are very often unclear, as is the duration.

As was mentioned, baselines for individual patients are probably important; that's probably well beyond reach of what we could

legitimately ask for right now. However, at the same time, we do have to think about what the next study is going to look at. After all, we've mentioned to CoAxia that blood flow measurements will be important, and the next question that they have to ask is what blood flow measurements do you need. And I wish we could give you some better answers on that.

DR. EYDELMAN: Thank you.

DR. HURST: Is that adequate, Dr. Eydelman?

DR. EYDELMAN: Yes. Thank you very much. We'll take what we can get.

DR. HURST: Okay. At this time, the Panel will hear summations, comments, or clarification from the FDA for 5 minutes.

DR. EYDELMAN: We do not have any summation comments at this point.

DR. HURST: At this time, the Panel will hear summations, comments, or clarifications from CoAxia, also, for 5 minutes.

DR. ALPERT: Thank you, Mr. Chairman.

First of all, we'd like to thank the members of the Panel for their time and attention to this very important discussion.

Secondly, on behalf of CoAxia, I want to thank the investigators and advisors, many of whom are the key leaders in stroke around the world, for their time and their involvement with the development of this product.

I would also note that the CoAxia team has invested 10 years

and \$100 million in the development and evaluation of FloControl and NeuroFlo, and the future is obviously a little bit uncertain. We have a currently marketed product that redirects blood flow, and we encourage the FDA to consider how we can provide training and education in the safe use of the product.

Lastly, this has been an interesting discussion here at the end. But I want to encourage both Panel members and the FDA to consider the practicality of conducting trials of the sorts that were just discussed by the Panel. How and when such trials should or could actually be done given the current knowledge in the field as you, yourselves, have identified is really a question. I remind you that patients remain in need of alternatives and we, together, need to identify appropriate means to get new products to them.

And with that, again, I thank you.

DR. HURST: Thank you very much.

I'd also like, at this time, to ask Ms. Kristine Mattivi, our Consumer Representative, whether you have any comments?

MS. MATTIVI: I would just like to thank the Sponsor for an awesome product and a great study and a lot of really interesting ideas and interesting directions for this to go. I agree with Dr. Toledano that, you know, the work needs to continue. This type of work is very important.

Perhaps this wouldn't be a poster child project for collaboration and communication between FDA and the Sponsor. It seems

like, perhaps, there were some areas where the collaboration could have been a little stronger and wound up in a little better direction in some places.

DR. HURST: Dr. Layton, our Industry Representative, do you have any comments?

Any comments?

DR. LAYTON: Yes. I'd like to comment to CoAxia, excellent presentations, excellent data. I understood a lot more today, appreciate what you did to present with it.

Also to the FDA, I thought they did a great job in their presentations, and I appreciate it also.

With respect to the device, there's no doubt about it in my mind, there are benefits, not statistically, unfortunately, but we don't always get the statistical significance relative to it. The device is safe, and we haven't seen any indications whatsoever of any issues related to the medical device, and I also felt that the risks were low relative to this interventional type of device. So it's tough one, no doubt about it. But I, myself, feel the benefits do outweigh the risks. And I know the statistical significance isn't there.

DR. HURST: Dr. Posner, our Patient Representative.

DR. POSNER: Yeah, I'd like to thank everybody. The presentations were great. I learned a lot, which I always do at these panels. And as someone whose father died of stroke, mother died of stroke, and I'm a

poster child for potential, there is a need for something that's going to be useful when they come in, and this is a step in that direction.

Oh, yeah. It's easy for me to -- because I know how much time and how much money has been invested already, but that's how science goes. I've been a researcher for over 35 years, and things don't happen overnight, and just hope that people keep plugging along.

DR. HURST: Thank you, Dr. Posner.

I'd like to thank the Panel, the FDA, and CoAxia for their contributions to today's panel meeting.

Dr. Eydelman, do you have any final remarks?

DR. EYDELMAN: I also would like to thank the Sponsor and all of our presenters during the Open Public Hearing who came to share their thoughts and views on the device.

I would like to thank all of the Panel members for very thoughtful deliberations.

And last but not least, I want to thank my team, who has spent an enormous amount of time preparing for today's deliberations.

DR. HURST: Thank you.

The December 10th, 2012 meeting of the Neurological Devices is now adjourned.

(Whereupon, at 3:48 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

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Gaithersburg, Maryland

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