DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING

Wednesday, December 10, 2008

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Hilton Washington, D.C./Silver Spring
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C O N T E N T S

C O N T E N T S (Continued)

PARTICIPANTS:

Robert A. Harrington, M.D., FACC, Acting Chair
Elaine Ferguson, M.S., RPh, Designated Federal Official

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE
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John M. Flack, M.D., MPH
Robert Harrington, M.D.
A. Michael Lincoff, M.D., FACC
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INDUSTRY REPRESENTATIVE (Non-Voting)

Jonathan C. Fox, M.D., Ph.D., FACC

FDA (Non-Voting) Members

Robert Temple, M.D.
Dwaine Rieves, M.D.
Alex Gorovets, M.D.
Scheldon Kress, M.D.
Anthony Mucci, Ph.D.

P R O C E E D I N G S

Call to Order

DR. HARRINGTON: Why don't we go ahead and get started. My name is Bob Harrington. I am a cardiologist at Duke University, and I will be serving as the Chair for today's meeting.

I am going to read some opening remarks and then I am going to ask the members sitting around the table to introduce themselves, let the audience know your affiliation plus your area of expertise so that people can understand the background from which you are approaching the questions.

For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized and we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee Members take care that their

conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of the meeting with the media until its conclusion.

Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks for lunch. Thank you.

Dr. Fox, if we could maybe start at your side of the table and go around and make the introductions.

Introduction of Committee

DR. FOX: Jonathan Fox. I am a cardiologist. I am the Industry Representative for the Committee.

DR. LINCOFF: Mike Lincoff. I am a cardiologist and Director of Clinical Research at The Cleveland Clinic.

DR. SAHAJWALLA: Maya Sahajwalla. I am a radiologist and a nuclear medicine specialist, and I work at the Naval Medical Center in Bethesda.

DR. PAGANINI: I am Emil Paganini, adult nephrologist, senior consultant for critical care nephrology at the Cleveland Clinic Foundation.

DR. DEMETS: Dave DeMets. I am a biostatistician,

University of Wisconsin.

DR. FOGEL: Mark Fogel. I am a pediatric cardiologist and Associate Professor of Cardiology and Radiology and the Director of Cardiac MR at Children's Hospital of Philadelphia.

DR. TATUM: I am Jim Tatum. I am Associate Director at NCI in the imaging area. I am a radiologist and nuclear medicine physician, but spent 25 years of my life in nuclear cardiology.

DR. TEERLINK: John Teerlink, University of California, San Francisco, San Francisco VA Medical Center, Director of Heart Failure and Director of Clinical Echocardiography.

DR. FLEMING: Thomas Fleming, Department of Biostatistics, University of Washington.

MS. FERGUSON: Elaine Ferguson, Designated Federal Official, FDA.

DR. FLACK: John Flack, Professor of Medicine and Physiology, Chair of the Department of Medicine and Chief of the Division of Translational Surgery and Clinical Epidemiology at Wayne State University.

DR. SACHDEV: Vanda Sachdev. I am a cardiologist specializing in Echo here at the National Institutes of

Health locally in Bethesda.

DR. GEVA: Tal Geva, Chief, Division of Cardiac Imaging at Children's Hospital, Boston.

DR. NEATON: Jim Neaton, Biostatistics, University of Minnesota.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University specializing in medical cognition, drug safety, and risk management.

DR. KASKEL: Rick Kaskel, Director of Pediatric Nephrology at Einstein in New York.

DR. RAMSEY: Ruth Ramsey. I am a neuroradiologist. I am Medical Director, Premier Health Imaging, and a Clinical Professor of Radiology at the University of Illinois in Chicago.

DR. MUCCI: Tony Mucci, statistician with the FDA.

DR. KRESS: Scheldon Kress, Medical Officer, FDA.

DR. GOROVETS: Alex Gorovets, Clinical Team Leader, Imaging, FDA.

DR. RIEVES: Hi. Dwaine Rieves, Division Director of Imaging and Hematology at the FDA.

DR. TEMPLE: Bob Temple, Office Director of ODE-1. That is the ODE that has Cardiorenal in it.

DR. HARRINGTON: The first item on the program is

Dr. Rieves to make opening remarks. Dr. Rieves, maybe you could pause so Elaine can read the Conflict of Interest Statement for today.

MS. FERGUSON: Good morning. I would like to first remind everyone present to please silence your cell phones if you have not already done so, and I would also like to identify the FDA press contact, Sandy Walsh, if she could stand up if she is here now. She said she would stop by perhaps a little later.

I would also like to recognize Laurie Davie, who assisted with the travel part of this meeting. She is sitting at the registration desk if any of the committee members have any concerns or comments about the travel arrangements.

Conflict of Interest Statement

The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the Industry Representative, all members and temporary voting members are special Government employees or regular Government employees from other agencies and are subject to Federal conflict of

interest laws and regulations.

The following information on the status of this Committee's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. 208 and 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this Committee are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. 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.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of this Committee 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. 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of Imagify (perflubutane polymer microspheres), injectable suspension, proposed for use as an ultrasound imaging agent indicated for patients with stable chest pain being evaluated for inducible ischemia for the detection of coronary artery disease based on assessment of myocardial perfusion and wall motion. Imagify is sponsored by Acusphere, Inc. This issue is a particular matter involving specific parties.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and temporary voting members, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

With respect to the FDA industry representative, we would like to disclose that Dr. Jonathan Fox is serving

as the non-voting industry representative, acting on behalf of all regulated industry. Dr. Fox's role at this meeting is to represent industry in general, and not any one particular company. Dr Fox is employed by Astra Zeneca.

We would like to remind members and temporary voting members 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 Committee of any financial relationships that they may have with any firm at issue.

Thank you.

DR. HARRINGTON: All right, Dr. Rieves, now we are ready.

FDA Opening Remarks

DR. RIEVES: Good morning.

[Slide.]

On behalf of our Division, I thank you for participating in our review today of New Drug Application 22-349, which is for a product generally referred to as AI-

700 Injectable Suspension and also known as perflubutane polymer microspheres.

[Slide.]

Echocardiographic contrast agents are drugs that consist of particles commonly described as bubbles or porous spheres about the size of red blood cells or smaller. After intravenous injection, the particles generally traverse the pulmonary vasculature and enter the systemic arterial system where they assist in echocardiographic visualization of the heart and vasculature.

The agents consist of a gas either surrounded by a molecular shell or compartmentalized within a porous sphere matrix. The gas within the particles provides the contrast-enhancing acoustic signals for echocardiography.

AI-700, as we will hear later, is a drug proposed for use with echocardiography as an imaging tool to assist in the detection of coronary artery disease using a rest and pharmacologic stress technique.

[Slide.]

Today's meeting follows a couple of notable regulatory actions related to ultrasound contrast agents. In 2007 and 2008, the labeling for the two approved agents was updated to include a boxed warning pertaining to the

risk for serious cardiopulmonary reactions including fatalities as shown here.

The boxed warning specifically encouraged health care providers to assess patients for the presence of any contraindication to the agents, to monitor closely patients with pulmonary hypertension or unstable cardiopulmonary conditions, and to always have resuscitation equipment and personnel available when the agents were administered.

[Slide.]

The safety of ultrasound contrast agents was discussed at this committee earlier this year, and here I highlight some of the opinions voiced at that meeting.

The discussants noted that in some situations a thorough evaluation of safety may require data from randomized, controlled studies. This perspective is particularly notable because imaging studies have, over the last many years, predominantly been single-arm studies including the major AI-700 studies we are discussing today.

Other perspectives pertain to the importance of premarket patients being representative of patients likely to receive the agents in the postmarket setting, the importance of postmarketing studies to characterize important but uncommon reactions, as well as the potential

utility of animal studies to signal cardiovascular safety problems.

These considerations regarding the safety of marketed agents are somewhat applicable to today's discussion. But today's discussion is uniquely different in that we are discussing the safety as well as the efficacy of a new contrast agent submitted to the FDA for marketing approval.

[Slide.]

As part of our background material, we supplied copies of our imaging guidances that contain certain very important study design concepts that have evolved over many years and have formed the basis for almost all contrast agent efficacy assessments and approvals.

[Slide.]

One of the most notable concepts from the guidances pertains to diagnostic effectiveness. Diagnostic effectiveness of an imaging agent can, of course, be based upon clinical outcomes indicative of direct clinical benefit. However, diagnostic efficacy may also be based solely upon the assessment of performance characteristics, such as the assessment of sensitivity and specificity.

In this concept, we acknowledge that the clinical

benefit of the diagnostic information from the contrasted image may be self-evident, such that clinical studies are not needed to establish the clinical usefulness of the information as when a contrasted image detects a brain mass, a vascular lung lesion, or intracranial hemorrhage.

In this paradigm, the performance characteristics generally compare the non-contrasted image and the image obtained using the contrast agent. In general, one anticipates that the contrast agent will add diagnostic value over the non-contrasted image in order to justify exposure to the contrast agent's safety risk.

To reiterate, at the conclusion of the premarket data collection, the benefit from a new imaging contrast agent must either be self-evident, or if it is not, then, that benefit should have been established in the clinical studies.

As we will see shortly, the sponsor of AI-700 performed clinical studies generally consistent in design with those studies used to assess most other contrast agents--that is, an assessment of diagnostic performance characteristics.

[Slide.]

The ultimate risk and benefit assessment for

diagnostic imaging agents differs somewhat from that for therapeutic products in that the interpretation of the clinical data may require more understanding of the clinical importance of the diagnostic information in the context of the risk associated with the drug and the unique risk associated with a misdiagnosis.

Ultimately, however, the risk-benefit assessment is somewhat similar to that for other drugs including therapeutics, and involves a degree of judgment much as one might use when assessing an oncologic drug that offers a very modest survival advantage despite considerable safety risk.

[Slide.]

Our agenda today is fairly straightforward and consists of Acusphere's summary of the AI-700 data followed by a break and our FDA summary and comments upon the data.

Subsequently, we have allotted some time for questions to the presenters, lunch, and open public hearing, and finally, the discussion of our questions.

I want to emphasize that our review of AI-700 is ongoing and the Committee's comments and response to our questions should importantly help us interpret the submitted data, and to focus our subsequent review efforts as we move

towards completion of this NDA review.

Again, we appreciate your attendance and thoughts, and I will return the podium to our chairman.

Thank you.

DR. HARRINGTON: Thank you, Dr. Rieves.

The next series of presentations will be from the sponsor and leading off will be Michael Slater, who will make introductory remarks and then introduce the speakers on behalf of the sponsor.

Sponsor Presentations
Introductory Remarks

[Slide.]

MR. SLATER: Good morning, ladies and gentlemen. My name is Michael Slater. I am Senior Vice President of Regulatory Affairs and Operations at Acusphere.

[Slide.]

I will start this morning's presentation from Acusphere with the agenda and some introductory remarks.

Following my remarks, Dr. Michael Picard, past President of the American Society of Echocardiography, will discuss the use of ultrasound contrast agents for the detection of myocardial ischemia.

He will be followed by Professor Senior, who uses

both ECHO and SPECT in his practice, to show you some images obtained from the AI-700 studies.

Dr. Richard Walovitch will discuss the efficacy results from those studies, and he will be followed by Dr. Howard Dittrich, who also uses both ECHO and SPECT in his practice, to talk about the safety of this product.

We are very pleased today to have Professor John Lambris with us. Dr. Lambris is past President of the International Complement Society, and he will discuss the innate immune response and complement activation and, in particular, how it relates to the removal of intravenously injected micro particles.

Finally, Dr. Walovitch will conclude with some remarks about the risks and benefit of AI-700.

[Slide.]

We have developed AI-700 to address an unmet clinical need that was first identified in the 1980s. Echo cardiologists had a vision for a contrast agent that would enable perfusion imaging with stress echo, which would allow for a wide range of information to be captured in one convenient, low cost, and radiation-free test.

[Slide.]

As you know, two ways to stratify patients for

invasive angiography are nuclear SPECT imaging and stress ECHO cardiography. Both of these have significant limitations.

SPECT is the preferred method because it's capable of assessing myocardial perfusion, a sensitive marker of coronary artery disease. But it is expensive, time consuming, and exposes both patients and health care workers to ionizing radiation.

Stress ECHO is a low cost and convenient technique that obtains a wide variety of anatomical information including wall motion. But this is a less sensitive mark of cardiac disease than perfusion.

[Slide.]

Now, historically, agitated saline was used for imaging but these air bubbles do not persist in the blood so early efforts on creating an ultrasound contrast agent focused on encapsulating air, nitrogen, or fluorinated gases with natural materials like albumin or lipids, and these agents have been used successfully to enhance the endocardial border of the left ventricle in patients with suboptimal imaging. However, these early generation agents are not approved for perfusion imaging. Their natural material shells are fragile and break under imaging

conditions.

Our goal was to develop an agent to maintain a strong echo signal during cardiac perfusion imaging. We worked with acoustic physicists to engineer robust micro particles from synthetic materials to achieve this goal.

The materials used in AI-700 are polymers which are biodegradable. They are used in dissolvable sutures and in some drug delivery products, and we maintain tight control over the size distribution.

The average size of these microspheres is around 2 microns, well under half the size of a red blood cell. We control them to have at least 99 percent of them less than 10 microns in diameter.

The product is stable in vivo, it travels with the red blood cells. This gives you the prolonged visualization of blood flow through several minutes of imaging, and then they are rapidly cleared from the circulation.

The gas contained within the microspheres is exhaled within minutes.

[Slide.]

As Dr. Rieves has mentioned, the indication for Imagify is as an ultrasound imaging agent which is indicated for patients with stable chest pain being evaluated for

inducible ischemia for the detection of coronary artery disease based on the assessment of both myocardial perfusion and wall motion. This is accomplished with rest and stress techniques.

We are proposing that use of AI-700 initially be limited to those patients who are indicated for pharmacologic stress testing, which is the way we performed our clinical trials.

In clinical application, this agent will be used along with other clinical information available to the physician to triage the patient for more invasive testing such as angiography.

[Slide.]

Let me assure you that we are committed to patient safety and providing whatever information will help the Advisory Committee and FDA assess the risks and benefits of AI-700. We are also receptive to proposals for strategies to better evaluate the risk to benefit profile and to reduce risks during clinical use of the agent.

One question that FDA has asked you is about the importance of establishing the added value of AI-700 over non-contrast ECHO. AI-700 adds perfusion information that is not available from non-contrast ECHO, and as Dr. Picard

will discuss shortly, it is well known the perfusion is a more sensitive marker of disease than wall motion.

[Slide.]

We did compare AI-700 with non-contrast ECHO in Phase 2 and having reviewed the data at an end of Phase 2 meeting with the FDA, we all agreed that Phase 3 should evaluate the performance of AI-700 relative to angiography and SPECT with clinical outcome measures.

After the start of the Phase 3 trials, with a change of division leadership at FDA, we were asked to change both ongoing Phase 3 studies to the current non-inferiority design, which compares AI-700 with SPECT, which of course is approved and widely used for the perfusion imaging indication.

However, as you will hear, this did result in a loss of patients to the efficacy population. Results from those trials will be presented today and demonstrate that AI-700 enables ECHO to detect disease in intermediate risk patients presenting with stable chest pain.

[Slide.]

AI-700 is the first imaging agent to provide simultaneous assessment of cardiac perfusion and wall motion in one test.

We will present the case that AI-700 is clinically comparable to SPECT, it has potential advantages over both non-contrast ECHO and SPECT, potential advantages over non-contrast ECHO as I have mentioned, include the ability to obtain perfusion information as well as wall motion, and also, importantly, an increased number of evaluable images.

Potential advantages over SPECT include real-time anatomical imaging with high spatial and temporal resolution, and the ability to obtain rest and stress wall motion information in a faster procedure, is widely available, cost effective, and involves no ionizing radiation.

[Slide.]

Turning to safety, you will see in our safety presentation that there were no deaths or immediate life-threatening events observed in the studies. There are safety signals from animal studies and from clinical trials include in the occurrence in a small cohort of patients of cardiopulmonary effects that are self-limiting or treated with standard care.

The physiological response due to the injection of micropods that may be responsible for some of the observed events will be discussed in more detail by Dr. Lambris, who

is expert in this area.

Some of the adverse events are due to the stressor agent, the rate of adverse events seen with AI-700 and dipyramidal stress appear to be comparable to other pharmacological stress procedures routinely used in this patient population for SPECT imaging with dipyramidal and adenosine, and somewhat lower than that described in the literature for non-contrast ECHO with dobutamine.

We also present risk mitigation strategies today. As I mentioned, initial use will be limited to those patients who are indicated to pharmacological stress. We are also proposing post-approval safety surveillance studies as have recently been required for other approved ECHO contrast agents, and we have proposed contraindications for at-risk patients in the NDA, for example, patients with acute cardiac conditions or obstructive pulmonary disease.

[Slide.]

In our presentation today, we will present the case that AI-700 is the first imaging agent to conveniently provide assessment of both cardiac perfusion and wall motion, that the acute safety risk of AI-700 can be managed with standard care, and that with the selected target patient population, with appropriate contraindications, and

with the proposed post-approval safety surveillance studies, AI-700 has a favorable overall risk to benefit ratio.

Thank you. I will now introduce Dr. Michael Picard.

Use of Ultrasound Contrast for the Detection of Myocardial Ischemia

DR. PICARD: Good morning.

[Slide.]

I am going to very briefly discuss the diagnostic tests that we currently use in cardiology to diagnose coronary artery disease. I guess I should apologize in advance to the cardiologists on the panel. This may be a bit simplistic, but I hope it will help all panelists get on an even playing field.

My goal is to show you where some of the gaps and deficiencies currently exist and particularly why with echocardiography there are some deficiencies and why there is a need for AI-700.

[Slide.]

I think to do this best, we should first look at the pathophysiology of coronary artery disease and myocardial ischemia, the development of myocardial ischemia.

On this schematic I have shown you some of the

stages or the steps that are involved.

We obviously start with the narrowing of the coronary artery. That is the primary state. If the heart undergoes a stress or increased work, and there is a need for increased oxygen, when there is a narrowed coronary artery, there becomes an imbalance between what can be supplied and what is needed. That will develop into a perfusion defect.

If that perfusion defect persists for a period of time, then, it will impact the contractility of that region of the heart muscle supplied by that artery, which will result in a regional wall motion abnormality.

Again, if this continues over time or increases in severity, the electrical and metabolic milieu of the myocytes change so that we can detect on electrocardiogram some changes consistent with myocardial ischemia, and again with further progression, patients will develop, as lactic acid builds up, patients will develop symptoms such as the classic chest pain.

[Slide.]

Now, the gold standard to detect coronary artery disease is invasive angiography, coronary angiography. But angiography has several limitations. Most prominently, it

is an invasive test, and with that, it has an attendant mortality risk. There is exposure to ionizing radiation so there is risk of malignancy.

With the iodinated contrast that is used, there is risk for contrast-induced nephropathy and renal disease, and ideally, because of these risks, we would want the benefit to be high and particularly focus this test on patients who have significant coronary artery disease.

But many studies have shown us that a significant minority of patients will have a normal angiogram when undergoing this test, and so we are exposing patients without significant disease to this test.

For that reason, there is a need for non-invasive gatekeepers, if you will, to screen for coronary artery disease, and appropriately triage the right patients to invasive angiography.

The current guidelines for chronic stable coronary disease tell us that there are two imaging stress tests that are available and recommended, the first being the nuclear myocardial perfusion imaging, which I will also refer to as SPECT, single photon emission computed tomography, and stress echocardiography.

[Slide.]

Now, there are two ways to do the stress imaging. We can either do it with exercise or with pharmacologic agents. Both of these will develop that controlled state of ischemia that is required for the detection by these imaging tests.

Now, in practice, exercise is the preferred method. As clinicians, the exercise test not only provides us the information about coronary disease but also tells us about the functional capacity of the patients, and that may be important as we decide how to prescribe exercise and their rehabilitation, also, help us in terms of treatment goals, and tell us how much work a patient can do before they will actually develop myocardial ischemia.

However, as many as 50 percent of the patients at risk or needing a diagnosis of coronary artery disease, or testing for coronary disease, cannot exercise or cannot exercise sufficiently to do a substantial workload to induce that ischemia.

For that reason, pharmacologic agents are used to mimic the effects of exercise.

With the stress ECHO, we used dobutamine, an inotropic agent, so we are increasing the oxygen demand of the heart, and with nuclear myocardial perfusion imaging, we

typically use vasodilator drugs. So we alter the supply of blood to the heart so that normal coronary arteries will dilate when exposed to the vasodilato so blood will increase in areas supplied by normal coronary arteries, and the blood flow will not increase in areas that are supplied by diseased coronary arteries, so we pick up that mismatch.

[Slide.]

I should also point out before I discuss this slide that the patients who can't exercise typically are patients that we are very concerned about the risk of coronary artery disease so that we are willing to accept a higher risk because there is added benefit in those patients.

Now, if we look at myocardial perfusion imaging, a few comments are worth noting. It is currently the most common test that we will use in the non-invasive arena for imaging stress.

The reason for that is that we are able to assess myocardial perfusion if you remember from that ischemic cascade slide. With computerized software we are able to quantify that perfusion. However, there is limited anatomic information available from that test as you see in contrast to echocardiography.

Limitations include the fact that there is exposure to ionizing radiation, so again there is that risk of fatal malignancy. As also noted by the prior speaker, because we are handling nuclear-labeled agents, there is environmental impact, there are regulatory issues, there are biohazard issues for both patients, physicians, and the technologists who handle these agents.

In addition, the test is more expensive than the echocardiogram, so this adds to our escalating costs in cardiac imaging, and the test takes a longer period of time than the stress echocardiogram.

It can take up to six hours in many patients, and also is dependent on the supply of the radio-labeled technetium. There are very few sites around the country or in North America that manufacture the agents so that, when the factories are shut down, there is no agent available for this type of testing, and these tests can't be performed.

[Slide.]

Now, with echocardiography, I think the primary advantage is that this is a real-time or provides a real-time assessment of both the anatomy, the cardiac structure, and the cardiac function, and not just of the left ventricle but of the entire heart.

So, unlike SPECT, where there is a series, a summation of the heart beats required, we are seeing each individual heart beat in real time. So the diagnosis can be made immediately. There is no processing of the imaging that is required.

Also, importantly, since we are looking at other aspects of heart structure and function, if this test is negative, yet the patient has chest pain, then, we can identify several other potential etiologies for that symptom.

For example, aortic stenosis, which can present as chest pain, pericarditis, and other pericardial diseases. Also, we can assess the regurgitant valve lesions, we can assess pulmonary hypertension that can develop with exercise and may be the trigger for chest pain.

So, we get a lot of other information besides just the status of the coronary arteries.

In addition, there is no ionizing radiation. The test can be performed relatively efficiently and quickly, as short a time as 15 minutes or, on average, probably 30 minutes, but certainly in less than 60 minutes.

It is widely available. Most cardiology practices, and certainly many primary care practices, have

ECHO machines available, so that this test can be done on site at the time that it is needed, particularly in outpatients.

In contrast, the nuclear test may not be available on site, particularly in primary care practices, and those patients may have to get that test elsewhere.

In contrast to nuclear imaging, the spatial and temporal resolution is higher. Sso that will allow us potentially to see smaller areas of ischemia or perfusion defects with higher assurability.

Now, there are certainly some very important limitations to the stress echocardiogram. First, as is obvious, there is no information about perfusion with the current stress echocardiogram, and also, importantly, a significant minority of the patients do not have adequate imaging quality to assess the wall motion, the ventricular regional dysfunction or regional function, and the reason for this is that ultrasound doesn't pass very well through air, and so that if we have a patient with lung disease, with COPD, or an obese patient who has a larger chest, we may not get as much ultrasound into the heart, to have it bounce off the heart and come back to the machine.

[Slide.]

As you are all aware, for that reason, ultrasound contrast agents have been approved to enhance the images in these patients with suboptimal echocardiograms basically to opacify the left ventricle and to delineate the left ventricular endocardial borders.

So, that is a good thing because it enhances our imaging and takes those 25 percent of poor quality ECHOs and makes them sufficiently diagnostic. However, it is important to point out that the safety and efficacy of the two, currently approved agents, Optison and Definity, have not yet established their safety and efficacy with exercise stress or with pharmacologic stress imaging, what we are talking about today.

[Slide.]

So, if we go back to the ischemic cascade, as I pointed out, we use angiography, the invasive test, to see the anatomy, to see that narrow coronary artery, and if we want to use a non-invasive screen, we can use SPECT imaging to assess that perfusion defect, or we can currently use a non-contrast stress echocardiogram, which allows us to see the regional wall motion abnormality.

As you see, that wall motion abnormality is a little bit higher up the chain. So that is why the

detection will not be as sensitive a test as tests that assess for perfusion defects.

Now, I should also add we now have CT angiography and magnetic resonance imaging of the heart that will also allow us to assess coronary artery disease. They are currently less available to the wide group of patients, so they are less commonly used as screening tests. But, again they function sort of in this range, again lower than the current stress echocardiogram.

With the addition of AI-700 ECHO, two things. One is we get that enhanced image quality or ability to assess the wall motion to see the endocardial borders better and we increase our ability to assess regional wall motion abnormalities. But, more importantly, we now can assess myocardial perfusion, so it gets us down at the level as the nuclear myocardial perfusion imaging.

[Slide.]

So AI-700 addresses some very important clinical needs. Its advantages over SPECT, I have outlined the speed of the test is better, there is no ionizing radiation, it is more widely available to primary care patients, lower cost.

It provides us that real-time imaging, and that complete cardiac assessment with high special and temporal

resolution, and its advantages over the non-contrast ECHO are obviously the perfusion that we are going to be talking about today, and the increase in the valuable images so that there are less patients that need to be referred to other tests because of a non-diagnostic or incomplete imaging, and the vasodilator that is used for the stress is actually safer than the dobutamine that we currently use in stress echocardiography.

I think, taken in toto, the synergy of looking at both perfusion and wall motion together is also very, very important. There are situations where there are mismatches, where there is decreased physician confidence in the interpretation, so being able to see both at the same time really helps the practicing physician make appropriate calls on the stress test.

[Slide.]

Now, I would like to introduce Professor Roxy Senior, who will show you some examples of imaging with AI-700.

AI-700 Imaging

DR. SENIOR: Thank you. Good morning, ladies and gentlemen.

[Slide.]

As an investigator in this study who has administered AI-700 in nearly 100 patients in the study, I find AI-700 to have a performance which is robust in the sense that it can be easily reconstituted without requiring any complicated procedures, can be administered, it is easy to use in that it can be given in a single bolus, and you can obtain an image over a prolonged period of time because of the prolonged contrast enhancement, as a result of which one can assess perfusion and function simultaneously and as you have heard from Dr. Picard, that does provide synergistic information for the detection of coronary artery disease.

For the next part of the presentation, I will go through a few points first. I will just summarize what I am going through for the rest of the presentation. The first what I am going to discuss is what happens when we inject the AI-700, the sequence of events or sequence of images that we obtain, the scan planes that we use, and then I will show you an example of normal myocardial perfusion with the AI-700, how the images look.

Then, I am going to show you examples of detection of subendocardial perfusion defects with the AI-700 which is unique, because it has got a high temporal and spatial

resolution, and this is one of few matching techniques. So you can look at subendocardial defects unlike SPECT imaging, which doesn't have a good spatial resolution and therefore, you miss the subendocardial resolution defect that helps to localize coronary artery disease and increases the accuracy of detection of coronary artery disease. More importantly, sensitivity.

Then, I will show you another example of how a non-diagnostic echocardiography meaning when you do an ECHO, you don't see good images, and we would normally send those patients to other imaging modalities, you know, patient inconvenience, more tests but, with this agent, converting that into diagnostic study.

Then, I will move on to show you an example of how you can just see the perfusion defect without wall motion abnormality as has been shown by Dr. Picard in the ischemic cascade, and makes such a technique more sensitive compared to stress echocardiography where you don't assess perfusion but where you only look at wall motion--that is, if you don't inject any agent to look at perfusion.

[Slide.]

So, here what we see is an image where you see the contrast has been injected and you can see it in the right

ventricle now, and as the contrast moves through the primary circulation into the left side of the heart, you can see the opacification of the left ventricle.

You can see clearly the wall thickening, which is very important to assess, and you can see the contrast going into the myocardium, into the microvasculature, and I must tell you that this is the only technique at bedside where you can look at microvasculature in the manner that we are looking at it now, at the bedside.

No other technique is available at the bedside to look at the microvasculature, and what you see here as we go on is a white sheet coming up that is just high energy impulse clearing the microwell from the myocardium and looking at replenishment of the myocardium.

[Slide.]

Now, these are the scan planes which we obtained images. The first is the apical four-chamber view. It is called four chambers because you can see all the chambers. But down below what you see here is just the left ventricle because we are interested in only the left ventricle, we are honing onto the left ventricle, and on the right is the lateral wall which is supplied by the circumflex artery.

Then, you see at the top the apex, and you see the

whole of the septum, the distal part of the septum and the apex as supplied by the left anterior descending artery, the proximal part of the septum, and this view is supplied by the right coronary artery.

Then, we go on to the next view, which is the two-chamber view because you see both the left ventricle and the left atrium, and when we look at the left ventricle only, on the right is the anterior wall where you see the left anterior descending artery territory, and on the left is the interior wall where you see the right coronary artery territory.

Then, we move on to the third view, which is the three-chamber view, where you see the left ventricle, the left atrium, and the aorta. But here you see only the left ventricle because again we are interested in looking at the left ventricle.

On the right is the septum supplied by the left anterior descending artery. On the left is the posterior wall, which is supplied by the left circumflex artery. So, by obtaining all these views, it gives you a tomographic depiction of all the walls of the heart, depicting the three vascular territories that are supplying the heart.

Now, the other point I would like to emphasize,

all these three views that you see are acquired within three to four minutes. It just takes three to four minutes to acquire one to the other, so we finish the study in three to four minutes giving just one injection.

This is an example of a normal study. Actually, you can see the wall motion is normal, the perfusion is homogeneous, and myocardium, so it is a completely normal study.

[Slide.]

Now I move on to some case discussions here. This a 64-year-old white male with atypical chest pain with a host of risk factors for evaluation of chest pain.

[Slide.]

What we see here first is a non-contrast image and you can see the left ventricle. But you can appreciate that you don't see the septum that well but, as soon as we inject the contrast, you can see the septum, the lateral wall very, very clearly, and you can see the homogeneous contrast opacification of the myocardium, and this is a normal resting study.

Then, the third view is where vasodilator is injected and what you see here very clearly is a perfusion defect extending from the lateral wall to the apex right

down to the distal septum.

In the distal septal area, where you see is a subendocardial perfusion defect. In fact, you can see that in the epicardial region, which is more towards the left. You can see the contrast but there is a subendocardial defect there while the rest is transmural defect. But, with that you can also appreciate what is underlying wall motion abnormality, and so according to this image, this patient has a circumflex disease and with a possible left anterior descending artery territory because it involves the septum and the apex.

[Slide.]

If we go on to the next image, and this is a coronary arteriogram, and you can see here sequential severe lesion in the left circumflex artery territory, and what you see here is that the circumflex artery actually is wrapping around the apex supplying the part of the apex and the distal part of the septum. That is why it was causing the perfusion defect even there.

[Slide.]

Now, this is the example from the same patient looking at SPECT images and you see here an apical lateral perfusion defect which normalizes at rest. But you don't

see the perfusion defect in the distal septum because as I have said, SPECT doesn't have the resolution to pick up subendocardial defects.

[Slide.]

So, in summary, we have a patient here who has got flow-limiting left circumflex stenosis, which was predicted by AI-700, also by SPECT in this case.

[Slide.]

We move on to another example of a 71-year-old white male with exertional chest pain with hypertension and hyperlipidemia, and has atrial fibrillation.

[Slide.]

Again, on the left you see a non-contrast image. As an echocardiographer, as a cardiologist, when you look at this image, you know, you look at it, you shake your head and say sorry, I can't go on any further, because you can't see the left ventricle very clearly, you can't even assess the left ventricular function.

These are the patients that we will straight away refer to MRI for assessment of LV function, for SPECT imaging for assessing perfusion. So we are going to send the patient for two different tests to get the information.

We will try to do the study, of course, and we

will charge the patient for doing that study, send the patient for SPECT, send the patient for MRI, so we are going to do three tests. But here, with injection of contrast, you can now clearly see the left ventricular function, now you can make a diagnosis that this patient has got normal resting LV function and normal perfusion.

This patient then went on to have a vasodilator stress and with the vasodilator stress, you can clearly see a perfusion defect in the septum, the distal septum and the apex, and there is underlying wall motion abnormality.

This patient clearly has left anterior descending artery stenosis.

[Slide.]

This is the coronary arteriography of the same patient. You can see the left anterior descending artery has got significant stenosis in the mid-LAD region as predicted by AI-700.

[Slide.]

SPECT also showed similar disease. So, in summary, we have a patient with flow-limiting LAD stenosis which was predicted to have by AI-700. This patient, as I have said, you know, normally, would have gone on and had other tests to make this diagnosis.

[Slide.]

Now, we move on to another patient who is a 77-year-old white male, previous infarction, with chest pain, hypertension, and hyperlipidemia.

[Slide.]

Again, on the left you see a non-contrast image. Now, here we see a very nice wall motion but we don't see perfusion unless we inject contrast here. So, here we see perfusion, which is completely normal. So it's a completely normal study in the sense that it has got normal function and normal perfusion.

Then, we went on and did vasodilator here in this patient, and what you see here is a clear perfusion defect which is transmural in the lateral wall, and the apex. But there is a subendocardial defect from the mid-septum on to the distal part of the septum, and so according to this study, according to the perfusion defect, this patient has multiple vessel disease.

Now, what you note here is absence of any wall motion abnormality. So this is an example where if we just had been looking at wall motion and not perfusion, we wouldn't have picked up disease.

In fact, when the patient underwent coronary

arteriography, the patient had severe left circumflex stenosis and that accounted for this large perfusion defect in the lateral wall but also you can see there is a defect. There is a narrowing in the LAD region which is less severe than circumflex, and that is the reason for the subendocardial perfusion defect.

So, subendocardial perfusion defect picks up moderate disease, while transmural perfusion defect means severe disease. Yet, the wall motion was completely normal in this patient.

The SPECT did not pick up the disease actually. You can se that SPECT is completely normal. Now, one of the three readers thought there was a defect in the anterior wall but put it down to attenuation artifact.

In summary, this patient has multiple flow-limiting stenosis correctly diagnosed by AI-700, SPECT did not show any evidence of disease.

[Slide.]

In summary, AI-700 does have a robust performance. It allows simultaneous assessment of wall motion and perfusing in real time, and that has a synergistic value for the detection of coronary artery disease.

It clearly depicts subendocardial perfusion

defect, which as I have mentioned, is important to diagnose moderate disease and to localize disease. It is very important to localize where the disease is, and then finally, it has the ability to convert poor quality images to diagnostic quality images.

In this study, 25 percent of images were non-diagnostic. With AI-700, 99 percent of the images became diagnostic, so these patients need not have been sent to any other test.

So, here, as a cardiologist, I think I am quite excited to know that if you have an agent like that, which can be given at the bedside, and no other technique besides echocardiography can be used at the bedside, and we can assess cardiac structure, function, and perfusion at one sitting, because we can interpret the data very quickly, rapidly, I think this is the type of agent that all cardiologists I think would like to see in our practice.

Thank you.

[Slide.]

We move on to the next speaker, Richard Walovitch.

Clinical Efficacy

DR. WALOVITCH: Thank you very much, Dr. Senior. What I am going to do today is provide you with an overview

of the Phase 3 efficacy results for AI-700.

[Slide.]

The Phase 3 trials were international, multicenter, open-label, safety and blinded efficacy studies that were conducted in North America, Europe, and Australia.

The objective of these trials were to demonstrate efficacy and safety of AI-700 stress ECHO in stable chest pain patients being evaluated for inducible ischemia for the detection of coronary artery disease.

The trial design was the same for both studies. They were non-inferiority studies using a ratio of AI-700 ECHO performance to that of SPECT for each parameter, accuracy, sensitivity, and specificity.

[Slide.]

The comparative standards for both trials were Technetium 99m, imaging with gating and quantification. The dosing was two injections of AI-700, one during rest and one during stress. The stress in all cases was dipyridamole for ECHO, and vasodilatory stress for SPECT with the majority of those being dipyridamole same day.

The key inclusion and exclusion criteria were the same for both trials. It was adults, stable chest pain, indicated for pharmacologic stress testing.

The exclusion was clinically unstable conditions within 7 days, or change in the status between the protocol required imaging procedures. There were differences, however, in the inclusion and exclusion criteria. For the 32 trial, everyone had to have a same day ECHO and SPECT procedure.

For the 33 trial, everyone had to have had or had been scheduled for a recent coronary angiogram.

There were differences, as well, with regards to exclusion. For the 32 trial, anyone who had a recent CABG was excluded, and CABGs were excluded from the 33 trial.

[Slide.]

There were a number of components to the efficacy evaluation in these trials. There was independent laboratory assessment of a variety of imaging data. With regards to the angiographic LVG data, we had an independent core lab that assessed the degree of stenosis using QCA.

There was also a nuclear cardiologist. This was a non-blinded coronary artery disease reviewer, who in the absence of angiographic data, determined truth using SPECT data, ECG data, and clinical data, but did not have access to the AI-700 results.

For ECHO reading, there were three independent

blinded readers for each trial, and for the SPECT reading, there was one reader for the 32, and three independent readers for the 33.

[Slide.]

Our primary efficacy analysis was a stepwise analysis with accuracy being the principal primary endpoint. There is regulatory precedence for accuracy. Accuracy is a nice stepwise progression down to sensitivity and specificity in a population where disease prevalence is approximately 50 percent as in our trials.

It represents a balance of both sensitivity and specificity. Accuracy is also the only diagnostic parameter that includes all the patients in the intent to treat population, and it is also the most objective parameter, because either sensitivity or specificity can be read with 100 percent.

For example, for sensitivity, you just call everything disease, you have 100 percent sensitivity. The converse is true for specificity. But accuracy really requires training and expertise.

Now, in our trials, we evaluated the ratio of AI-700 ECHO performance to that of SPECT with a margin of 0.83 and an alpha of 0.05. There was a preservation of the Type

1 error rate for each step.

Success was non-inferiority for at least 2 out of 3 of the ECHO readers. If accuracy was met, we stepped down, and we looked at sensitivity and specificity.

[Slide.]

Now, the interdependence of accuracy, sensitivity, and specificity can be seen on this cartoon. When disease prevalence is approximately 50 percent, as it is in our trials, accuracy is a fair balance between specificity and sensitivity. However, if accuracy is low, there is no value to do any other assessments.

The objective of our trials were to have accuracy that was non-inferior to the comparator SPECT, and at the same time, maintain specificity and sensitivity within a narrow area for non-inferiority.

Now, when we look at disease prevalence, if disease prevalence is either very high or very low, accuracy is no longer a balanced representation of both sensitivity and specificity. With high disease prevalences, you can see here you are getting a stable estimate of sensitivity. You can see there is a tremendous variability and specificity.

[Slide.]

So, what I am doing here is showing you a

simulation of the lowest allowable ECHO point estimates using a margin of 0.83 and a sample size as we had in our trial, our 33, our larger trial.

Just for example, when you have this margin and you look at a SPECT value of 70, the lowest allowable value for non-inferiority would be 66. So, this margin of 0.83 really results in around ECHO values that can be no less than 5 percent of the SPECT reference value for the point estimate.

[Slide.]

Now, I would like to switch and talk a little bit about the definition of truth in our trials. The majority of patients had truth determined using quantitative coronary angiography. The criteria of disease in this assessment was 70 percent diameter stenosis or regional wall motion abnormality.

If they didn't have coronary angiography, we looked at the history for coronary artery disease, and that was the truth for 7 percent of the patients. The remaining patients did not have angiography or no history of coronary artery disease, had the assessment made by the non-blinded nuclear cardiologist who looked at the SPECT, clinical history, ECG without the AI-700 information.

[Slide.]

Now, this is study population sample sizes, the safety and efficacy, and Mr. Slater has already commented on the fact that the differences in these populations are primarily attributable to changes in the trial design, and we have done a number of sensitivity analyses, putting many of these patients back into the trial, and I will talk to you a little bit about that later.

One important thing on this slide is disease prevalence. If we take a look at the disease prevalence in the 32, we see it's 44. And here it's 58. So this is around the 50 percent disease prevalence I was talking about.

The rate of disease isn't much higher in the 33 as you would expect, because these patients had to be scheduled for the ECHO procedure. So, if it was an emergency cath, obviously, they wouldn't schedule them for a stressor study.

[Slide.]

So, now I am going to take you through the trial data for the 32 and the 33. I am showing you the absolute values for the parameters of accuracy, sensitivity, and specificity, and then I am going to show you p-values as they relate to the ratio for the comparisons.

When we look at accuracy, we are seeing a very consistent result for all the readers of around 70 percent and all three of the ECHO readers were non-inferior compared to the SPECT reader.

Now, when we look at sensitivity, we see a little bit more variability. We see that the first ECHO reader read with non-inferior sensitivity compared to the SPECT comparator but the other two ECHO readers were what we call conservative readers.

They were less likely to call out disease and they read with lower sensitivity, although the reader who read with the lowest sensitivity had the highest positive predictive value and read with very high specificity.

So, there was a tradeoff between sensitivity and specificity for these readers as you can see here, and the results of the trial were non-inferior accuracy with superior specificity.

[Slide.]

Now, I am going to switch to the 33 trial and here we are comparing the three ECHO readers versus the median SPECT reader, because we had 3 SPECT readers, we had to have an individual comparator, and we took the median value for that.

Here, once again you can see very consistent accuracy values for all the readers, the ECHO values are very similar to the SPECT non-inferiority for all three ECHO readers.

Now, when we are looking at sensitivity, and this is compared to QCA angiography, we see superior sensitivity here, and what you have is you have a nuclear reader that was a more conservative reader, read with higher specificity than sensitivity, and when we do this comparison, we can see that only one of the ECHO readers met all three criteria. But we end up having that tradeoff for this reader and this reader who ended up being superior on sensitivity, but didn't meet the non-inferiority margin for specificity.

[Slide.]

Here is our cartoon again and what we are seeing is a counterbalance. When accuracy is not inferior for these two modalities, readers either read conservatively or more aggressively. A conservative reader will have a tendency to demonstrate superiority for specificity but not make non-inferiority for sensitivity.

[Slide.]

The converse is also true.

[Slide.]

Now, I am going to show you all the data from the 33 readers. So you are seeing 3 ECHO readers, as well as the 3 SPECT readers, and we are starting off with accuracy, and once again you can see that even though we had a comparative SPECT reader who had a higher specificity than sensitivity, all 3 of the SPECT readers and all 3 of the ECHO readers read with very consistent accuracy.

[Slide.]

When we look at specificity, we see that there is some variability for both modalities.

[Slide.]

And when we look at sensitivity, we can also see variability more so with SPECT than with ECHO.

[Slide.]

So, we had a number of sensitivity analyses as I mentioned, as well as a number of secondary efficacy analyses. We looked at sensitivity analyses with different populations, adding back in the patients. We also looked at different relative risk margins of 0.83 to 0.87, which was the recommendation from the Agency, and the primary efficacy results of both trials were unchanged.

We also looked at the definition of truth, looking at a 50 percent stenosis instead of 70 percent stenosis.

Once again the primary results were unchanged.

Importantly, all of the ECHO readers showed positive correlation between disease severity and sensitivity. For example, in multivessel disease, all readers had greater than a 70 percent sensitivity. In addition, ECHO defect size positively correlated with the probability of coronary artery disease. So, in this analysis, we looked at single and multivessel detection by the ECHO-blinded readers, and they had an odds ratio.

Their odds ratio went up in single and went up more in multivessel, and the highest odds ratio in single vessel disease was the most conservative reader, the reader who read with the lowest sensitivity had the highest odds ratio in single vessel disease.

In addition, we did another analysis where in the patients who had coronary angiography, we looked at localizing the disease to one of three major vascular territories, and we were able to determine that when we called it a true positive for ECHO or SPECT, and they localize, we were able to see what degree of localization these two modalities provided, and for the ECHO readers, all six ECHO readers, the range was 84 to 97 percent of the sensitivity that they had on baseline. For the two SPECT

comparators, the range was between 69 and 74 percent.

[Slide.]

Let's just turn back to accuracy one last time here and take a look at the data across both trials, and you can see the consistency in the values all around 70 for all the ECHO and SPECT readers.

[Slide.]

Now, there are differences in our trials between sensitivity and specificity, and in order to better address that, we looked at a few integrated analyses, and one of those integrated analyses is a multi-reader receiver operator characteristic curve, which looks at the relative tradeoffs of sensitivity and specificity, and gives you an indication of whether each modality is doing the same degree of trading off. So let me show you that data here.

Here we have the six ECHO readers, three from each trial, and here we have the four SPECT readers, and I think you can see that the shape of these curves, as well as the estimated area under these curves are very similar. So it looks like they are making the same tradeoffs, the ECHO and SPECT readers, and the range of values are in the same area as well.

[Slide.]

Another thing that we did to look at the comparison of ECHO to SPECT is to move away from the somewhat arbitrary margin that we had and look at only superiority and inferiority.

There is a lot of subjectivity to selections of these margins, so we wanted to just look at something that is statistically defined, which is a superiority where the lower bound of the confidence interval must be above one.

So, when we do this, and we look at the 32, it's a pretty simple comparison. We have one SPECT reader and three ECHO readers, and what you can see here is these ratios for sensitivity and specificity, and you can see in the two pairs here that there is superior sensitivity for SPECT. But, in those same two pairs, there is superior specificity for ECHO. So here is the tradeoff between those two parameters we were talking about.

[Slide.]

When we look at the 33, it's a more complicated comparison. There are nine comparisons, but the results are very similar. There is a fair degree of tradeoff for both, resulting in a number of equivalent pairs for superior specificity for ECHO, as well as SPECT, a little bit of an advantage for ECHO for superior sensitivity and the pairwise

comparisons.

[Slide.]

Now, I would like to switch to something that Dr. Senior alluded to, and that has to do with the acoustic window quality of the studies.

We did an independent blinded read of acoustic window quality. We had the blinded readers who read the contrast in a separate read session rate the images on how interpretable the non-contrast ECHO image would be.

In that assessment, they determined that 27 percent of the images had poor quality. Now, we also looked at an analysis of the performance characteristics, accuracy, sensitivity, and specificity in poor window quality images, fair and good, and we saw that that performance was homogeneous, it was no differences.

In addition, the blinded readers commented that 99 percent of all images were evaluable, they were able to make assessments. We attribute this acoustic window quality properties a conversion to the better images to the prolonged myocardial enhancement in our studies, and the acoustic properties of AI-700.

We had greater than five minutes of myocardial contrast enhancement in over 80 percent of the patients in

our trials, and this was done by an independent blinded read, as well.

If we look at our integrated analysis, we believe that the results demonstrate that ECHO and SPECT are clinically comparable. There are similar tradeoffs for both modalities in sensitivity and specificity as indicated by the ROC analysis and the pairwise comparisons. We assert that the differences within and between the trials in sensitivity and specificity are primarily attributed to reader bias and are not modality specific.

I have shown you a lot of data on comparison of diagnostic parameters but the clinical question is really related to are we adding any incremental benefit for the physician with regards to stratifying these patients, because these patients are all presenting with chest pain, and this was a question that was brought up to us by Dr. Rieves at our pre-NDA meeting.

In order to address that question, we went back and did the following analysis.

[Slide.]

The objective of this analysis was to evaluate the ability of AI-700 ECHO to predict coronary artery disease in the context of standard clinical risk factors.

We pooled the data from the 32 and the 33 trial. I will tell you that the results are the same for each individual ECHO reader, and the clinical risk factors that we looked at are the standard clinical risk factors.

The analysis we performed was a logistic regression analysis where we looked at the odds ratio, the odds of detecting coronary artery disease among patients with risk factors compared to those without.

[Slide.]

The results of this analysis are here. We are doing one analysis with clinical factors in SPECT and another with clinical factors in ECHOs, and significant increases in odds ratio were seen for the parameters you would expect for gender and for age, and we saw that the highest odds ratio were obtained for the diagnostic imaging procedures, highest value was 5.3 for ECHO and 4.2 for SPECT. This data was recently presented at the AHA meeting last month.

[Slide.]

To try and put this all in context, we believe that the data that we have shows that we have a very consistent result with accuracy. Both trials met the primary endpoint of accuracy.

AI-700 was as accurate as SPECT for all blinded readers.

AI-700 ECHO was comparable to SPECT for sensitivity and specificity, although we acknowledge each trial missed one of the second tier endpoints. We believe this is attributed to the tradeoffs between sensitivity and specificity.

Importantly, AI-700 provided added clinical value over patients' risk factors, and we have concluded that AI-700 ECHO can detect coronary artery disease in stable chest pain patients being evaluated for inducible ischemia.

[Slide.]

I will turn the podium over now to Dr. Dittrich who will present an overview on safety.

AI-700 Clinical Safety Overview

DR. DITTRICH: Thank you, Dr. Walovitch.

I am going to present what I hope you will believe is a thorough overview of the safety of AI-700.

[Slide.]

First, let me begin with the populations that were examined and give you some definitions. Overall, there were 1,194 subjects who received AI-700 at any dose.

The gray area depicts those with known or

suspected coronary artery disease, and this we will call the coronary artery population. There were 11 percent who were healthy volunteers who received rest only, injections at various doses, 18 subjects in a separate trial with heart failure and lung disease.

Then, what we will focus on mainly is the suspected CAD patients and a subset of those who comprise both the pilot study, as well as the two pivotal trials.

You can see the dual injection was performed in most of them, and the intended dose in a dual injection in the presence of stress comprise most of these patients.

[Slide.]

This is what we will focus principally, the safety population. There were 911 subjects in the safety population, and this is composed of three trials, the two pivotal trials of 778 subjects, and one pilot qualification study. Virtually, all of the safety information will be from the 911 subjects.

There will be several plots I show you based on variables including blood pressure and oxygen saturation that includes only the 778 because the acquisition technique was slightly different, and this was a qualification study where there was greater variability, so we will focus for

those components just on the two pivotal trials.

[Slide.]

Again, these are patients, the CAD patients are those patients in whom there is chest pain, and they are either known to have coronary disease or suspected of having coronary artery disease. But these are the features from their history that may help delineate a little more what kind of patients they are.

You can see three-quarters had hypertension and hyperlipidemia, half had already undergone catheterization, 8 percent had undergone coronary artery bypass surgery, and there was 5 percent stroke rate, history of heart failure, and lung disease.

[Slide.]

I want to make a point about the timing of the safety assessments that were done. We followed safety out to 72 hours and that was based principally on the kinetics of the drug. If you recall, it is composed of a biologically inert gas that is cleared from the body via the lungs in hours with a t of 4 minutes.

The microspheres are removed rapidly from the bloodstream into the reticular endothelial system and cleared from the body over ensuing days. You will hear more

about how the body normally clears these particles. The microspheres are mainly composed, as was noted, of a biodegradable, biocompatible polymer that is already used in absorbable sutures and in depot drugs. So it is for this reason that all of the safety findings were conducted within the 72-hour time period.

[Slide.]

What I am going to show you, the key safety findings is that there is a transient cardiopulmonary signal manifested as a decrease in blood pressure, a decrease in oxygenation. The potential mechanism for these findings is a transient activation of complement as part of an innate immune response to clear particles from the bloodstream.

I will also present a risk mitigation strategy for these findings.

[Slide.]

Now, let me first begin with the adverse events. I need to point out I am going to do two things. I am going to talk about when these adverse events occurred, because the studies that were conducted involve confounding medications including dipyridamole and aminophylline for rescue. So it becomes difficult to decide what is

attributable to AI-700 unless we examine at several time points.

The other point that I need to make is that the adverse events I am reporting are all adverse events regardless of attribution. We will not go into the attribution as to the cause of the adverse event.

We are giving you the totality because, after all, the study will be performed ultimately in the presence of these other stressors, and the aminophylline rescue, which are actually more likely to cause the adverse events.

Of the entire population of 1,194, there were no deaths, and there were 11 subjects who experienced 14 serious adverse events.

Of the safety population, 72 percent of patients experienced 1 or more adverse events, 97 percent of these were mild or moderate intensity. The majority of adverse events, as you see when we look at the temporal occurrence, occurred during stress, and the majority resolved without treatment and without residual effects.

[Slide.]

Now, this is a build slide that takes a couple of minutes, and I am doing it to illustrate the timing, and we are going to do it in the context of the 14 serious adverse

events that took place in 11 subjects.

At the bottom we have the timing. The start of the first dose of AI-700, remember we give it in two doses, one at rest in the absence of any other drug, and then one after stress and the reversal of that stress. So the first period occurs here, and we have one component of the acute phase.

In this setting, we saw 3 patients with vasovagal syncope as a serious adverse event, and 1 subject with a combination of hypertension and vertigo.

The next point occurs with the infusion of the stress agent dipyridamole and includes AI-700 and aminophylline, which is given per protocol as a way of reversing the effects of dipyridamole and was given in approximately 95 percent of the subjects. Here is where the concomitant medications come into play.

During this period, we saw 1 subject with chest pain, that was a serious adverse event, 1 with mental status changes. Needless to say, we would anticipate chest pain to occur in a test in which we were attempting to induce controlled ischemia.

At the one-hour point after AI-700 until 24 hours post is another time period which we describe as the delayed

serious adverse events. In that case, we saw 3 subjects who had a combination of eye pain, blurred vision, vision disturbance at 18 hours, 1 SAE described as hypersensitivity at 1 hour, and 1 adverse drug reaction occurring at 3 hours.

Finally, beyond 24 hours, we had 2 events, a myocardial infarction, which occurred 2 days later, and had an intervening coronary angiogram showing significant disease at 24 hours intermediate, between dosing and the event, and then a subject at 24 hours who had a non-ST segment elevation MI.

I will continue to show the temporal relationship of the adverse events, but this was simply to demonstrate it first on the 14 SAEs that were identified in the safety population.

[Slide.]

This is a description of adverse events leading to discontinuation of the dosing. This occurred in 16 of the 911 subjects, 14 at rest, 2 during stress.

The most common adverse event resulting in discontinuation was hypotension that occurred in 5 subjects, 3 AEs at rest, 1 required treatment. The lowest systolic blood pressure value obtained that defined the adverse event of hypotension was still greater than 100 millimeters of

mercury and started from a baseline of 120.

There were 2 adverse events at stress, both which required treatment, the lowest blood pressure being 52 millimeters of mercury systolic starting from a baseline of 127.

Of the SAEs that resulted in discontinuation, 3 were vasovagal syncope without loss of consciousness, and we will discuss this a little more fully, and then the 1 subject with hypertension and vertigo. All adverse events resolved without residual effect.

[Slide.]

Now, I need to stop and talk briefly about vasovagal syncope because it has been highlighted in documents, and I certainly don't want to lecture to the panel, but I need to remind us that vasovagal syncope is commonly seen especially in stressful situations.

One could argue that presenting to a cardiorenal panel might be one of those stressful situations, nonetheless, it is typically seen in things like blood donation, phlebotomy, and I need to point out there is no injection of any drugs or agent in this setting, but it is very stressful and it typically relates to parenteral infusions or removal.

As a matter of fact, I note with interest that NIH has a trial being conducted actually using maneuvers to decrease the occurrence of vasovagal syncope in order to get blood donors to return for another donation.

I can imagine that a vasovagal event while donating might put you off from returning for another donation.

Another important thing to note is this is an open label study with no placebo control. So it is clear that everyone knew they were receiving an investigational drug which may add to the stress, and finally, the actual situation in which this test took place is stressful.

There are multiple observers, can be up to 7, the patient is supine in a dark room with these people surrounding and generally, because the drug has to be given in close connection with the ultrasound imaging for the right timing, there is a countdown, if you will, from 4, 3, 2, 1. So you can see it can be seen as a rather stressful situation.

Finally, I believe many of these truly were vasovagal events. Those of us who see patients who have fainted or with dizziness often make the diagnosis of exclusion, But in this situation we had a trained observer,

a cardiologist present, who had ready access to real-time telemetry and blood pressure reading, so could actually see the decline in blood pressure, a decline in heart rate, make a diagnosis, and that is demonstrated by the use of atropine, the standard treatment for this.

Again, I think we need to talk about the stressful situation in which these events did occur.

[Slide.]

Now, I am going in several cases to go into individual detail to allow the Committee to form an opinion on these individual patients. For one reason, it provides more information than just saying vasovagal syncope occurred; the others, that there are so few of any of these events we can actually show them to you.

The vasovagal syncope you see it occurred at rest and resulted in serious adverse event are shown here. Atropine was given. It resolved without residual effects. There were several during stress, neither of which received atropine during the stress period, and then two of them actually occurred at follow-up and neither received atropine for treatment.

So, of the vasovagal events, we see the three that occurred during rest.

[Slide.]

Now, I am going to move from vasovagal syncope just to an overall assessment or review of the most common adverse events in the safety population. Again, this is with respect to the relationship of the drug.

We have rest. So AI-700 alone, after dipyridamole is administered, and in the presence of dipyridamole stress and the use of aminophylline to reverse the dipyridamole, to discharge, and then the follow-up period. So, this timeline is not proportional. These are the most common adverse events given at this frequency for the entire study.

So, first, with AI-700 at rest, you see a low rate of headache, chest pain, nausea, flushing, chest discomfort. After dipyridamole stress is administered, and then with the second dose of AI-700, in the presence of peak stress, and then aminophylline reversal, we see these most common rates, and we note there is just a 3-minute time interval here.

Then, finally, from discharge to the follow-up out to 72 hours. So, this is intended to give you a depiction of the timing of events.

[Slide.]

As you know, in the pivotal studies, we did not have placebo control. But the sponsor did conduct one,

Phase 2 study, in which placebo was given. This is the 21 trial in which placebo was administered to 22 subjects, and AI-700 at the intended dose was administered to 22 subjects, the same delineation of timing is shown here with generally the same adverse events as shown previously, but dizziness was added as well.

Here, you can see the placebo effect. There is actually quite a high rate of headache when dipyridamole is administered in these subjects, and you can see generally the placebo effect, and now when we superimpose the effects of AI-700, there is really no remarkable difference other than there is dizziness at rest that was not present with placebo. Admittedly, in a small study of 22 subjects per arm, there appears to be no important difference between placebo and AI-700.

[Slide.]

Let me turn now from general adverse events to the two areas that we have identified that we would like to demonstrate in more detail.

First of all, this is the mean systolic blood pressure with error bars for the two pivotal trials. You can see baseline measure and then obtained at 5, 10, 30, and 60 minutes during rest with AI-700 given in this time

period, in the 5-minute time period, and the recovery pre-dose which in this area, dipyridamole is given and then the second dose of AI-700 with aminophylline reversal, the discharge time, and follow-up.

You can see despite the error bars that there is a decline in blood pressure from baseline into the first 5, 10-minute time period that returns, and, as well, a decline during the stress period, that returns to baseline.

[Slide.]

Turning now from the mean blood pressure for the entire population to the hypotensive adverse events, 38 subjects of the 911, or 4 percent, experienced 41 hypotensive events, 12 occurring at rest, with the lowest systolic blood pressure being 77 mm of mercury starting from a baseline of 104. The majority, 28, occurred at stress in 25 subjects, and 1 occurred at follow-up during a coronary arteriogram.

All patients remained conscious. As you will see, the events were generally short in duration, resolved without residual effects, and no subpopulation could be identified that appeared to be at increased risk for these hypotensive adverse events.

[Slide.]

Again, we are giving you the details so you can see what was determined to be a hypotensive adverse event. The far column is the age and gender of patient. This is the CAD status that was used for the primary endpoint. This is 70 percent stenosis yes or no, history of MI or the independent reader's assessment that there was disease, negative or positive.

This is the baseline blood pressure that I just showed before, obtained before AI-700, and this is the nadir blood pressure that was determined and constituted the adverse event, the time of the nadir, blood pressure relative to the dose, resting dose of AI-700, duration of the hypotensive adverse event, and whether or not it was resolved and received treatment.

I will show you the highlighted area. These are the only two subjects who received treatment for their hypotensive adverse event.

This was an event, a baseline blood pressure of 118, dropped to 105, occurred 30 minutes after the dose, received treatment, and had a 15-minute duration, and another subject who began at 156/92, dropped to a nadir of 108/63, persisting for 17 minutes, occurring 10 minutes after dosing. None of the other ones received treatment.

You can look for yourself at the lowest value of 77/50 as was described. But this occurred during the angio--I am sorry--this was a positive patient and occurred 5 minutes after dosing and had a 5-minute duration that resolved without treatment.

[Slide.]

Let me move now from hypotensive events to a summary of the respiratory adverse events, the other area of interest. There were 79 subjects in 911 patients, 2 of whom were treated with supplemental oxygen at rest, 6 of whom were treated with supplemental oxygen at stress. All of these resolved without residual effects.

Of these 98 respiratory adverse events, dyspnea was the most frequently observed, occurring in 40 subjects. There were 43 events, 4 occurred at rest. But you can see of the 40, 36 occurred during stress, again dyspnea being a common phenomenon in pharmacologic stress especially dipyridamole or adenosine agonist, 3 AEs occurred at follow-up.

The 13 AEs of dyspnea required treatment, all of which were during stress, and none of the AEs resulted in oxygen saturations that fell below 90 percent.

[Slide.]

The other respiratory adverse events occurred at a lower rate, and those are shown here.

This is the entire population. So, overall, there were 8.7 percent who had some kind of respiratory adverse event with a medDRA preferred term shown here.

Again, we have the rest group, which you can see the highest being 0.4 percent dyspnea. 0.4 percent cough. But most of them occurring after dipyridamole or after the second dose of AI-700 in the presence of dipyridamole, and then the discharge to follow-up time period.

[Slide.]

In order to examine the effects on oxygenation further, we looked first at the mean oxygen saturation changes following AI-700, and here we depict the means for the population of 778 at rest and again at stress with the oxygen saturation on the vertical axis and time on the horizontal axis.

You can see we see a drop in the resting state of less than 1 percent oxygen saturation, absolute change of 1 percent, less than 1 percent occurring at about the 10- to 15-minute time period, with a return to baseline, and slightly greater, but less than 2 percent drop during stress imaging.

So, we acknowledge this decline and especially when looking at the drug without any concomitant medication.

Now, I need to make one point of clarification. I gave you some information on the technology and how this study is conducted. But, for those of you who don't do ECHO, I need to remind you, as well, that during these studies in imaging, often, especially because of the body habitus of patients and the relationship of the heart to the chest, it is not uncommon to require significant breath holding during imaging of the patient, and that would occur especially immediately after dosing during the first 10 minutes.

[Slide.]

Again, to give you more detail on decreases in oxygen saturation, we have shown the population as a whole, this is a predefined definition that stated that there had to be an absolute decrease of at least 5 percent from baseline to a level below 90 percent, and this is again from the pivotal Phase 3 population.

Here, you can see identifiers with age and gender, whether or not they had a smoking history, their baseline oxygen saturation in the third column, the lowest oxygen saturation achieved, when it occurred relative to the rest

dose, and the subsequent post-dose oxygen saturation, and whether or not there were any concurrent adverse events at the time.

I will point out that there are drops. I would point you to this most prominent effect, a former smoker, 66-year-old male who starts at a baseline of 95 and drops to a low of 83 percent at 15 minutes after dose, and has associated cyanosis, facial flushing. This patient was treated with nasal prong oxygen and recovered to baseline within 3 or 4 minutes.

[Slide.]

To examine any other lung disease population a little more closely and give you some more information on this phenomenon, the sponsor had conducted a study, a small study in 8 subjects with moderate chronic obstructive lung disease as defined by impaired diffusion capacity, and decreased FEV1.

In this case, subjects were randomized to receive the two doses of AI-700 or placebo in a crossover design, and there were multiple spirometry performed in both settings. The main finding is that there was a decreased forced expiratory volume in the first second observed in all subjects regardless of treatment.

This was clearly due, according to the monitor and the expert in this field, to fatigue from repeated measures of spirometry. It is often difficult in patients with moderate lung disease.

I should point out, as well, that it is believed that a 15 percent change is necessary in order for it to be determined to be clinically relevant. The maximum mean FEV1 decrease for the treated group was 22 percent, and occurred at 15 to 20 minutes after the second dose compared to an 8 percent decline for placebo. So, this was determined to be the maximum difference, as well, between treated and placebo.

There were patients who met that clinically significant criteria of FEV1 decrease of greater than 15 percent occurring at 15 to 20 minutes post AI-700. In addition, 2 patients had a drop in oxygen saturation below the 90 percent level starting from a baseline of 92, 94, and dropped to slightly below 90.

They actually would not have met the criteria for the definition of decreased oxygen saturation I reported for the Phase 3 previously, but they did drop below 90. These drops were asymptomatic and occurred about 20 minutes post dose and recovered to baseline.

[Slide.]

The interpretation of the expert and medical monitor for this study were that there were transient subclinical spirometric changes that were observed in the absence of any adverse experiences.

Most, when examining the curves, were obstructive/restrictive changes. Two of 8 subjects, however, demonstrated primarily an obstructive change, and the mechanism for a transient subclinical bronchoconstriction may involve vascular airway interactions but, of course, we don't know whether it is due to local release or neurologic rebound.

Pulmonary function tests all returned to baseline levels for all subjects.

[Slide.]

Let me now turn to the adverse event of rigors. This occurred in a relatively low frequency but, because of the questions of complement activation and any question of immune mediated response, we wanted to give these values for you.

Thirty-nine subjects experienced 41 AEs of rigors, 9 occurring at rest, 3 of which were treated, 24 occurred during stress, 4 of which were treated, and I will stop here

to remind you, as well, that there may be some confusion when describing rigors in this setting of a rapid infusion of aminophylline for dipyridamole reversal.

As we all know, aminophylline can cause tremulousness and, in fact, these were reported at a time and subsequently, investigators were asked, in this attribution, many felt, in fact, that what they were reporting could have been due to the aminophylline. But these are all of the events without regard to attribution.

Common treatments were acetaminophen and Benadryl. Twenty-five of the events were mild, 14 moderate, 2 severe, and as pointed out earlier, 2 discontinued dosing due to rigors. All resolved without residual effects.

[Slide.]

Let me turn now from adverse experience to the laboratory findings and focus first on electrocardiogram and the methodology. This was done principally in the two pivotal trials, 12-lead electrocardiograms collected at baseline and at these time points post imaging sessions 1 and 2, and as well as at discharge and follow-up.

Continuous monitoring was performed from the ultrasound ECG machine. As many of you know, we connect leads for continuous monitoring of the ECG, and that

recording was maintained throughout the study.

In addition, 109 consecutive patients at 9 centers underwent 3-hour Holter placed immediately before the study and kept on for 3 hours.

The rhythm and ischemia assessments were performed by the investigators, but the core lab performed all the Holter analysis and over-read the abnormal 12-lead ECG QT/QTc intervals.

[Slide.]

The findings are straightforward. There is no indication of ECG-related changes attributable to AI-700.

No trend in QTc prolongation or other interval changes.

No increased rate of premature ventricular contractions when the mechanical index was 1 or less, and that was prespecified in the study.

Importantly, all the evidence by ECG of ischemia occurred during this stress section of the study in all but 1 patient who had it at rest, and all were reversible.

[Slide.]

The rest of the clinical laboratory findings. There were no shifts in clinical chemistries, coagulation or urinalysis.

There was a transient increase in total white counts and neutrophils. This occurred in the time period known as discharge, which is roughly 2 to 4 hours post dose, and an increase above the normal range occurred somewhere between 17 and 30 percent of patients, and as well, an increase in neutrophil occurred in 50 percent of patients above the normal range at that same time point. All of them had returned to normal range by the time of the follow-up.

[Slide.]

I would now like to ask Dr. Lambris to come up and speak to the issue of innate immune response.

Innate Immune Response and Complement Activation

DR. LABRIS: Good morning.

I am going to be very brief. I have only three slides. The goal of my presentation is to try to connect the immune response associated with the injection of AI-700.

[Slide.]

With this cartoon, I am trying to illustrate the possible connections of complement activation and the injection of AI-700. When the particle comes in contact with our blood, proteins like albumin will be observed on the surface of the particle. The formation will change, and that will initiate the activation of the complement system.

As a result of this activation, we are going to have generation of C5a and C3a. C3a is an excellent biomarker. I will come back to this. C5a is the anaphylatoxin which is associated with hypotension, neutropenia, and neutrophilia.

In addition to the generation of these anaphylatoxins, the C3 fragments will bind to the surface of the particle, and that will initiate the doses by macrophages, cytokines, and granulocytes, and as a result of this process, cytokines will be released and the virus effects.

To assist the in vivo inflammatory response of AI-700, a study was conducted in which 12 individuals, healthy individuals, were subjected--actually, 10 received AI-700 and 2 placebo. I should mention here the dose of AI-700 was a single injection and the single injections received in Phase 3 trial, although the total amount is the same, the single injection is twice the amount.

In this study, the following tests were performed: the skin prick test for the hypersensitivity reaction, C3a to measure the levels of complement activation, C3, tryptase, a surrogate marker of histamine release, and CRP as a module of total information.

As expected, no hypersensitivity reactions were observed with the injection of AI-700 in healthy subjects. The C3a levels increased within 10 minutes and that was associated with a decrease of neutrophils and white blood count cells.

I should say here that in the people that received the AI-700, there was not observed any hypotension. The C3a, neutrophils, white blood count cells normalized in 30 minutes post-dose. However, the neutrophils and white blood count cells increased above the baseline at 2 to 8 hours, and that was normalized by follow-up.

The vital signs in the two groups were no different.

[Slide.]

To summarize, I would like to bring your attention some nonclinical findings would support the clearance of AI-700 by the macrophages.

The decrease in blood pressure and oxygen saturation may reflect normal clearance of AI-700 microspheres from the bloodstream.

That is associated with levels of complement activation which was observed 10 to 15 minutes post-dose. These changes were transient and again they are associated

with the duration of complement activation.

I should mention here that complement has been associated with hypotension. However, the amount of complement activation that was observed in these observations is much higher than the one observed in this standard.

The increases in neutrophil levels and the inflammatory events, like rigors and pyrexia, may be due to the cytokines which are known to affect temperature control and also to increase the release of neutrophils from the bone marrow.

I would like now to switch back to Dr. Dittrich to continue with the safety analysis.

AI-700 Safety Overview (Continued)

[Slide.]

DR. DITTRICH: We described a decrease in blood pressure and oxygen saturation in a small cohort. That may be a manifestation of the normal clearance of AI-700 microspheres from the bloodstream, and the increase in neutrophil levels and inflammatory events. The rigors and pyrexia may be due to that subsequent release of cytokines.

When we presented these data, the blood pressure, the oxygen saturation changes to experts in the context of

this normal innate immune complex response, their reaction was is there an overlap of these phenomenon within individuals. In somebody trying to assess the safety of this compound, can they understand the distribution of these events.

[Slide.]

We constructed a Ven diagram as a means to depict where these are happening. This is again the two, Phase 3 studies, and we describe, first, the neutrophilia occurred that is reaching a level above the upper limit in 321 subjects, slightly less than half.

When we first look at the inflammatory response AEs, pyrexia/rigors AEs, that occurred at anytime during the study, there were 38 such subjects with actually a proportional overlap compared to neutrophilia in the whole population.

[Slide.]

The key question is what about the blood pressure and oxygen change, and when we look first at blood pressure, and this was defined as a decrease in systolic blood pressure from a baseline of at least 40 mm of mercury, or a 25 percent change, or a drop to less than 90 mm of mercury, three criteria.

There were 63 subjects and again the overlap is proportional to that for neutrophilia compared to the entire population and very little overlap with these inflammatory AEs.

Finally, when we examined the drop in oxygen saturation, we see again a proportional overlap with the neutrophilia and no overlap with these other inflammatory response AEs and minimal overlap with those who had a decline in blood pressure.

Our conclusion from this limited information is this does not appear to be a syndrome focused in a small number of subjects but rather distributed more broadly across the population.

[Slide.]

So, the key safety findings from the studies is that there is a transient effect on oxygen saturation, a minimal rate of transient respiratory adverse events, and as well, a transient effect on blood pressure, a few cases of hypotension at rest.

You have heard the potential mechanism for these findings related to the normal clearance of microparticles from the bloodstream. Importantly, there is no evidence that the effects of AI-700 are additive to the key variables

of a pharmacologic stress study that of dipyridamole or ischemia if it occurs, and even the aminophylline reversal.

[Slide.]

To put all of these data into some context, it is important to show the data relative to what we know about other pharmacologic stress studies.

First, we will go through briefly again the most--these are not the most frequent from our studies But, based on the literature, these are event rates occurring at greater than 5 percent from any of the tests available.

So, you see again there is very little activity after dipyridamole alone. But, in total, in the resting and stress and follow-up event rate, as shown here, with the key variable with the highest finding of 35 percent headache rate. But, as we pointed out, that was roughly equivalent of the placebo rate or it was seen as equivalent to placebo in that other study.

Now, how does this compare when contrasted with the literature results from non-contrast cardiac imaging studies? This is dipyridamole imaging, adenosine SPECT imaging, and dobutamine ECHO from the literature.

I think you can see that many of these, and again many of these are taken from the frequency at greater than 5

percent are similar to the dipyridamole imaging from the literature in some cases perhaps less than adenosine and less than dobutamine when those data are available.

We would submit that on the totality of these adverse events, shown here, that there is certainly no signal that exceeds or goes beyond even dipyridamole imaging alone.

[Slide.]

Let me turn now to the cardiopulmonary risk mitigation. The strategies proposed for AI-700 in the proposed label are very similar to recommendations for rest/pharmacologic stress imaging studies, and include that it would be contraindicated in acute coronary syndrome, respiratory failures, severe COPD, high degree A-V block.

It is clear that pharmacologic stress testing is not conducted in an unstable patient. It is reserved for stable patients.

Monitoring of vital signs, ECGs, and oxygen saturation as it is being done now would be undertaken, and that readily available resuscitation equipment, medications and trained personnel be available.

We believe these strategies are adequate to mitigate cardiopulmonary risk with AI-700 with the following

addition, and that is, the proposed labeling would specify because of this relationship of contrast media with high ultrasound mechanical index imaging that it would specify mechanical index should not exceed 1.0, and that is how it was conducted in the studies, the Phase 3 studies.

[Slide.]

Let's talk now about potential life-threatening serious adverse events.

In the safety population of the size we presented, event rates of greater than 4 percent could be excluded.

We believe a post-marketing safety study is needed to assess the potential for deaths or life-threatening serious adverse events, and that is in agreement with this committee's recommendation that there was a need for infrequent serious events to be obtained in well-designed post-marketing observational studies, and Acusphere is prepared to discuss those post-marketing studies with the FDA with regard to a safety registry for acute events, as well as a pharmacologic stress ECHO study comparing it to other pharmacologic stress tests.

[Slide.]

How do we compare or how can we compare the risk of AI-700 against other modalities? The two methodologies--

and you have heard them discussed at length--are SPECT myocardial perfusion using adenosine agonist stress, and ECHO non-contrast wall motion using dobutamine. Dipyridamole is used in Europe extensively with ECHO non-contrast. But dobutamine is the stressor of choice in this country.

The literature gives us some guidance on comparable risk for life-threatening adverse events, and the literature reports an event rate as low as 1 in 1,600 with pharmacologic SPECT imaging, and as low as 1 in 140 life-threatening serious adverse events with dobutamine. That's the context in which the serious adverse events or life-threatening ones should be made.

[Slide.]

The conclusions from the safety review are that overall AI-700 is well tolerated, there is a small marginal difference compared to dipyridamole SPECT. However, there is no ionizing radiation risk with AI-700.

It produces transient cardiopulmonary safety signals in less than 3 percent of patients at rest, and it is effectively managed with the standard measures already in place for pharmacologic stress testing.

The risk of serious adverse events is mitigated by

label restriction and the strategies that have been proposed which are similar to those of current pharmacologic stress imaging procedures, and finally, post-marketing safety study to evaluate the rate of life-threatening serious adverse events should be conducted.

Thank you.

[Slide.]

Dr. Walovitch.

Concluding Remarks

DR. WALOVITCH: Thank you very much, Dr. Dittrich.

I have the great pleasure after working on the development of AI-700 for over 10 years to be here today to provide you with some concluding remarks on what we believe is a compelling argument in support of AI-700's favorable risk-benefit ratio.

The lack of ability to assess myocardial perfusion has long been recognized as a major limitation of stress ECHO imaging. It is with this understanding that we initiated our development program with AI-700.

[Slide.]

The goal of that program is to provide a new tool to assess clinical need for the assessment of coronary artery disease. This tool would be a comprehensive

evaluation of myocardial structure, function, and perfusion.

It would have to be a safe procedure without ionizing radiation which could be a hazard to patients, health care providers, as well as have environmental impact, and increasingly more importantly in this day and age, it would have to be readily available to all and a potential to provide cost savings.

[Slide.]

You have heard a lot about the limitations of pharmacological stress procedures. They are listed here. Ionizing radiation from SPECT, the fact that SPECT is less convenient, less available, has limited anatomical information, is part of the contributing to the rising health care costs specifically with regard to imaging procedures.

We talked about dobutamine non-contrast ECHO, that it is a more complex, many-step procedure, less safe than vasodilatory SPECT imaging. No information on perfusion is provided, and a certain percentage of the patients have non-diagnostic images.

[Slide.]

I have talked to you about the efficacy of AI-700, that it provides diagnostic performance that is clinically

comparable to dipyridamole SPECT; that it is a strong independent predictor of coronary artery disease in chest pain patients; that it can improve the quality of the ECHO images thus increasing the value of the stress ECHO procedure.

[Slide.]

Dr. Dittrich has reviewed the safety, concluded that it is overall well tolerated, that it does produce transient cardiopulmonary safety signals. But they are in a small percentage of the patients, and that we have developed risk mitigation strategies, label restrictions that will help us understand the performance of this agent better and that we have post-marketing safety studies that will be conducted to further evaluate the threat of life-threatening SAEs.

[Slide.]

We have concluded that AI-700 dipyridamole ECHO benefits outweigh its risks. It is the first effective imaging agent to conveniently provide assessment of perfusion and wall motion.

It has demonstrated comparable safety to dipyridamole SPECT.

The literature data indicates that dipyridamole

ECHO is safer than dobutamine ECHO, the current procedure.

So, in conclusion, the acute safety risk of AI-700 ECHO is offset by its unique added benefits of being a single procedure to provide both perfusion and wall motion information.

DR. HARRINGTON: Thank you for the nice summary of all of your data, plus also keeping on time.

What I would like to do now is we are a couple minutes early, which is always a good thing, so let's take a break for about 15 minutes and be back here sometime between 10:20 and 10:25, and we will hear from the FDA and their review of the issues.

[Break.]

DR. HARRINGTON: We are now going to move to the FDA presentations, if I could ask everybody to take their seats. I have also been asked by the FDA organizers, this is for the panel's consideration, that you can eat lunch here in the hotel. There is a set of tables set aside for the panel, and I was given the reminder, as well, to remember not to discuss things at lunch regarding today's presentations, but that should be reserved for an open forum. But if you want to have lunch, there are tables reserved for the panel in the restaurant.

I now want to turn to Dr. Kress, who will begin the FDA presentation, and we will have a series of FDA presentations including the first presentation of the questions for the panel to consider. This will go on for about an hour and then we will have some time before lunch to question this morning's presenters.

Clinical and Statistical Review of the Application and FDA Introduction to Questions

DR. KRESS: Good morning.

[Slide.]

My name is Dr. Scheldon Kress. I will be providing an overview of the major preliminary findings from the FDA's review of the NDA. I will emphasize the major diagnostic outcomes with a focus also upon safety.

Subsequently, Dr. Anthony Mucci will provide comments upon the statistical aspects of the diagnostic efficacy outcomes.

[Slide.]

My discussion will consist of three major portions. Following an introduction and background, I will discuss two sets of clinical studies, three supportive studies are of particular interest.

Study 04 provides important safety data pertaining

to elevation of inflammation biomarkers. Studies 20 and 21 provide the main data source evaluating the additive value of AI-700 contrast echocardiography over non-contrast echocardiography.

Subsequently, I will discuss the two, Phase 3 clinical studies. Finally, I will summarize the major efficacy and safety findings.

[Slide.]

As previously described, AI-700 is a suspension of microspheres of approximately 2 microns in size. Following intravenous injection, the particles traverse the vascular system and echocardiography permits detection of increased contrast between blood-containing and non-blood-containing structures.

The particles consist of a rigid porous shell made up of phospholipid and a synthetic polymer, as well as the gas perflubutane.

Elimination of AI-700 from the body is proposed to involve exhalation of the gas, while the particulate component is thought to be ingested by macrophages and other cells comprising the reticular endothelial system.

[Slide.]

The proposed indication is as stated. AI-700 is

an ultrasound imaging agent indicated for patients with stable chest pain being evaluated for inducible ischemia for the detection of coronary artery disease based on assessment of myocardial perfusion and wall motion. AI-700 echocardiography is accomplished with rest and stress techniques.

As emphasized within the NDA, AI-700 echocardiography is to be used as a screening tool to assist the clinician in stratifying patients for referral to coronary arteriography.

[Slide.]

Supportive Study 04 provides important background information. As shown here, this study was designed to explore potential inflammatory and immunoreactivity responses to AI-700.

Overall, 12 healthy volunteers were enrolled and most participated in both stages of the study. In Stage 1, the volunteers received an initial AI-700 or placebo injection. Stage 2 began more than a year later and consisted of a skin test for AI-700 reactivity along with administration of a second AI-700 dose to non-reactive subjects, or placebo administration to prior placebo exposed subjects.

Overall, no subject developed a positive skin test result, although the AI-700 exposed subjects did develop increases in biomarkers of inflammation.

[Slide.]

Elevation of complement component C3a is generally regarded as a marker for serum complement activation. In Study 04, all subjects who receive AI-700 experienced increases in C3a and these results are summarized here.

In general, the peak concentration appeared evident at the 6-minute time point following AI-700 administration with the levels returning to baseline by the 2-hour time point.

Of note, two subjects had baseline levels in the 30s and peak C3a levels of 1,034 and 1,430 at six minutes. Post-dose C3a levels in placebo subjects showed no notable changes from baseline.

[Slide.]

C-reactive protein is generally regarded as a biomarker indicative of vascular information. Unlike C3a, CRP levels were measured less intensively during the study. But the major findings are cited here, with measurements obtained at baseline 120 minutes and 24 hours following AI-700 exposure. Overall, all AI-700-exposed subjects

experienced increases in CRP as shown at the 24-hour point. No placebo group subjects experienced CRP elevations.

[Slide.]

This figure shows average neutrophil counts following AI-700 or placebo exposure. As shown on the y axis, the average neutrophil counts did not deviate beyond clinically important levels but the overall pattern of neutrophil count alteration is notable in that the data suggest a relatively abrupt decrease in neutrophils following AI-700 administration, followed by a rebound increase over the subsequent hours.

This pattern may correlate with some of the white blood cell count abnormalities also detected in the Phase 3 studies.

[Slide.]

Overall, Study 04 showed that in healthy volunteers who received an AI-700 dose of approximately twice that proposed for market use, the product caused complement activation as signaled by increases in C3a, increased C-reactive protein, and alteration in white blood cell counts.

These biomarkers were not assessed in coronary artery disease patients and the extent to which an

inflammatory response may accompany the proposed market dose is unclear.

[Slide.]

An important consideration in assessing an imaging contrast agent relates to the data that verify that the contrast agent adds diagnostic value to an image obtained without the contrast.

For example, the detection of wall motion abnormalities on rest and stress echocardiography can signal coronary ischemia even without the use of contrast. Consequently, data should be available to verify that contrast adds value to the non-contrasted image.

The Phase 3 studies evaluated wall motion and myocardial perfusion together without a methodology that would assess the added value of contrast. However, Studies 20 and 21 are proposed to provide data that verify the added value of AI-700 contrast to non-contrasted echocardiography.

[Slide.]

Study 20 was an exploratory study in which patients underwent baseline non-contrasted echocardiography followed by contrasted echocardiography.

This study could only detect fixed wall abnormalities as it did not utilize stress components.

Additionally, the study only evaluated AI-700 doses that exceeded those proposed for marketing. Hence, Study 20 provides no information regarding the added value of AI-700 to non-contrasted rest/stress echocardiography.

[Slide.]

Study 21 appears more informative, because it examined both rest and stress echocardiography, and also included a group of patients who received a placebo instead of AI-700. As shown here, this exploratory study consisted of three stages with healthy volunteers enrolled in the first stage.

The study is most notable for the results from the patients enrolled in the second and third stages. All patients underwent rest echocardiography and SPECT followed by dipyridamole-induced stress echocardiography and SPECT.

In Stage 2, patients were randomized on placebo or one of two dose cohorts of AI-700, a dose lower or higher than that proposed for marketing.

In Stage 3, patients received an AI-700 dose that approximated that proposed for marketing.

[Slide.]

The major performance characteristics from the stress phase of Study 21 are shown here. The dose cohorts

are shown in the rows with the emphasis placed upon the approximate market AI-700 dose of 0.040 mL/kg and the group of patients who received placebo instead of AI-700.

Using SPECT as a reference test for the presence of coronary disease, the column shows the sample sizes along with the sensitivity, specificity, and agreement with SPECT.

Given the relatively small sample sizes, the results are variable. However, as highlighted, the results for the approximate 0.04 mL/kg market dose are similar to the results obtained for patients who received placebo including sensitivity of 33 percent for AI-700 compared to 43 percent for placebo, and a specificity of 88 percent for AI-700 compared to 80 percent for placebo.

The agreement 73 percent and 68 percent was also similar between the two cohorts. Consequently, these findings raise questions as to the added value of AI-700 compared to the results that could be obtained without the use of AI-700.

[Slide.]

The next several slides summarize the major finding from the Phase 3 clinical studies, Studies 32 and 33.

Both studies were single arm, multicenter studies

in which each center had to qualify for participation based upon technical performance established in Study 23, a pilot study. All patients were to undergo echocardiogram and SPECT evaluations both at rest and stress following administration of dipyridamole.

The AI-700 dose was 0.04 mL/kg administered over 3 to 10 minutes. The primary endpoint compared the performance characteristics between AI-700 echocardiogram and SPECT with respect to the specified "truth standards" for the presence or absence of coronary artery disease.

Both studies used centralized ECHO image assessments which readers were masked to clinical data.

[Slide.]

The difference in design features for Studies 32 and 33 are summarized here.

The eligibility criteria for both studies selected patients with a history of chest pain with Study 32 also requiring that patients have a clinical indication for undergoing rest/stress SPECT imaging, while in Study 33, the patients had to have recently completed coronary arteriography or be scheduled for coronary arteriography.

Hence, Study 32 eligibility criteria selected patients who were more likely to resemble the potential

market population compared to the eligibility criteria for Study 33. The two studies also differed in the number of SPECT readers utilized with a single reader in Study 32 and three readers in Study 33.

The true standard expectations for the presence or absence of coronary artery disease also somewhat varied between the two studies with both studies using similar criteria but with the expectation that most patients in Study 33 would have coronary arteriography data available.

[Slide.]

The analytical plans for both studies evolved during the conduct of the studies. The original analytical plans consisted of sensitivity and specificity estimates where echocardiography was compared to truth standard that, depending on the study, consisted of coronary arteriography or SPECT and clinical outcomes.

FDA recommended modifications of the primary endpoint analytical plans to consist of a hypothesis testing approach where AI-700 sensitivity and specificity were compared to that of SPECT in a non-inferiority design that included performance expectations for SPECT.

[Slide.]

Most of the recommended modifications were

incorporated into the analytical plan although some changes were made as shown in the text. The plans noted that sequential non-inferiority analyses will be performed for echocardiography versus SPECT, first for accuracy followed by sensitivity and specificity.

The analytical plan text further noted that if the accuracy endpoint is met, similar analyses will be performed for sensitivity and specificity.

As detailed in the last couple of bullets, the performance characteristics were to be assessed in the modified intent to treat population, and the outcome calculated for each of the three AI-700 readers.

Success was assigned to an outcome if the lower bound of the two-sided 95 percent confidence interval for the relative risk ratio was greater than 0.83 for at least two of the three AI-700 readers.

The sponsor has noted that the lower bound of the confidence interval was selected based upon clinical and logistical considerations.

[Slide.]

This slide highlights one of the alterations in the plan study conduct. Specifically, Study 32 AI-700 performance characteristics became available prior to the

completion of Study 33 ECHO reads.

Because the Study 32 sensitivity findings appeared low, the Study 33 read was halted, and the highly qualified readers were retrained to enhance disease detection.

This retraining was performed prior to any Study 33 analyses, and the final database reflects the results of the retrained readers.

[Slide.]

This slide shows the major baseline characteristics in the studies, the average age approximating 60 in both studies and both studies consisting predominantly of Caucasian/white males.

[Slide.]

The patient disposition and coronary artery disease prevalence, based upon the truth standard findings, is shown here. Overall, 321 patients were enrolled in Study 32, 457 in Study 33.

The modified intent to treat population consisted of 285 patients in Study 32 and 377 patients in Study 33. Patients were excluded from the mITT population predominantly due to the lack of SPECT images or a truth standard.

Overall, these exclusions consisted of 36 patients

in Study 32 and 80 patients in Study 33. As shown at the bottom of the slide, the prevalence of coronary artery disease was generally higher, 58 percent in Study 33 compared to 44 percent in Study 32.

[Slide.]

This slide summarizes the primary endpoint results for Study 32. Shown in the rows are the results for accuracy, sensitivity, and specificity, along with the relative risk ratio lower confidence interval bounds for each parameter.

The columns show the results for SPECT as well as each of the three echocardiography readers. As highlighted here in yellow, AI-700 achieved non-inferiority success upon the accuracy outcome with the results generally similar to those for SPECT and the lower bound of the confidence interval exceeding 0.83.

However, the results for sensitivity are particularly important since AI-700 is proposed for use as a screening tool. In this study, sensitivity for SPECT was 78 percent while ECHO sensitivities were recorded as 77, 57, and 50 percent with AI-700 not achieving non-inferiority expectation.

As shown in the last row, AI-700 specificity

findings met for the non-inferiority expectations.

[Slide.]

Study 33 efficacy findings are shown here. Similar to Study 32, AI-700 non-inferiority for accuracy was demonstrated. Unlike Study 32, success was also shown for sensitivity. However, it is important to note that the SPECT values for sensitivity was 61 percent, a value considerably lower than the 78 percent reported for Study 32. As shown in the table, AI-700 non-inferiority for specificity was not demonstrated in Study 33.

Overall, the major AI-700 perform characteristics showed consistency between the two studies only for accuracy.

Non-inferiority for specificity was shown in Study 32, the study that probably most approximated the market population, while non-inferiority for sensitivity was shown in Study 33, the study where patients were already determined to need coronary arteriography.

As noted at the bottom of the slide, the SPECT comparator performance characteristics were remarkably variable between Study 32 and 33, raising questions about the robustness of the non-inferiority conclusions.

[Slide.]

The next few slides summarize the major safety findings. Overall, AI-700 was administered to approximately 1,200 patients and healthy volunteers. Of special focus are the 911 patients in the Phase 3 safety database.

Because these patients received the proposed marketing dose and generally followed procedures anticipated for the proposed market use of the drug, my safety summary will focus upon serious adverse events and the events prompting AI-700 discontinuation.

[Slide.]

The evaluation of AI-700 safety is complicated by the study procedures, specifically, the confounding effects associated with dipyridamole induced stress testing.

As illustrated here, patients underwent an initial AI-700 administration with echocardiography and were observed for at least 60 minutes.

Subsequently, dipyridamole was administered and shortly thereafter the second AI-700 dose was administered for stress ECHO cardiography.

Given the known risks associated with dipyridamole stress testing and the lack of a comparator group in the studies, it is especially difficult to interpret the serious adverse events associated with the second AI-700 dose.

Therefore, we generally will emphasize the reactions that occurred following the initial AI-700 dose.

[Slide.]

Overall, 11 patients experienced serious adverse events. This table shows the numbers of patients experiencing certain types of events coded by key words. The events that followed the first AI-700 dose are highlighted. Overall, serious adverse events occurred in 4 patients following the first AI-700 dose, and 7 patients after the second dose.

While the events following the second dose might reasonably be attributed to stress testing, the events after the first AI-700 dose are particularly notable especially in the 3 patients who experienced syncope.

The 3 syncopal events occurred within minutes following the AI-700 dose, and all consisted of bradycardia and included 1 patient each with transient junctional cardiac rhythm and heart block.

Two of the patients also experienced hypotension with the bradycardia. All events were treated with atropine and generally resolved relatively rapidly.

The patient who experienced vertigo and hypertension had a blood pressure of approximately 180/100

at baseline and was hospitalized for observation and anti-hypertensive therapy after her blood pressure increased to an approximately 200/120 shortly after AI-700 administration.

[Slide.]

Overall, 17 subjects had AI-700 permanently discontinued because of adverse events, including events classified as serious for 4 patients.

Of the 17 subjects that had AI-700 discontinued, 14 experienced these adverse events during the first AI-700 dose, all during or within a few minutes of the AI-700 dose.

The clinical manifestations of these events were relatively variable, and the most common manifestations are listed here. In general, hypotension was experienced by 7 patients, syncope by 3 patients, and rigors in 2 patients.

Isolated occurrence of multiple other symptoms were reported including weakness, flushing, dizziness, and nausea, and an additional 7 patients required temporary interruption of the AI-700 dose or dose adjustment.

[Slide.]

To illustrate the more extreme pattern of events, I cite the experience of a 72-year-old female who had a history of angina and prior myocardial infarction.

Within one minute of AI-700 initiation, the patient complained of flushing and dizziness. She was reported to subsequently experience near syncope coincident with the development of a junctional cardiac rhythm, with a heart rate of 39, and blood pressure that was not measurable.

The AI-700 was discontinued, atropine administered, and the patient's signs and symptoms resolved over the subsequent several minutes. She was subsequently hospitalized for observation.

[Slide.]

In these studies, most serious adverse events followed the administration of dipyridamole. This slide summarizes the non-serious adverse events in the Phase 3 safety database based upon the occurrence of the events prior to dipyridamole.

In general, the most common events include those previously mentioned, including headache, flushing, hypotension, rigors, and dizziness.

[Slide.]

This slide summarizes the most common non-serious adverse events that occurred at anytime within the Phase 3 safety database experiences.

In general, the events are similar to those previously described or consistent with those generally associated with stress testing. Highlighted are alterations in white blood cell counts that were reported as adverse events.

In general, these observations were regarded by the investigators as mild to moderate increases and appeared in a temporal pattern similar to the shifts in white blood counts observed during the exploratory clinical studies.

[Slide.]

I summarize here our major preliminary findings from the review of this NDA.

With respect to the exploratory clinical studies, we note the signals for inflammatory events following AI-700 administration and the study's inability to clearly delineate the added value of AI-700 to non-contrast echocardiography.

In the Phase 3 studies, we cite the equivocal diagnostic efficacy findings as well as the lack of delineation of the added value of AI-700 to the electrocardiographic testing.

Of special concern in these studies were the relatively uncommon but important safety signals for various

cardiovascular reactions.

Dr. Anthony Mucci will now provide comments upon the statistical aspects of the diagnostic efficacy outcomes.

Thank you.

Anthony Mucci, Ph.D.

DR. MUCCI: Hello. I am Tony Mucci. I am the statistical reviewer for this application.

[Slide.]

Here is an outline of what I will be talking about. I will discuss the trial design, then, I will give a critique and comments on the performance characteristics, sensitivity, specificity, and accuracy. Some of these comments will be very general.

Then, I will discuss the criteria for non-inferiority studies in this particular application, then, I will give the trial results and the conclusions.

[Slide.]

The trial design. There were two, single-arm, crossover non-inferiority trials.

The standard of reference was angiography where available, approximately half the time in Study 32 and virtually all the time in Study 33. When angiography was not available, there was a clinical assessment.

The standard of reference was what determined disease prevalence, which was 44 percent in 32, and 58 percent in 33, which means disease prevalence was close to 50 percent in both studies.

Diagnoses were at a patient level, not at a vessel level, so the concordance in diagnoses between images and the standard of reference did not require localization of disease.

[Slide.]

The comparator, as mentioned multiple times already, was SPECT imaging. The endpoints: Sensitivity, specificity, and accuracy. The hypotheses for each of these endpoints was a null hypothesis that the risk ratio was at most a certain margin, non-inferiority margin. The alternative was it exceeded that margin.

The success criteria was that the lower limit of the 95 percent confidence interval of the risk ratio must exceed the margin simultaneously for 2 out of 3 readers for all 3 endpoints.

[Slide.]

Here are some general comments on sensitivity, specificity, and accuracy.

Sensitivity, specificity, but not accuracy, are

largely independent of disease prevalence. They provide true positive/negative rates in patients with and without disease, and they impact the pretest probability of disease in the sense that a practitioner with knowledge of these, in addition to simple knowledge of expected prevalences, can have his decision affected by these numbers.

Accuracy provides only a "correctness" rate. It doesn't distinguish among various sensitivity and specificity levels.

[Slide.]

Here is a manufacturer example in which I set disease prevalence at 50 percent so there is no bias in the prevalence. There is parity among disease in normal patients. The risk ratio is set at 0.87.

The acceptable you will notice that the accuracy and specificity are at acceptable levels, but the sensitivity is not. The specificity here I set at 70 percent for both. I am calling this "new test" and "old test." New test in this case would be the test drug. The old test would be the comparator.

So, even when you have 50 percent prevalence, and even when one of the measures is the same for both old test and new test, you can have an extreme imbalance in the other

measure and still pass the accuracy test.

[Slide.]

Now, I am continuing with the limitations of accuracy here but as confined to the studies where, in Study 32, first, disease prevalence was set--well, not set--but it turned out to be 44 percent.

The Agency threshold was set at 0.87, and you will note these are averages over readers in order not to present a crowded picture here. There is acceptable accuracy and specificity but unacceptable sensitivity.

[Slide.]

In Study 33, the reverse happens. Here, prevalence was close to 60 percent and specificity is the measure in this case that is marginal whereas, sensitivity and accuracy are successful.

[Slide.]

Now, I want to move away from that and talk about the non-inferiority design elements in the trial with non-inferiority design elements as currently understood.

There are two features. One is the level of performance of the comparator, because you are comparing something to a control. You want to make sure the control is consistent.

The comparator (SPECT) historical performance from ACC guidelines is sensitivity at 89 percent and specificity at 75 percent.

The Agency recommended for this particular study that minimal performance levels be set at 82 percent for sensitivity and 66 percent for specificity, these numbers being 3 sigmas lower than the ACC guidelines for sample size 200. The sponsor prespecified SPECT minimum performance levels slightly lower than that, 76 percent and 59 percent.

[Slide.]

Now, the non-inferiority design elements continue with the risk ratios. The FDA recommended sensitivity be set at 0.87, specificity at 0.85. The sponsor prespecified at 0.83. As has been already mentioned, this has no serious consequences because when the thresholds were met, they were met more than sufficiently, and when they were not met, they were missed more than sufficiently.

However, I did add a slide here to indicate why we wanted the 0.83, and these are simply point estimates. The concern was that when the control value SPECT gets low, say, near 0.6, the ECHO value can drift towards a result which is near pure chance and still you might make your threshold.

[Slide.]

Concerns on the trial execution, Dr. Kress just mentioned this. After 32 was unblinded and examined, it was found out that low sensitivities had been recorded. So the sponsor scrapped the existed image reads in Study 33, retrained the Study 33 readers toward greater sensitivity, and then those readers re-read the existing images. The primary analysis is based on that re-read.

[Slide.]

This is the busy chart, which has already been shown. These are the actual results for the three readers for the two trials. As you can see with the highlighted items, accuracy was successful for all readers, whereas, in Study 32, the specificity criteria was met for two readers. But these two readers did not overlap with the single reader who made the sensitivity threshold.

In Study 33, there is a reverse where the sensitivity was met by all three readers, but only one reader met the specificity. I want to call special attention here to the ovals.

The concern here is that the SPECT performance, the comparator shifted from 32 to 33. There was no consistency in SPECT performance. It was at 78 percent sensitivity in Study 32 and then dropped to 61 percent in

Study 33. So, you are comparing your test to a comparator which is shifting in its performance.

[Slide.]

Results. Minimal comparator performance. SPECT performance met sponsor's pre-specified minimum performance criteria--that is, the lower bound of the expected performance for the comparator. It met this for specificity but not for sensitivity.

The risk ratio results. No two readers simultaneously met the sponsor's non-inferiority margin for sensitivity and specificity together in either of the studies, while all readers met the pre-specified non-inferiority margin for accuracy.

[Slide.]

Conclusions. Accuracy alone is not acceptable in the study where you are dealing with a possible gatekeeper. You would in particular want high sensitivity in these cases.

The sponsor also did not meet the pre-specified ratio risk criteria for sensitivity and specificity.

The inconsistency of SPECT performance levels from trial to trial, especially for sensitivity, can compromise the validity of the non-inferiority design.

That's it.

DR. HARRINGTON: Thank you.

Now, we are going to hear the questions being presented to the panel. We are going to have the discussion of the questions this afternoon, but the FDA wanted us to have these for our consideration as we think about questions to both the sponsor and the FDA.

Alexander Gorovets, M.D.

DR. GOROVETS: Hi. My name is Alex Gorovets, Clinical Team Leader in the Imaging Division of Office of New Drugs in CDER, FDA.

[Slide.]

I would like to take this opportunity to thank the company representatives and my FDA colleagues for their presentations and to thank in advance the Advisory Committee members for their consideration, insight, and advice.

[Slide.]

My task today is on behalf of our Division to pose the questions to the Committee and to list the issues on which we seek the advice.

Our questions are pretty straightforward and I will shortly go over the issues which we would like you to address. We would like advice and comment on the efficacy

data, safety data, and benefit and risk assessment.

[Slide.]

For our first topic, we request the Committee to discuss the extent to which the Phase 3 data provide persuasive evidence of diagnostic efficacy. We are particularly interested in the Committee's comments upon any importance of finding consistency between the two studies in terms of the parameters of diagnostic reforms, and upon the importance of the performance characteristics of comparator, which is SPECT, and on the evidence to show the added value of AI-700 ECHO over non-contrast ECHO.

[Slide.]

Our second request pertains to safety. Specifically, we request the Committee to discuss the extent to which the Phase 3 data provide persuasive evidence of safety for a diagnostic agent.

In this discussion, we suggest the Committee particularly consider the rate and nature of the reactions prompting AI-700 discontinuation, as well as the overall size of the safety database and the single arm design features of the Phase 3 studies with outcomes confounded by the pharmacologic stress testing.

Finally, we suggest the Committee also discuss the

potential importance, if any, of the exploratory study on biomarkers of inflammation as signals of potential safety concerns.

[Slide.]

As our third request, we request the Committee to vote in response to a question pertaining to the overall safety and efficacy of AI-700. Specifically, does contrast enhancement of rest/stress echocardiographic imaging with AI-700 provide sufficient diagnostic benefit to justify the risks associated with this product?

[Slide.]

Finally we request the Committee to discuss the need, if any, for additional studies. We are particularly interested in comments pertaining to whether these studies should be obtained prior to or following marketing, as well as a discussion of the nature of the studies.

For example, please comment whether the focus should be upon efficacy or safety, or both, and the potential need for control groups.

I think you for your attention and return the podium to our Chairman.

DR. HARRINGTON: Thank you.

It's about 10 past 11:00. We have until noon

scheduled for questions. We have a big panel and I suspect there are going to be a lot of questions. I have also been informed by Elaine that there were no scheduled speakers for the open public session so we will have that period open to us for more questions.

So, just so that people don't feel that they have to rush their questions. If there are things after lunch, we will have another hour if needed, and then we will have plenty of time devoted to the specific questions.

Procedurally, again, we have a large panel. Elaine will help me keep track of who is next in the queue. I will ask you to raise your hand or to hit your light so I know who wants to speak. Please wait until I identify you so that we can keep some order.

Procedurally, we sort of have two ways we can go here. We can spend our time talking with the sponsor on specific questions, and the FDA. To try to eliminate some of the back and forth, I would like to, if it's okay with the panel, start with the sponsor.

So, if you have specific questions you want to inquire of the sponsor, that is where I would like to start. Certainly, if there is something that requires clarification, don't hesitate to bring the FDA in. But,

perhaps just to keep it organized, we can go sponsor and then FDA.

I will open, and I thought I saw Dr. Lincoff followed by Dr. Tatum. Why don't we start with you, Mike.

Questions to Presenters

DR. LINCOFF: I have two questions to start if we have time, or we can split it, I can go later.

The first, if I could get some more detail regarding the diagnostic criteria. That is, were they based, were there readers reading perfusing and wall motion, and if so, what proportion of the diagnoses were made on the basis of perfusion and wall motion?

I want to get a feel if this technique is principally a perfusion technique similar to SPECT, or how much contribution there was to making the diagnosis by the wall motion information that is one of the purported advantages that the sponsor has been stating with this type of imaging technique.

In other words, how many patients, for example, wouldn't have been an abnormal test based on perfusion but the additional information provided by the wall motion brought in the positive finding.

DR. WALOVITCH: This is Rick Walovitch from the

sponsor. With regards to perfusion and wall motion, we didn't discern if the information was coming from perfusion or wall motion.

Our comparator was SPECT, and it was gated so we took the totality of the information. But I can let Dr. Senior comment on his perspective from doing the trial with regards to the relative contribution of perfusion and wall motion.

DR. SENIOR: The data is not really available splitting perfusion versus wall motion. But, from the agent that is used for the study, which is a vasodilator, dipyridamole, used at the dose of 0.56 mg/kg/minute, it has been shown in many studies previously that this dose infrequently causes wall motion abnormality but causes perfusion defects much more than wall motion abnormality because the mechanism is different, the way the vasodilator works with perfusion is there is a stenosis.

It increases the capillary resistance and therefore reduces the number of capillaries and you begin to see perfusion defect. But to induce wall motion abnormality, you need to increase the heart rate and increase the oxygen demand, like you do with dobutamine for which we use wall motion.

So, from the perspective of physiology, I think that detection is likely to be based on perfusion than wall motion. But I think both are important to appreciate, because if you see a small subendocardial defect, you begin to appreciate the wall motion abnormality also.

But in this study, I don't think there is data to look clearly between the difference of the two.

DR. LINCOFF: If I understand, that means that despite the multiple slides that reported the wall motion as complementary or synergistic or whatever, in fact, you can't quantify at all that wall motion made any difference to the findings, the readings of these studies?

DR. WALOVITCH: We do have some data in patients who had--we subtracted out patients who had prior myocardial infarction and just looked at those patients who had ischemic disease. So there was no resting wall motion abnormality. Slide on.

[Slide.]

In this analysis, where you are taking those patients who had angiography as truth, and you subtracted those patients who had prior myocardial infarction so they had prior resting wall motion abnormalities, you can see that the sensitivity performance is comparable to SPECT. So

that is about all we can show you.

DR. HARRINGTON: Dr. Tatum followed by Dr. Paganini, Neaton, and Fogel.

DR. TATUM: Let's continue to follow this line of discussion. Actually, you do get wall motion abnormalities with Persantine if you have a complex disease with steel [?] phenomenon, which is the intermediate risk, multivessel complex disease.

My question comes back to the use of aminophylline. During the ECHO, at what point was the aminophylline given with respect to the Persantine, was the imaging done in the window between the administration of aminophylline, I mean the Persantine and the aminophylline?

DR. WALOVITCH: Yes, it was. So, the aminophylline was given after. The dose of dipyridamole we used was a 0.56 dose, which is sufficient to induce hyperemia in most all patients, but is known to be a little light from an inotropic point of view.

DR. TATUM: I know this well.

DR. WALOVITCH: Okay.

DR. TATUM: In the case of the comparator study, it was said that 95 percent of the patients got aminophylline to complete it. Was that given prior to

imaging or not?

DR. WALOVITCH: No, the aminophylline was always given after the ECHO imaging was completed.

DR. TATUM: In the comparator SPECT study, when was it given, before imaging?

DR. WALOVITCH: No--yes, before the imaging, but after the administration of--

DR. TATUM: You just wiped out the wall motion. You wiped out that part, you do not have the same study.

DR. WALOVITCH: I am confused because--maybe you could elucidate.

DR. TATUM: You did the imaging during the pharmacologic stress, which was continuing onward for the ECHO.

DR. WALOVITCH: Right.

DR. TATUM: The comparator study, you had ablated that particular component, which will persist into the imaging phase if you don't wipe it out with aminophylline.

You have the same problem with the adenosine in which you said a significant number of those were done with adenosine. It is not the same pharmacologic stress test you are doing anymore.

So, you have got a little bit of a study problem

here in that there is a difference in what is going on hemodynamically at the time of imaging with ECHO and at the time of imaging with SPECT.

DR. WALOVITCH: All AI-700 studies had dipyridamole as the stressor.

DR. TATUM: I understand.

DR. WALOVITCH: There were a few of the SPECT that didn't have it. The first pass extraction of cardiolyte is pretty high. So what is happening is the cardiolyte is getting fixed, and then--

DR. TATUM: But this comes back to the first question that was asked, and that was what was the component of the wall motion piece in making this, and if we can't break the two out, and we have got different stressors, it complicates things.

DR. WALOVITCH: There is no wall motion from the SPECT on the stress.

DR. TATUM: There is not?

DR. WALOVITCH: There isn't.

DR. TATUM: I disagree.

DR. WALOVITCH: It's resting wall motion, isn't it?

DR. TATUM: It's post-stress, and if you set up a

steel, you have ongoing ischemia, you will have wall motion abnormality. You will also have transient dilatation of the ventricle. So, you have got things with high degree disease where you are missing that particular component.

One more question here. In the comparator study, it was mentioned that quantitation was used for the SPECT, which I know doesn't exist for the ECHO.

In looking at the slides that came through, I saw different quantitative packages. Was there one, or was everybody using their own?

DR. WALOVITCH: It was one. Yale was the core lab, so Franz Walker was controlling. He was the independent core lab. The blinded readers were Marcello de Carli, Amy Escancria, Raymond Taifer, and Jim Udelson.

DR. TATUM: I just want to make sure you were using one quantitative package because that's a bias if you have got different ones, and it biases the readers on how you are doing this type of thing.

The last thing I just wanted to hit on was on the AEs, actually, it seems a little bit more than I am used to with dipyridamole, I have only done a few thousand.

My question is, however, do you have the data on the safety profile for the comparator trial versus the ECHO

piece so that you could possibly begin to break out which could be attributed to the contrast agent versus the pharmacologic?

DR. WALOVITCH: The only thing we have is what was shown to you by Dr. Dittrich, the Phase 2 pilot study, which was a very small sample size.

DR. TATUM: Okay.

DR. HARRINGTON: Dr. Temple, did you want to jump in and clarify something, or did you want to wait your turn for questioning?

DR. TEMPLE: No, I wanted to follow up on Dr. Lincoff's question.

DR. HARRINGTON: That's fine.

DR. TEMPLE: The little study, No. 20, does actually look at people who do and don't get the test drug so in that one, you can, but only with a small sample size, see what the benefit of the contrast was for, say, sensitivity and specificity, and it was, what, 40 versus 60, that little study. But that is what is missing from a lot of the rest of it, I take it, that's your question.

DR. HARRINGTON: Dr. Paganini.

DR. PAGANINI: Mr. Chairman, I have three major areas of questions. Do you want me to proceed with each

one?

DR. HARRINGTON: Why don't we do one and see if the other committee members want to weigh in on that, and then proceed down your list. I think we are going to have plenty of time to go through all the questions.

DR. PAGANINI: Let me start with, then, specifics to inflammation. You have mentioned that inflammation is a signal by C3a, C5a, and C-reactive proteins. I might want to point out to the FDA that in their Device Branch, C3a, C5a is activated by cuprophane exposure.

Blood exposure to cuprophane membranes was described in the early to mid-eighties with a series of very good research done on that. You might want to look at your Device Branch to see what they have come up with, with C5a and C3a.

Why I say that, white cells drop down very, very rapidly early on in exposure, as is done here. They are sequestered into the lungs, which then creates a low O , which we have seen here. We also see low blood pressure in those exposures, which we see here.

Then, after about 15 to 30 minutes, or within that time frame, there is a release of white cells from demarginating white cells, as well as a release from the

lungs of the sequestered white cells, which gives you the high white cell post, which we see here.

So, I think there is bioincompatibility that was defined by the cuprophane exposure to blood is very similar to what you are seeing here and bioincompatibility with the plasticizers.

Along those lines, do we have any type of plasticizer delivery to the body with this being sequestered into RES system? Plasticizers generally go to liver and brain. Have you looked at any deposition of plastic material or poly-whatever in any of those organ systems?

Third, along these same lines, the activation of the inflammation system has been associated with a propagation or prolongation of acute kidney injury.

In all of the studies, I saw no renal review, so this sort of hedges into my second question. Either in CKD Stage 3, 4, or 5, there has been no background of kidney dysfunction, very large population of people who would get this, and, second, any acute kidney injury associated, not just within 24 hours, but within the first five days or even longer term with that, and I will wait for the other questions.

DR. HARRINGTON: Maybe as the sponsor is preparing

the answer, one of my questions had been with this activation of complement, do we see any corresponding activation of thrombosis. I realize you said these are going to be stable CAD patients in the label but I am interested whether or not you have any data, for example, on D-dimer, or FBA, F1.2, et cetera.

Maybe you could handle the complement questions now.

DR. WALOVITCH: I will provide some background on some preclinical studies that may help explain some of what is going on. We have done some paladian labeled studies with microspheres, and we injected them into rats, and we saw that they localized in the RES system of the liver and spleen, and that is where the recovery was for these agents.

With regards to the kidney, we have not seen any morphological or histological changes in any animal studies at repeat doses in two species. We have also done studies in humans, as you know, looking at renal parameters, creatinine and BUN, and we didn't see any changes there either. So, that is the kidneys and the distribution with regards to thrombosis, maybe I will have Dr. Dittrich comment.

DR. DITTRICH: We specifically had no measurements

beyond that 72-hour time point, and specifically not to D-dimer or other parameters. The only phenomenon we saw related are those myocardial infarctions that occurred at Day 1 and Day 2. Again, one was after an angiogram.

DR. HARRINGTON: Let me just make sure that Emil's question was answered. So, you do have data on serial creatinine measures, that there has been no change in kidney function at least measured by either creatinine or creatinine clearance, which I think was your question, Emil.

And then my question, Dr. Dittrich, is you had no measures then of thrombosis markers in that early phase, just complement?

DR. DITTRICH: That's correct, complement. There were no changes in coagulation parameters, platelet counts, but nothing specifically on more sensitive markers of thrombosis.

As to renal function, slide up.

[Slide.]

We didn't show all of the data, we pointed out they were negative. For the mean population along with the mins and max, you see BUN, creatinine, and uric acid at baseline, discharge and follow-up in this setting.

Let's change to the next slide.

[Slide.]

As well, looking at shift tables, just bifurcating. We had so few patients above a creatinine of 2.5 in this study, it's not enough to show. But using creatinine shift of 1.5 greater or less, you some--more detail would also show that many had changed, of the ones that had changed, changed from 1.4 to 1.6 over the period of time.

DR. HARRINGTON: Go ahead, Emil.

DR. PAGANINI: Just a quick follow-up. The population of CKD, Stage 3 or greater, is going to be a population that potentially this would be used in, and the data that so far has been collected for creatinines of 1.5, I am not sure what that means without a body weight, et cetera, or an effective EGFR.

It would be nicer to see the EGFRs on that, but a 1.5 plus or minus is a break point that is a little bit low. Usually, the break points are 1.9 or greater.

DR. DITTRICH: Correct, but we had so few even at that level.

DR. HARRINGTON: Emil, before you go to your next question, are there other avenues of questioning along this regard?

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DR. MATTREY: Just a couple of questions. One is what is the particle load and the dose of 0.08 mL/kilo, or how many particles per mL is there in this preparation?

DR. HARRINGTON: Why do you ask that question?

DR. MATTREY: Because of the fever and the macrophage activation data suggests a particulate type reaction, and I am curious to know what the particle load was.

DR. WALOVITCH: Slide on.

[Slide.]

Here are some of the specification, mean diameter. We have already talked about the particle number is 1.5 to 2.7 billion/mL. These are small particles, 2 to 2.6, no particles over 20 microns in size with 99 percent of the particles less than 10 microns.

DR. HARRINGTON: Before we come back to you, Emil, we have got Dr. Fogel, then, I think it's Dr. Neaton, then down here.

DR. FOGEL: I just wanted to go along the lines of question of the particles and the number.

I know that there are particles that are somewhere between 10 and 20 microns, and those are fairly significantly large compared to red blood cells.

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I guess the question I have is even with only having 1 percent or 0.1 percent, you still have a significantly large number of those particles considering there is a billion of them, and was there any data concerning whether or not these particles clumped together?

My question simply goes to the fact that you already have a compromised patient who might have stenosis or COPD, or whatever, could these clump together and be a mechanistic reason for some of the adverse events that you are seeing.

DR. WALOVITCH: There was a negative charge on the particles so zeta potential was negative 30 millivolts, so they are not going to flocculate together.

When we look in vivo, we can see histologically, non-birefringement material in histological sections, and we don't see agglomeration, we don't have any, you know, in vivo live data to guarantee that.

DR. FOGEL: From a hemodynamic standpoint, though, the larger particles in a blood vessel that is under pressure and has a flow of a certain number of liters per minute, the particles of certain sizes are going to come together in the center of the vessel. I assume this is more static rather than dynamic.

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DR. WALOVITCH: Let me show you the size distribution. Slide on.

[Slide.]

There are some technical limitations to the technique and I could have Dr. Straub comment on them, but this is really the size distribution we are looking at. So there are very few between 10 and 20, and maybe Dr. Straub can comment what are the limitations of this assay with delineating between 10 and 20.

DR. FOGEL: You still have, on the y axis, you still have percentage, and I am looking at numbers. I mean if it's 0.1 percent of a billion, that is still a lot.

DR. WALOVITCH: Right, it's still a large number. Dr. Straub.

DR. STRAUB: That 99.0 percent or less than 10, which means that you could have potentially a percent of a billion between 10 and 20. But there is only a dose of 0.04 mL/kg, so you have to think about the total dose and it gets diluted out rather rapidly.

There aren't many relative to each other of these, any particles that could be greater than 10, and they are going to be diluted out, and they are not going to find each other, they are going to be separated by blood cells. They

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are not likely to clump together in vivo and then they get RES, and we monitor respiratory effects.

DR. HARRINGTON: Do you have more questions along that line, Dr. Fogel? No.

DR. NEATON: Can you tell me precisely the order in which the tests were done in each study, the SPECT, ECHO, and the ANGIO?

DR. WALOVITCH: Slide on.

[Slide.]

This is what happened for approximately 80 percent of the patients. They have their resting SPECT imaging. Then, they went to the ECHO lab. They had the first dose of AI-700. There was an hour wait. Dipyridamole was given in a four-minute infusion.

Two minutes after the end of the infusion, they were administered sestamibe and then a minute after that, they received AI-700, and then an hour later or so, after safety, they had the stress SPECT. They were given the aminophylline and immediately after the AI-700 imaging session, they were discharged two or three hours post AI-700.

DR. NEATON: So, 32 was same day SPECT and ECHO, the 33 wasn't. Are there patients for which you have SPECT

data on a different day?

DR. WALOVITCH: The majority of patients in 33 had the same day, as well. But there are patients who did have the SPECT before or after the AI-700 before angiography. There was a few days that was allowed.

DR. NEATON: So, there is potentially some comparator safety data on SPECT on a different day is what I am trying to get to.

DR. WALOVITCH: We didn't collect that.

DR. NEATON: You didn't collect it.

DR. WALOVITCH: No.

DR. NEATON: Okay. The second question is who was unblinded to the interim data that was being assessed by the readers in terms of disease presence or not in the company?

DR. WALOVITCH: No one.

DR. NEATON: No one. Okay. And the third question just to be sure I understand it, in 33, essentially the gold standard of the truth is almost everybody is ANGIO.

DR. WALOVITCH: Correct.

DR. NEATON: In 32, the majority is SPECT plus history.

DR. WALOVITCH: Correct.

DR. NEATON: So, it doesn't surprise me that

sensitivity is different between the two studies for SPECT.

DR. WALOVITCH: The problem with the 32 is that we had one SPECT comparator, and when we looked at the 33, we saw that the variability of SPECT was very similar to the variability we saw in ECHO. So that is what our explanation is with the difference in the performance of the trial.

DR. NEATON: Do you have data on what the kind of sensitivity and specificity of SPECT is against ANGIO and 32?

DR. WALOVITCH: Yes, we do.

DR. NEATON: That might be worth looking at.

DR. WALOVITCH: In the 32 trial, you see the comparison of accuracy, sensitivity, and specificity in the MITT population, the Modified Intent to Treat, and in the population where angiography was the truth standard - slide on.

[Slide.]

What you are looking at here is the three ECHO readers and the SPECT readers for accuracy, sensitivity, and specificity. You can see that the values are all very similar except for the SPECT reader for specificity where there is a drop in specificity in the ANGIO-only cohort.

You have to remember when ANGIO wasn't the truth

in the 32, part of the truth was this unblinded nuclear cardiologist who was also using SPECT data.

DR. HARRINGTON: Dr. Sahajwalla.

DR. SAHAJWALLA: In the briefing document, there is a mention of a safety study with a direct injection in rats at 1.4 times the human dose.

In that clinical situation, did it ever happen that they ended up giving more than the prescribed dose like it is all very, you know, strict time entered and the dose could have been injected, and the tech did not start scanning at the proper time, or had not set up the technical parameters directly. So did you ever inject more than what was the prescribed dose?

DR. WALOVITCH: Yes. The early clinical development we used higher doses than the clinical dose, and in some of the Phase 3 patients there were a few overdoses. But the performance characteristics and safety was unremarkable. It was just a handful of patients in the Phase 3.

DR. HARRINGTON: Dr. Flack.

DR. FLACK: A couple of comments and questions. One, I think Jim Neaton's point about the truth standard being variable, is something that has been bothering me

throughout this whole presentation.

I wouldn't expect that a true standard, which really is clearly less than a gold standard here, that consists of anatomy, function, history, and possible clinical outcomes in one study, and then mostly anatomy in another study, I wouldn't expect that the performance of these tests would be the same in predicting that because you are shooting at two different versions of the truth.

The question I have is, is there any benefit to picking up a positive test here in the absence of critical coronary artery stenosis that someone can go in and either surgically repair or angioplasty, is it of any clinical benefit to pick that up, because if it's not, from my vantage point, I would probably make the argument that throwing all that other stuff in there is really muddying the issue because essentially what you are trying to do is pick up critical stenosis.

I don't know of anything proven that would help me decision-making-wise with a patient if they come back with a positive test. But they have got negative critical stenosis outside of just by flying by the seat of my pants and intensifying the treatment of their risk factors.

Finally, I need some help in trying to understand

how a reader comes to say a test is or is not positive. With the flow data, for example, is there any conversion of this data to some kind of scale, or is it simply you look at it, you get a good image, and at the end of the day, you say that it is or is not, is there anything that is digitized and that you can sort of look at more reliably across tests.

DR. WALOVITCH: I will address the first question by asking Dr. Picard to comment on the overall clinical relevance of what we are seeing and the value of it, and then I will handle the second question myself with regards to the definition of disease and the relative ability of the blinded readers to make an assessment.

DR. PICARD: Well, I think there are two ways to look at a screening test, obviously, as has been discussed, identifying the patients who should go on for the invasive test, and identifying critical disease. But there is certainly value in clinical practice to identifying those patients who don't have critical disease.

One, as you mentioned, we might intensify their medical regimen, or at least identifying a cause. We identify that they have coronary disease. It may not be critical, but it certainly is a cause for their symptoms. So we would want to treat them for coronary disease,

certainly work on modifying their risk factors to prevent progression of that disease.

Certainly, the patients who we have already identified as having a mild form of coronary artery disease over time when you are looking for progression of disease in those patients using a test like this, it shows that they still have mild disease. It is certainly reassuring that you are on the right path in terms of your treatment regimens.

DR. WALOVITCH: Regarding the definition of disease and what the blinded readers were looking at, I am going to show you something from the ECHO blind read training manual. Slide on.

[Slide.]

So, we provided them with some information on what should be called normal and what should be called abnormal, what is a reversible defect, what is a fixed defect, and this was an iterative process. These were people who were trained in stress ECHO and they made their assessments, they looked at angiograms, and they refined their ability to detect disease, and that is pretty much the process that we went through. We had both analogue and digital data.

They had the video tapes as well as side-by-side

images of digital clips and the three apical views where they looked at the replenishment curves that Dr. Senior showed you, and they looked at the rate of replenishment. But there was no quantification. It was an iterative process with a truth standard.

DR. HARRINGTON: We have about 15 minutes. Remember we will have more time after lunch.

We have Dr. Day, Dr. Fleming, back to Emil, Fogel, DeMets, Temple. We have quite a long list here, so if I could try to get people to focus on their one key question so that other speakers can get in before lunch, and then we will come back to questions after lunch.

Dr. Day.

DR. DAY: I would like to focus on some sequencing effects throughout all of this. There is an increase in various adverse events after the second dose, for example, headaches increase tenfold, and generally the explanation for this is the addition of the second agent.

I understand why that design was used in this study, but couldn't there be a confound here, and part of it could be due to the AI-700 itself? So, have you considered doing another study of the general same design but without the addition of dipyridamole?

DR. WALOVITCH: Dr. Dittrich.

DR. DITTRICH: I won't address the additional study design, but you are absolutely correct. Although it is well established that headache is a common feature of dipyridamole, and if again the best we can do is again show you the placebo control slide, that was presented, in fact, with a headache rate describe in both placebo and active. Slide on.

[Slide.]

That is our information for drug alone in the small population and the headache rates. I am afraid there is nothing other. It's a problem that was discussed by both the FDA and us with regard to this.

Before you stop and it is slightly off topic, I am sorry, Dr. Harrington, but it is related to the 21 study, because the Agency has made a great deal out of the efficacy from this 20, 21 study. But please remember this was conducted in early 2000 with entirely different imaging technology, and the technology has evolved substantially in that period of time.

I think that point needs to be made. I won't suggest that it would have been different necessarily. But the company needs to know that.

DR. DAY: Just a final comment. I would like to come back later with some questions about the risk minimization plan, and I hope there will be time for that at the end.

DR. HARRINGTON: There absolutely will be.

I am going to go to Dr. DeMets. I will come back to some of the people who have already had a chance to speak and see if we can't get some of the new folks in.

David.

DR. DeMETS: My question relates to the fact that there has been some differences between the Study 32 and Study 33.

Something was learned in 32 in terms of grading these images, and that was transferred to the grading of 33. I am not sure I understand the details of that. But my question is did you take the new grading system and apply it to 32, because the images are fixed, they are not changing. But my question is how you interpret them.

So, maybe my lack of understanding it is a stupid question. But my question is, have you applied the new training, or could you apply the new training guidelines to the images that were obtained in 32?

DR. HARRINGTON: David, if I could take the

liberty, because I had a series of questions along the same topic, can you just explain in more detail exactly what happened that made you make this change, and then who did the retraining, and then I have the same question of David.

Did you go back and apply that retraining to the first set of images?

DR. WALOVITCH: Slide on.

[Slide.]

What happened was we did the 32 trial, unblinded it, and what we saw was that the nuclear reader was reading aggressively, calling out disease. We had two out of three ECHO readers who were very conservative. They had the same degree of accuracy but they were less likely to call out small defects.

So, we trained them this iterative process with angiograms, and we trained those 33 readers, we said, you know, be comfortable, call it out, trade off your sensitivity and specificity so that you increase sensitivity. But you will probably drop specificity, and these are the things that we did. We just told them to push their sensitivity by calling out the smaller defects. There were no major changes in the reading instruction.

There were a few things that we did learn, that

people do better if they are awake in the morning than late at night, and that they can't read the videotapes and digital clips serially, they have to read them serially. They can't read them simultaneously. But the basic thing was we, as a sponsor, went back and trained them.

We weren't unblinded to the data. We just assumed that if these readers were reading conservatively, our Phase 3 readers would be reading conservatively. So, without looking at the data, we just said let's start over, let's get them to read more aggressively. We know the Agency is interested in them reading aggressively, and it is worth trading off our specificity for sensitivity.

We knew that in the 33, when we are comparing to the truth standard of angiography, we had to demonstrate sensitivity or we would be in real trouble. The thought was that we had a problem with these trials from the concept of we need to study the intended population, which is more the 32, but we need to have a truth standard that is homogeneous, which is the 33. So we did one of each.

We couldn't do both, we couldn't get people who didn't need to go on to angiography from the 32 to actually have angiographies. So that was the dilemma in the trial design.

I just want to at this time clarify one thing. Dr. Mucci talked about the minimum criteria of success for the trials, and in our trials, the minimum criteria of success was something that we had in place for the 32 trial, and we met that minimum criteria of success. It was a 76 on the sensitivity and a 59 on the specificity.

But there was no minimum performance criteria for the 33 trial that was specified in the protocol or in the statistical analysis plan. The reason our values were lower than what has been reported in the literature is because we know that registration trials are very rigorous with regards to their blind read methodology, they are fully blinded.

A lot of what is in the literature where the values are higher are usually single institutional studies, and they quite often are studies where they are published obviously. So there is sort of a bias towards good studies being published.

So, we believe that the results of our trial, because we believe the SPECT data was done with a standardized core lab, the imaging data was in accordance to ASNC guidelines. Bad studies were eliminated so we believe that SPECT data that we obtained in our trial was the true performance of SPECT in the patient population we studied.

DR. HARRINGTON: David, did you have your question answered?

DR. DeMETS: I assume that the answer is they did not re-read the 32.

DR. HARRINGTON: Could you just answer Dr. DeMets' question?

DR. WALOVITCH: Sorry about that. We didn't re-read the 32. I apologize.

DR. HARRINGTON: We have about 6 or 7 minutes to go. Let's have Dr. Fleming followed by Dr. Temple. If we have time, we will get to you, Dr. Teerlink, et cetera, but, if not, we will get you right after lunch. We will keep the list going.

Tom.

DR. FLEMING: I have a two-part question. Studies 32 and 33 provide a population where the truth is about 50 percent with CAD as assessed by the gold standard.

So, I can think of four approaches to trying to use a diagnostic. One would be to do an unbiased coin flip, and I would be right 50 percent of the time.

One would be to use non-contrast ECHO that would be based on a wall motion assessment, one based on SPECT that would be based on perfusion, and one based on the AI-

700 ECHO that would be in theory trying to get the perfusion and the wall motion benefit.

So, my two-part question, and the first one actually is somewhat related to Dr. Tatum's observation. My first question is, isn't it disappointing that the evidence suggests that AI-700 ECHO isn't better than SPECT, that when you are looking at a combination of perfusion and wall motion, you are not doing better than perfusion alone?

The second part of the question is as we look at this Study 21 data that the FDA had provided where there is a suggestion of only very modest improvement in the AI-700 ECHO against non-contrast ECHO, it seems as though you are not doing much better than just wall motion alone either. Is it, in fact, am I right, that there is nothing in Studies 32 and 33 that will provide us evidence about the relationship of contrast versus non-contrast ECHO. So, essentially, we only have Study 21? So, a two-part question for the sponsor.

DR. WALOVITCH: Let me see if I have got this right. Let's deal with the 21 trial.

DR. Fleming: Start with the first. There is a lot of data in 32 and 33 to contrast with SPECT, and my understanding is here, you are trying to get the combination

of perfusion and wall motion versus just perfusion alone.

Why shouldn't I be disappointed if the evidence is indicating you are not getting anything better in accuracy?

DR. WALOVITCH: The reason is it is a brand-new modality. SPECT has been around for 10 years, the readers are well versed on reading these images. Our readers in our trial were looking at ECHO images for the first time. They don't have many years of experience.

In addition, the SPECT imaging--

DR. FLEMING: Essentially, you are asking us, on this issue, to take it on faith that this diagnostic, while it didn't perform any better here, in the future, when it is used in a more educated way, will, in fact, perform better.

DR. WALOVITCH: That is my assumption. I am not saying that that is what will happen. I am just saying that the reason that we didn't perform better is because at this point in time, this is an equivalent tool from the perspective of the performance characteristics.

You have to take into consideration that there is a learning curve, and this learning curve occurs over years in the community, and tools get better over time.

DR. FLEMING: Before the Chair cuts me off, a second question.

DR. HARRINGTON: I was actually going to encourage you to keep going.

DR. FLEMING: Okay. The second question gets to whether contrast beats non-contrast. Specifically, when we add perfusion to wall motion, are you beating wall motion. Those data from 21, limited as they are, is suggesting that that difference, too, is really modest.

Is that the only data you can put forward to enlighten us about what the addition is of contrast to non-contrast ECHO?

DR. WALOVITCH: I would like to put forth the 21 data with a little bit different perspective. Slide on.

[Slide.]

This is the data from the cohort that was randomized. It is true that one of these doses is lower than our clinical dose and one is higher. The dose that was shown to you, the additional cohort, was an asymmetric dose, and there was a problem. We gave a higher dose at the beginning and a lower dose after the stress. So that cohort, the data was confusing; the readers had a hard time interpreting it.

When we just look at the data in the randomized cohort where the patient population was the same, we see a

trend with the performance characteristics. When AI-700 was given, there was an increase in sensitivity and specificity numerically.

So, it is a very small sample size. The other data we have is from the Phase 3 program where we look at the baseline ECHO window quality, and we see that 27 percent of those images were considered poor quality, and when we look at the diagnostic yield from that trial, we see that 99 percent of the images were evaluable.

That is a slide from the core. Slide on.

[Slide.]

DR. FLEMING: Before you leave that slide, it does seem to be confirming what I had said my interpretation is of the FDA presentation. In these 21 patients, 68 percent success rate on the placebo is what you are showing.

FDA pointed out that at the 0.04 dose, it's 73 percent, you are giving a pooling that is around 75, 77 percent.

Now, that is based, first of all, only on 20-odd patients per arm, so we have to take that with great caution. Secondly, that delta is 5 to 10 percent, not a delta of 18 to 20 percent that you are seeing when you are contrasting to a coin flip.

So, my interpretation of this is that there is a substantial enhancement over a coin flip that you get with just the non-contrast ECHO alone, and therefore, it becomes even much more complicated to understand the extent to which the contrast is adding anything important beyond non-contrast.

DR. HARRINGTON: Go ahead, Dr. Tatum, and then we will go on to Bob Temple before lunch.

DR. TATUM: One point I want to continue to make in case we are missing it, is SPECT gated was never given a chance, because the aminophylline, it's not a comparator study, so it was taken out of the equation in the comparison. So that's one thing.

The other thing to remember is that when you are using Persantine, you frequently don't get wall motion. So you have given up the wall motion abnormality you would have created using dobutamine or stress for the perfusion piece, and it is a wash. That is exactly your question.

DR. HARRINGTON: Dr. Temple, and then we will break.

DR. TEMPLE: I think my question is very similar to what Tom and Dr. Flack were asking but, since I understand so little of this, you could just tell me I am

off the wall.

The question I have is whether you gain enough by doing any of these tests compared to your clinical judgment to make it seem worthwhile.

For example, in Study 33, somebody decided all these people needed an angiogram. Okay. So, I guess the sensitivity for the positive one must be 100 percent. But what was the specificity there? Those are all people who were thought to have a lesion.

How did the clinical judgment compare with what they found here, and if you were thinking about doing these tests, you must think there is some chance the person has an anatomical lesion or sensitivity and specificities in the range of 70 percent enough to change your mind?

Again, I want to emphasize for everybody I know nothing about all this, but that's the question I would ask, why would anybody let things with this degree of error change their mind.

Another possibility, of course, would be to allow people to do these tests and then have a third party expert come in and make clinical judgments and see what the specificity and sensitivity of that overall post facto clinical judgment was. But anyway, that's my question and

anybody feel free to say that's silly.

DR. HARRINGTON: Go ahead, Dr. Tatum.

DR. TATUM: So, in the real world frequently you are getting these tests when you know that there is disease, or you may even know the anatomy. The question is the severity of disease, the amount of dysfunction, do I use the medical versus the vascular treatment.

Those are the questions you are asked more frequently, risk stratification, outcome prognosis, making decisions about clinically how are you going to proceed with the patient.

It is not so much--I tell my residents now, the patients you have walking in, particularly I work in a VA, they have got disease. The question is that you are really trying to figure out what to do next, what is the risk, the dysfunction is a huge piece of what you need to look at.

DR. TEMPLE: But the proposed label is to help you decide whether to do an angiogram. That is sort of what I am asking about. Would this change your view, would a finding here change your view about whether you should do the angiogram, is it strong enough to do that, because it has a considerable error rate on both ends.

DR. HARRINGTON: Dr. Teerlink, I will give you the

last comment, and then we are moving on to lunch.

DR. TEERLINK: I just wanted to modify a bit what you just said, because I also work at a VA. So absolutely in our patient population, they are presumed to have coronary disease until proven otherwise.

However, it is important to keep in mind there are 10 million of these tests done in the United States a year, and in the community, the way these tests are done, are exactly as Dr. Temple is alluding. So I actually do believe that as a label is written and as we have been discussing, the issues around sensitivity are going to be really crucial because the primary labeling and everything else is really geared towards this as a screening test, not as you are suggesting, which is also how we use lots of things, as a test to kind of modify our diagnosis.

I would put back the emphasis on the issue of sensitivity and say it is frequently used as a screening test in the real world.

DR. HARRINGTON: Good discussion. I want to thank the sponsor and the FDA for their presentations this morning.

Let's meet back here exactly at 1:00 because we have a long list of people still wanting to ask questions.

[Luncheon recess at 12:00 Noon.]

AFTERNOON SESSION

[1:00 p.m.]

DR. HARRINGTON: If everybody is back in their seats, we can begin again. We are still continuing with the panel's questions to the sponsor, and as I said this morning, we had no speakers for the open public hearing, as we will co-opt that time to you to ask more questions.

Again, I would like the panel to continue their questions for the sponsor, and then we will specifically devote some time to questions to the FDA. We could use the full hour or we can get to the questions sooner. I just want to make sure that everybody is heard.

Fred, you were next after the break, and then, Vanda, you would be after that. John, you are after that.

Fred, go ahead.

DR. KASKEL: I just wanted to ask a couple of questions. The data on the type of drugs that these patients were on, vasoactive drugs, I didn't see a lot of detail as to the different classes of drugs, and I just wonder if that is worth looking at in terms of possible interactions with the agent.

You have these patients with probably ACE inhibitors or ARBs, and other agents. I think it is

probably worth taking a look to see if there are any groups there that might give you some information.

Then, I can't add too much more to the renal issues that my distinguished colleague, Dr. Paganini, reviewed with you, but just to mention about the blood pressure hemodynamics.

The agent obviously caused some changes in blood pressure. You followed that out over a period of hours. I am just wondering if it wouldn't be worth doing on a small subset of patients what we call the ambulatory blood pressure monitoring where we could see over the course of time what happens to their blood pressure, systolic, diastolic, throughout the day after the agent is given, as well as through the night to see if the diurnal pattern was affected.

We have data to show that in patients in that age group, if they have blunted nocturnal dipping for any number of reasons, they are at high risk for cardiac event. So, again, looking at a group that might be at risk for a reaction to the agent.

Then, finally--

DR. HARRINGTON: Fred, let me stop you and get the two questions; so concomitant medicines, follow-up study

with ambulatory blood pressure. Why don't we start with those and then I will let you get your third one in.

DR. KASKEL: Thank you.

DR. WALOVITCH: With regards to concomitant medications, we saw no indication of drug-drug interaction. They were on what you would expect for this population, a lot of them were on anti-hypertensives and lipid-lowering drugs, as well as ACE inhibitors.

We didn't look at adverse experiences per se for patients on different drug therapies. But we saw nothing in the data that would indicate there was any drug-drug interaction.

DR. HARRINGTON: Before you move on, do you actually have data where you could actually show us what medicines they were on? Do you have a table of concomitant medicines, which I think is what your question is, Dr. Kaskel.

DR. WALOVITCH: We can generate one and provide it to you within a few minutes, which we will do.

With regards to blood pressure, I will turn it over to Dr. Dittrich.

DR. DITTRICH: Again, I can only clarify the data presented in the core, which gave blood pressures at time

points. As we show this, you will see the mean blood pressures are at a time specifically after stress--

[Slide.]

--from 60 minutes, and then discharge often occurred during that day, as well as a follow-up period, which was around 72 hours. But as far as ambulatory blood pressure monitoring, no, that was not performed or in any other study.

DR. MATTREY: Are these standard deviations or standard error bars?

DR. DITTRICH: Standard deviations.

DR. MATTREY: Thank you.

DR. HARRINGTON: Go ahead, John, did you want to clarify?

DR. TEERLINK: Just to clarify in the blood pressure issues, Slide CC-82 says lowest report of blood pressure was 77 mm decrease from baseline 104. Slide 76 says that it was 52 mm and then we have a report of a 72-year-old woman who had an undetectable blood pressure.

Are these the same patients who you have different data for or are these three individual patients and how should we look at the extremes, because means I find to be obviously less informative. I think it was useful to go through the individual cases of blood pressures, but I am

trying to get how many had these extreme drops.

DR. DITTRICH: Slide up.

[Slide.]

Exactly. I apologize because we showed differences between hypotensive adverse events or lowest blood pressures, and the other one you are talking about was actually the slide related to when a drug was discontinued.

They get presented in different contexts. But the slide we showed you of actual values for hypotensive AEs are all inclusive. Next slide up.

[Slide.]

This again is all the resting hypotensive adverse events and the nadir blood pressure.

DR. TEERLINK: So, the 52 mm is during stress.

DR. DITTRICH: Correct.

DR. TEERLINK: So, that is not included in this group.

DR. DITTRICH: That is correct, and that I think was in the context of discontinuation. In an attempt to match what was presented to you by the FDA, we gave some of those same--but we believe the resting hypotensive AEs gave the best picture in that case because, of course, we know what dipyridamole can do to systemic blood pressure.

DR. FLEMING: Just a clarification on the slide that preceded this one, CC-82, you referred to there being 38 patients that had 41 hypotensive events in the 911 patients, and yet in your briefing document, on Table 18, page 97, you say there are only 31. Can you explain that difference? You said there were only 31 patients with hypotensive AEs in the 911 in your briefing document.

DR. DITTRICH: I am sorry, this is because there are different preferred terms I am told. I don't have access to what was given in the briefing document. They may have been decreased blood pressure.

DR. FLEMING: Well, they are listed the exact same way. I mean they are listed as your totality of patients that had at least one hypotensive adverse event in the 911 people.

DR. DITTRICH: Then, I think we will have to look at both together to give you the answer to correct the difference.

DR. HARRINGTON: If you guys could check on that. Let me turn to Bob, he has another question, and then get back to Dr. Fleming.

DR. MATTREY: I am curious, these hypotensive crisis versus the vasovagal. I mean that 72-year-old lady

sounds like a vasovagal where the blood pressure bottomed out and you couldn't measure it. Are they different? Are you calling the hypotensive events the same as the vasovagal reaction, or are they different people?

DR. DITTRICH: No. Once again, it is related to the serious adverse event that was identified, related to the vasovagal event is the hypotension, and as Dr. Teerlink pointed out, unmeasurable blood pressure, but this is a phenomenon of decreasing heart rate, unmeasurable blood pressure.

DR. HARRINGTON: Are there any more questions about the blood pressure before I let Dr. Kaskel ask his other question?

Do you have an answer for Dr. Fleming?

DR. DITTRICH: Yes, we have that. Slide up to answer Dr. Fleming.

[Slide.]

This is the time of the 9/11, hypotension as an AE versus blood pressure decreased versus blood pressure systolic decreased. Those are the preferred terms used.

DR. TEERLINK: And those are independent. And those are mutually exclusive or could one patient have been reported as being hypotensive?

DR. DITTRICH: I think the bottom, there you see was counted only once in the total column.

DR. FLEMING: These are the data that you give us, these are the exact data in Table 18 of the briefing document. So, then, how does this match with Slide CC-82, that says there are 38 people with 41 events?

DR. DITTRICH: That is merged.

DR. WALOVITCH: You are adding the 31 with 6 on the one for the 38. So you are getting the total there, and we put all the terms together so that, in your briefing document, you didn't have to look at the difference, which is really just a reportability by the investigator. So, there are 38 patients. Some of them have more than one event, so that is why there are more events than patients.

DR. HARRINGTON: Is this blood pressure?

DR. DITTRICH: Yes.

DR. TATUM: On this slide, dipyridamole, the second dose to discharge. So, in the seven minutes of infusion, you are recording whether there is hypotension, that is 0.4, and the other one is after the dose after 7 minutes.

DR. WALOVITCH: Correct.

DR. TATUM: And that is 18.

DR. WALOVITCH: Correct.

At this time it is of value to give a clarification on the dipyridamole. I would like to ask Dr. Senior to make a comment.

DR. SENIOR: I think it was a question related to the effect of aminophylline on wall motion with SPECT. Now, the dipyridamole was in use for 4 minutes and followed by 2 minutes later the technetium was injected, and third minute AI-700 was injected. Then, the imaging was continued for 5 minutes. So a total of 8 minutes went by after dipyridamole injection following which aminophylline was injected.

Now, the peak of dipyridamole is between 3 to 4 minutes, and whatever wall motion occurs would occur at that time, and the fact that at 60 minutes you can still see wall motion is because of the stunning effect that still remains.

So, after 4 or 5, 7 to 8 minutes, even if you give aminophylline, that is not going to change the wall motion abnormality if it's there.

Secondly, we didn't have any problem anyway because we were using, you know, these are clinical patients being assessed for coronary artery disease, and we give them aminophylline to most of our patients to reverse the side effects so they can go home quicker.

There is no data to suggest that if you give aminophylline you actually compromise the gated SPECT. The whole protocol was actually performed by the nuclear cardiologist involved with this.

So, we don't feel that aminophylline actually compromise the gated SPECT effect.

DR. HARRINGTON: Dr. Tatum, did you want to comment?

DR. TATUM: I disagree. I do not give aminophylline for that particular reason, and there is a difference, because you reverse the flow, it depends on the severity of the ischemia whether you are still going to see it later.

Of course, if it is severe ischemia, you will see it, but less flow--I think there is a problem. The issue I have with this is regardless of what you believe or not, the protocol is different for the two agents. You have made the change. It's not the same.

DR. HARRINGTON: Let's hold that discussion because we have a specific question about how we view as a committee, the comparator. So, your input there is going to be critical.

Dr. Kaskel, I know you had another question.

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DR. KASKEL: The last question is a follow-up on the biomarker issue and acute kidney injury. We really don't have enough information with just the creatinine, it's a poor man's marker of the injuries.

So, along those lines, there are two biomarkers that are in trial now, clinical trials in NIH. One is called KIM, K-I-M, one is called NGAL, and they are both useful, non-invasive markers that can be used on the urine to see if there is any signal.

On the positive side, if you were to get this sonogram, the ultrasonographer to go down to the renal arteries and get a doppler of the kidneys when you give this agent under different conditions, you would have more data to see if there was any resistance changes in the utility of an agent, of a test like that, in looking at a transplanted kidney to see if it is rejecting, getting some really fine markers.

So, again, in the next design, if you were to take a small subgroup and look at the kidneys, we would like that, a quarter of the blood supply goes to them.

Thank you.

DR. HARRINGTON: John, we are going to go to Vanda and then we will get you on the list here. We have Dr.

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Teerlink, Dr. Day, and then Dr. Flack.

DR. SACHDEV: This is a question about how the sensitivity was determined for both the ECHO and the SPECT. Could you clarify whether localization had anything to do with it so that if either imaging technique, for example, had an anterior perfusion defect, and the angiogram showed a completely different, like a circumflex lesion that was significant, was that counted as a positive test?

DR. WALOVITCH: The primary analysis did not require localization. It was either disease or no disease. But, as I mentioned in the presentation, we looked at localization in those patients who had angiography, and we looked at the ability to localize to the angiographic defect as defined by major coronary arteries LAD, LCX, and RCA, and that data is shown here. Slide up.

[Slide.]

What you have here is, you have the three ECHO readers and the SPECT readers, and then the 33, we are showing you the three ECHO readers and the median SPECT reader, and this is percent correct localized.

So, what we did is we took their baseline sensitivity and we saw, if they had it localized, how close would they be to their baseline sensitivity, and you can see

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the values here. They are above 80 for all the ECHO readers, and they are between 70 and 80 for the SPECT readers for localizing angiographically defined defects.

DR. HARRINGTON: Dr. Day.

DR. DAY: My question has to do with risk minimization. Is this an appropriate time to shift to that topic? It won't take long.

DR. HARRINGTON: Sure. If it is going to be a prolonged discussion--

DR. DAY: I think it's brief.

DR. HARRINGTON: Okay. That's one of the topics I want to get to later today, but go ahead.

DR. DAY: I do have some questions. Today, we heard about risk minimization during the administration of the drug, and there is also a riskMAP, a risk minimization action plan in the briefing documents from the sponsor on page 137, for example, Section 6.5, and there are two components, safety surveillance and proficiency training plan.

For the proficiency training plan, there is a training program with different components, and one item then says "and demonstrated proficiency," and then the trainee gets the product. So there are three steps - get

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trained, demonstrate proficiency, get the product.

So, could somebody tell us a little bit about how proficiency would be demonstrated?

DR. WALOVITCH: The full training program hasn't been worked out, and we haven't discussed it in detail with the Agency, but it would be very similar to what we do with our blinded readers.

We would start with showing them some images, and there would be an iterative feedback loop with truth standard and results from our trial, as how people read it correctly, what were the things they would focus on.

We would have a sonographer and we would have cardiologists who were already trained in the procedure. We would have like Centers of Excellence, which would be based upon centers that have worked with us in the Phase 3 program. Those would be centers where people would be trained and once there was demonstrated proficiency at the site for that individual, they would be able to do the procedure.

DR. DAY: So, there would be some specific outcome measures looked at and demonstrated proficiency?

DR. WALOVITCH: Proficiency is based upon the diagnostic performance. It is not going to be based upon

outcome related measures.

DR. DAY: This would be for anyone who administers the drug, not only the physician but anyone in the physician's staff. So, say, a nurse, would the nurse have to go through this training?

DR. WALOVITCH: There would be training for administration and there would be training about contraindications. But for interpretation of imaging, it would be a cardiologist with stress ECHO experience, would be the only person who would be reading the images.

DR. DAY: I was focusing more on the administration than the reading of the results. So, this is not a certification process. There are some drugs where the professionals go through some kind of training, and then they have to be, you know, pass a test or something of the sort. So, you are not envisioning anything like that?

DR. WALOVITCH: No. I am reluctant to comment more until we talk to the Agency about what their views are, as well, because this is sort of a plan that we have. But we haven't really engaged the Agency.

DR. HARRINGTON: Dr. Day, you will have the chance later in the afternoon to make suggestions if you have such a plan.

DR. DAY: The last part of the action plan could include labeling. You have mentioned what is in the labeling, and I would just like to point out that patient counseling, the only thing that is in there is contraindications, have the patient tell you whether they have COPD or pregnancy, and so on, and so forth.

Have you discussed or thought ahead to anything additional that might be in that section?

DR. WALOVITCH: To be honest, not really.

DR. NEATON: I guess I am a little bit confused, because I thought a strong justification for this whole approach was the broad availability, ECHOs everywhere, lots of folks can do those. So, now you are talking about a much more limited use of it.

I think that is important because I would think that if it is really a broad group of investigators out there that eventually use this, you are not going to see the same levels of accuracy and sensitivity and specificity as you are seeing in the study.

I just wonder what you think about that, because we don't have any controlled safety. This has been done in 28 centers, highly selective, I presume, and now we are going to use it in a big way, where we can't expect the same

performance I don't think.

DR. WALOVITCH: The difference between our trials and the practice of medicine are large. Obviously, in the practice of medicine it won't be totally blinded so there will be some familiarity with the information that is being acquired.

We, as a sponsor, have an obligation to make sure whoever is going to use this tool, that they are trained. I think the fact that there is a large base of stress ECHO physicians out there who we can train to use this tool, and we can't automatically assume that without working with them, we feel comfortable they will be able to do it.

Maybe Dr. Picard can comment a little bit on this.

DR. NEATON: Already in your trials, you had to train them twice, and so I am a little concerned about the notion of being able to train a large number of practitioners to do ECHOs, and to get the levels of accuracy that is even close to what you have achieved here.

DR. HARRINGTON: You are concerned, Jim, about the generalizability of this and moving it into a broader population.

DR. NEATON: I would like to know what has been the accuracy, have you used the 28-site investigators

instead of expert leaders, that's the more relevant number in my mind.

DR. HARRINGTON: Dr. Picard, do you have a comment?

DR. PICARD: I would want to make a few comments. First, if we look at diffusion of a different technology, stress echocardiography, I can remember 18 years ago when I took a trip to Indiana University and learned how to do stress echocardiography from Harvey Feigenbaum.

He was the person who essentially invented that procedure, and he personally trained a group of people, and it became a pyramid, and then we went and trained, and so I think you are dealing with a very similar model here.

Again, I can't speak for the sponsor but the champion is trained, then that trained person trains other people, and I think there is a snowball effect, and obviously, one has to be very careful about performance and proficiency to make sure those people are being appropriately trained, and the training is appropriate.

The other is just a point about availability. ECHO, when you just look at numbers of echocardiograms that are performed across the country compared to nuclear scintigraphy, even what we might call a limited number, a

smaller number of users of echocardiography, it is probably going to be a higher number than the users and practitioners of stress scintigraphy, just because of the sheer numbers of clinical cardiologists who practice echocardiography.

I think that when you diffuse this technology, if you diffuse it appropriately, even though it may not be used by every single practitioner of echocardiography, either the numbers are going to be fairly widely available.

DR. HARRINGTON: Dr. Teerlink.

DR. TEERLINK: Thanks. I have three directions. I would like to reinforce what Jim just brought up actually in terms of the ECHO.

I think to use Mike's example, I doubt, however, that any of us are now, having had 15 years more experience, better than Harvey Feigenbaum was then--maybe a little. But I think when you pick the experts, you train them intensely on a technique, you work very hard and then you retrain them on the technique, given direct feedback with cardiac cath results, I am at least viewing this as the best we are going to see from this test performance.

I think that is a point Jim was trying to make. I would be hard pressed to say, and you suggested, and I will give you a chance to disagree with this. But you suggested

you thought the community would get much better, and I think that is not true at all. So, that's the first.

DR. HARRINGTON: Did you have a question?

DR. PICARD: Again, if you will allow me to use the stress echocardiography analogy, we started that test using a videotape, and then the technology evolved so that we could digitally capture the images, do side by side comparisons, which improved our diagnostic accuracy.

I think the same thing applies here. The imaging equipment is constantly getting better, the way we are processing the signals now is so much better than it was a year or two ago, that the detection of the contrast signal will become automated, there will be quantification software, just as there are with nuclear scintigraphy.

I think the technology is a moving target, so I wouldn't necessarily say that the performance today is the ceiling. I would be very optimistic that, in fact, we are going to be able to do better, because of the enhancements to the technology, in addition to the expertise of the readers.

DR. HARRINGTON: John?

DR. TEERLINK: I just want to say I don't share that optimism.

The second point is in clinical practice, many centers either do nukes or ECHO, because you do what you are good at. The reason they do that is because there is an assumption--maybe this is an assumption, but some trials have suggested this, that stress ECHO is as good as is nuclear in this proper setting, in the appropriate centers.

What we have here is an agent that is taking stress ECHO, the stress ECHO, which is showing wall motion abnormalities with an agent called dobutamine, and now shifting the agent that you are giving to dipyridamole, which shifts it to a perfusion based study.

Given that most of these centers are trained to do dobutamine ECHOs, and now be switching to Persantine, what I think you are asking is you are actually asking people who do dobutamine ECHOs to switch to Persantine ECHOs.

So, to me, the meaningful comparator here is how do Persantine ECHOs compare to dobutamine ECHOs, because there seems to be a very reasonable reason to do that.

So, since you have never tested the efficacy of this agent in response to dobutamine, should your label include an exclusion for dobutamine stress testing, or should you specify that it is only meant to replace SPECT imaging.

DR. WALOVITCH: With regards to the label, the focus is for those patients who cannot exercise and the only data that we have is with regards to dipyridamole. We don't have data for dobutamine.

DR. TEERLINK: But practically, you are asking most of the physicians who are going to be converting, are going to be converting from dobutamine stress ECHO--

DR. WALOVITCH: Correct.

DR. TEERLINK: So, you are going to be asking them to abandon an established diagnostic modality for something that you haven't tested head to head.

DR. WALOVITCH: We are asking them to switch to a safer and more easily reproducible--

DR. TEERLINK: And we know it is safer then dobutamine ECHOs--because I don't see a head-to-head comparison.

DR. WALOVITCH: There is no head to head. We have not presented data here that is head to head, we have historical data on relatively large enrollment trials and registry trials on the safety of dobutamine.

I also would like to make a point, if I can, about the issue of dobutamine ECHO and dipyridamole ECHO. In the United States, dipyridamole ECHO is not used as a stress

test because the allowed dose of 0.56 mg/kg is not sufficient to induce wall motion abnormalities.

The only experience with dipyridamole echocardiography as a diagnostic test is essentially in Italy where patients are allowed to receive 0.84 cc/kg, and at that higher dose, numerous studies have shown an equivalency of a high dose dipyridamole ECHO to a dobutamine ECHO in head-to-head comparisons in Italy for the wall motion detection.

Now, what we are doing here is not wall motion detection. We are primarily playing on the vasodilator for its perfusion capabilities, just as we would with nuclear.

I think that to ask for comparisons in this regard is not exactly where the question should be focused.

DR. HARRINGTON: Before you sit down, Dr. Picard, I want to follow up on something that the sponsor just said and get your perspective on this.

The sponsor just said this would be for people who are not eligible for regular exercise but they would be pharmacologically stressed. The trial didn't actually study that. The trial took people who you chose to give a pharmacologic stress to.

Can you tell me the group of people who can't be

stressed, older, multiple comorbidities, et cetera, is that the same group, do we have enough information, in other words, on the target population?

DR. PICARD: Unless we really delve into the data in detail. But it is hard to answer that question specifically but the kinds of patients that we are going to deal with, at least in my practice, would be the patients who are going on to non-cardiac surgery and we are trying to assess their cardiac risk to see whether it's safe to give them general anesthesia.

These may be patients with peripheral vascular disease, so they can't exercise sufficiently on a treadmill. They may have arthritis in their knees, so that they can't exercise. They may be patients who have hypertension who are treated with a beta blocker, and so that I can't get their target heart rate up sufficiently on the treadmill to achieve adequate stress.

Yes, I could send them home for a week and wean off the beta blocker, or maybe their atrial fibrillation will rebound or whatever, but there is an urgency to get them to surgery the next day. So, there are a lot of different patient subsets where I think that it is appropriate to do this type of test.

DR. HARRINGTON: I fully agree with that. Certainly the patients that we refer for pharmacologic stress are, as you say they are older, they have comorbidities, et cetera. Do you think that was the target population in the clinical trials that we are looking at?

DR. PICARD: I think if we just take our general or my general experience where about 40 to 50 percent of the patients who come in for a stress test, whether it be nuclear or ECHO, are not able to do it adequately with exercise, and I would assume in this trial, if it's the same population, about 40 or 50 percent of them probably would have met that profile, but enrollment eligibility was not specifically inability to exercise.

DR. HARRINGTON: That is really helpful.

John.

DR. TEERLINK: I just wanted to finish up with the second question and get to the third question.

One point that I asked was given that this has never been tested in the setting of dobutamine, and certainly there will be a temptation to say, well, gee, if this opacifies the ventricle really well, and 27 percent or whatever number we want to come up with of the stress ECHOs aren't appropriate visualization, but with this you get 99

percent visualization. I would be really interested to use this agent in dobutamine stress ECHOs to just get better wall motion quantification.

So, given that it has never been studied, does the sponsor agree that they should have a label exclusion for it not to be used with dobutamine? I ask that question, follow up on that, and then I have one quick--

DR. PICARD: I think I have to defer to the sponsor to answer that question. But I also want to make sure that the panel understands that dobutamine, as a drug, has never been approved for stress ECHO cardiography.

DR. HARRINGTON: Does the sponsor want to answer Dr. Teerlink's question?

DR. WALOVITCH: We wouldn't mind having that limitation on the label.

DR. TEERLINK: I didn't think so. And then the final question was just in terms of your understanding of the communication between the FDA and the primary endpoint, was it made clear to you by the FDA that accuracy would not count as a valid primary endpoint, and if so, when did that become apparent? If it wasn't apparent to you, why are we sort of hearing it now from the FDA that you didn't hear it before?

DR. HARRINGTON: Let me clarify because that was one of my key questions for the FDA. I would like maybe both the FDA and the sponsor to explain to us what exactly was the conversation, what did you tell them should be the primary endpoint, and what did they hear, which is I think your question, John.

DR. WALOVITCH: Michael Slater, please.

MR. SLATER: Let me address that. We certainly had many discussions with FDA about what the primary endpoint should be, and certainly we agreed to include sensitivity and specificity in those protocols.

We never really had a discussion on the acceptability of accuracy. We have always assumed it is acceptable. In fact, one of the influences on that is that FDA's own regulations on diagnostic radio pharmaceuticals, which are clearly analogous, do specify accuracy as the appropriate endpoint.

I can quote. The claim of disease or pathology detection or assessment is established by demonstrating in a defined clinical setting that the diagnostic radio pharmaceutical has sufficient accuracy.

Our position has always been that regulations are, if anything, more important than guidelines. But the truth

is we never had a debate about whether accuracy was acceptable.

DR. HARRINGTON: Let me just make sure that I understand. So, you never actually had the discussion as to what would constitute the primary endpoint and had an agreement upon that. You took information from the guidance literature, but you never clarified that and said, hey, is this okay. Is that a fair characterization?

MR. SLATER: We repeatedly submitted our statistical analysis plans to the Agency. So they were well aware of what we were planning to do. They didn't respond to say accuracy is not acceptable.

DR. HARRINGTON: Dr. Rieves, would you like to comment, help us try to understand this?

DR. RIEVES: Well, Tony, fill me in here if I am off on this. That is generally in line with my understanding of the situation also, that we recommended sensitivity and specificity as the main, the primary endpoints for the clinical study.

The sponsor chose this hierarchical approach accuracy, specificity, and the studies were well underway at this time and just proceeded at that point. This did not go through an SPA process if I remember correctly. At that

time, we don't stop the sponsor from pursuing that, if it's against our recommendation. But that is an option. It's an option.

DR. HARRINGTON: I am going to do two things here, one of which is that the sponsor said that this is what FDA writings, that they have to guide, and, Dr. Mucci, in your conclusion, your statement is accuracy alone is not acceptable as a sole primary endpoint.

Would you help us try to reconcile the two perspectives of what the sponsor's reading and what you are writing in your conclusions?

DR. MUCCI: Well, to contextualize, in diagnostic imaging, we have never accepted accuracy alone as a primary endpoint, and besides that, if you look at the hypotheses, the hypotheses are in this study, and these are the sponsor's hypotheses, that first you have to establish accuracy, after which you also have to establish sensitivity and specificity.

It's in the hierarchical sense, it is not that you establish one and then you explore whether you have established the others. Both must be established.

DR. HARRINGTON: To be able to declare a victory, so to speak.

DR. MUCCI: Yes.

MR. SLATER: I don't want to interrupt, but--

DR. HARRINGTON: Let me hear from Dr. Rieves and then I will get to you.

DR. RIEVES: Sometimes I catch myself thinking, because I see this not only in FDA documents, I see it in sponsors and publications, the word "accuracy," oftentimes it seems as if it is used as a substitute for reliability, it is not used in the statistical meaning of that.

Our guidance documents, my perspective is that they tried to clarify our interpretation of that term accuracy to really mean that our regulations are talking more in the colloquial, the reliability aspect, not in a statistical aspect.

DR. HARRINGTON: So let me hear from the sponsor and then I will get to you.

MR. SLATER: Slide up, please.

[Slide.]

If we can look at the approvals of some other agents in this area, at least two of them, Lexiscan and Myoview, do have agreement, which is I think mathematically equivalent to accuracy as the endpoint according to their package inserts or their oral agreement.

I heard Dr. Mucci was the statistician on the Lexiscan approval, so perhaps he can help us.

DR. MUCCI: Agreement is not accuracy. Agreement is a Kappa measure or something like a Kappa measure in the absence of the standard of truth. It does not mean accuracy. Accuracy is with relation to a standard of truth.

DR. HARRINGTON: Go ahead, Jim, and then Bob.

DR. NEATON: Could I just ask, because I am a little confused here, if all three endpoints had to be hit, why did you have a hierarchical scheme for doing that? That is a pretty stringent criteria.

MR. SLATER: I am going to ask my statistical colleague on that.

SPONSOR: The analysis plan did not, in fact, specify that all three had to be hit. That is exactly why it was hierarchical. All the Alpha was allocated to accuracy. Had accuracy not been hit, then, sensitivity and specificity would have been off the table. But, given that accuracy was hit, and then there was testing for sensitivity, specificity.

DR. MUCCI: But there was testing, and the testing was essential. It wasn't simply exploratory. You have passed the first level, which is the accuracy. Having

passed that, you then test for sensitivity and specificity. Both hypotheses were there, and I would add that if you made the sensitivity and specificity, you would have had to make the accuracy.

DR. HARRINGTON: Let me go to Bob and then to Dr. Flack.

DR. MATTREY: I just need clarification. Typically, observational studies are evaluated by receiver/operator characteristics, because it is a balance between sensitivity and specificity, and you showed us an ROC analysis that looked pretty identical between the AI-700 and the SPECT.

Did you do a sensitivity analysis or power estimates on those ROCs and can we use the ROCs instead of accuracy, sensitivity, and specificity?

DR. WALOVITCH: Slide on.

[Slide.]

All we have is what we are showing you here. So, it is showing what you said, very similar areas under the curve and very similar shapes of the curve. But we didn't do any other analysis.

DR. HARRINGTON: I am going to again take the Chair's liberty. We have got some of the country's most

prominent statisticians here. Can you help us out, Tom, David, Jim, to understand this a bit better?

DR. FLEMING: This figure is certainly relevant. ROC analyses are certainly relevant because the issue is with the diagnostic, there is a judgment as to what leads you to call something positive or negative, and the more lenient you are in calling something positive, the better your sensitivity and the worse your specificity.

So, ROC is trying to get at the totality of that difference if we are going to use an ROC analysis. Now, we have to do a non-inferiority margin on an ROC analysis, and I haven't seen that laid out.

It is relevant to call our attention to this, but I want to return later in the discussion as to the formulation of proper margins for non-inferiority, because I think they are trying to claim that they are similar and ruling out they are unacceptably worse as opposed to claiming they are better. Certainly these analyses don't establish that they are better.

DR. HARRINGTON: And we are going to come to that topic. David or Jim, do you want to add to that?

DR. NEATON: I actually thought the hierarchical approach that they took with accuracy and then going to

sensitivity and specificity made sense.

DR. HARRINGTON: Okay. John, do you want to ask your question?

DR. FLACK: Is there any information data available for this test and how readers over time, when they have to re-read tests they have already read, perform as well as at a point in time or between readers, the agreement with some kind of Kappa or some kind of agreement statistic?

DR. WALOVITCH: What we did do in the 33, as we indicated, we stopped the reading and we had them re-read the whole database. So, what we can show you is the effect of the first read, which was blinded, to the second blinded read after the retraining. Slide on.

DR. FLACK: That is different.

DR. WALOVITCH: Okay. Well, that is all the information we have. We have studied readers, and told them to read aggressively or conservatively. We published some data in the Euro Echo last year showing that we could take a reader and say, okay, read aggressively, they will read aggressively, read conservatively, trade off sensitivity for specificity while maintaining accuracy. That is the limit of what we have.

That was done on around six or seven readers, I

think we had.

DR. FLACK: I will just offer one observation that has hit me all day listening to this, and that is that I think a reader to really, first of all, this looks like it is very operator dependent and you are going to get different answers.

So, a positive test from one reader doesn't tell you the same thing for a patient as a positive test from another reader does, because there is just too much variability, and until there is some kind of objective way to maybe help buttress the subjectivity, it is a little bit like reading tea leaves here.

I think you are going to have trouble with this, or we are going to have trouble with this, and the characteristics of this test and how it agrees, the readers agree with one another in how stable a reader over time is reading the same test, really is an important type information for quality control and should be available, and if that is not available, that is a real problem.

DR. WALOVITCH: We have that data. I wasn't sure what you were getting at. I can show you the intra- and inter-reader variability. Will that help? Okay. Intra-reader variability, slide up.

[Slide.]

Here, we are looking at the ability of the readers to make the same primary diagnosis months apart reading the same imaging studies, and here you are looking at the 32 trial, ECHO and SPECT reader.

The inter-reader reproducibility is around 80 percent, and in the 33 trial, we have one ECHO reader who has 100 percent inter-reader reproducibility, as well as one SPECT reader with 100 percent inter-reader reproducibility.

Now, I could show you the inter-reader data, as well.

DR. FLACK: So, this is for positive and negative tests.

DR. WALOVITCH: Right. All they are doing is saying if they called it positive, are they calling it positive again; if they called it negative, are they calling it negative again. It's around six months apart, the same image.

DR. NEATON: How many patients are involved?

DR. WALOVITCH: Thirty to fifty.

SPONSOR: Ten percent.

DR. WALOVITCH: Ten percent. So it's more, sorry. It depends on the trial.

DR. DAY: What other information do they have about the cases, if they review each one, do they have some narrative?

DR. WALOVITCH: Nothing. It's totally blinded, all information.

DR. FLACK: Can you show it between reader?

DR. WALOVITCH: Yes. Slide on.

[Slide.]

In the 33, it's the only place we have 3 ECHO readers and 3 SPECT readers. So here we are seeing Reader 1 versus Reader 2, 2 versus 3, 1 versus 3, and you have 1 nuclear pair that does better than the other ECHO or SPECT pairs.

DR. HARRINGTON: Dr. Picard?

DR. PICARD: I just wanted to add one point to amplify what Dr. Day said. I think it is very important to remember that a core lab ECHO reader here is reading the ECHO without any other information.

In clinical practice, we know the age of the patient, we probably have a cardiogram during the stress test, we know the risk factors on an electronic medical record. You can pull up the last cholesterol.

You know a lot about the patient. In fact, I may

be caring for that patient, so I know why I ordered that ECHO. So it's a lot more in your head when you are interpreting that echocardiogram or that stress nuclear test.

So, this is really one end of the spectrum and we wouldn't expect a perfect read, I think without that other information.

DR. HARRINGTON: Thank you.

DR. FOGEL: Two questions. One is a safety question and one is an efficacy question.

The safety question. Except for Slide 83, I haven't seen any data regarding how the AEs were distributed among patients with disease versus without disease, and I am just wondering patients with coronary artery disease that you are trying to detect, did they have any more adverse events than those that didn't have any coronary artery disease. Except for Slide 83, which just takes the 12 patients who had hypotension at rest, I couldn't find any other data regarding that distribution.

My efficacy question is we have all been talking about how the endpoint was positive disease or negative disease, and I guess I was wondering if we are not going to localize it, and Dr. Senior in his presentation said that

localization was very important; if we are not going to go by localization, but just by presence or absence of disease, I was wondering what the mechanism is of being able to actually characterize the diagnosis as correct or not if we are not going to localize it, because maybe you are getting the right answer for the wrong reason.

So, if you could maybe address the safety question first.

DR. WALOVITCH: Dr. Dittrich.

DR. DITTRICH: Dr. Fogel, you are right. We haven't taken the other adverse events, such as flushing, headache, et cetera, and examined them versus the primary endpoint definition of disease or no disease, we haven't done that.

But for the two key ones, which we have presented, one you pointed out, 83, describes the CAD status relative to positive/negative, and the other one, the oxygen saturation decline also I believe had the disease positive/negative.

We found no difference with regard to any trend that there was a predominance of one or the other.

DR. FOGEL: So serious adverse events were equally distributed?

DR. DITTRICH: We only had 11 patients to distribute among 911 with a 50 percent disease prevalence. I am not sure on a statistical basis we could even, if it were eschewed one way or the other, one could draw any conclusions.

DR. FOGEL: So, were all the SAEs in--could they have been in the coronary artery--

DR. DITTRICH: In fact, they weren't.

DR. FOGEL: There were three patients with syncope at rest.

DR. DITTRICH: That's right. We can go through the narratives if you would like.

DR. FOGEL: No, no, no, I just thought that you had the data.

DR. DITTRICH: Again, I would point out the definition in this case is the angiographic finding of 70 percent or greater, or a history of MI, or the composite read including SPECT and an interpreter. So it is not as binary an endpoint, if you will. It's a rational endpoint for efficacy but I am not sure it depicts disease in some important binary way.

But to answer specifically, of the serious adverse events, they are distributed, as well, of those 11 subjects.

DR. FOGEL: I just wanted to make sure that with the number of AEs that there wasn't more in the disease group than in the non-disease group, and I guess if somebody can answer the efficacy question.

Why is just disease positive or negative, and not, you know, it's in this territory or that territory?

DR. WALOVITCH: Disease positive or negative was the primary analysis. The secondary analysis, we showed you the localization data that indicated that ECHO was localizing just as well, if not better, than SPECT. Slide on.

[Slide.]

We just saw this a little while ago. So, we are maintaining our ability to localize correctly compared to our standard here in both trials, and the question is, to go on to further tests. So the way it was set up, disease/no disease, was Yes, if you have disease you go on to the test, I agree with you, you ought to be able to localize them in the right territory. This data supports that concept, it was just a second-tier endpoint, it was a secondary endpoint.

DR. FOGEL: I guess I was just wondering why it wasn't the primary endpoint.

DR. WALOVITCH: We weren't required to make a primary.

DR. HARRINGTON: Go ahead, Dr. Senior, and then it will be Dr. Lincoff, Paganini, Fox.

DR. SENIOR: It was the intention of doing analysis, I mean it was not a primary analysis. But I think we were interested in this data to look at, because clinically, if decision gets approved, we will also use it for indications where patient had a coronary angiography already.

We are not sure about the significance of the lesion, whether it is causing any flow-limiting ischemia in that area. So we will be doing a test to see whether that particular part of the heart will be affected if the patient exercises.

So, a correct localization of lesion certainly helps a lot with the test, a test which localizes the lesion, we will be using that test more than a test which doesn't really localize the lesion. So, this is clinically relevant I suppose.

DR. HARRINGTON: Dr. Lincoff.

DR. LINCOFF: I would like to get back to the truth standard and the efficacy. The angiography that was

used as the truth standard, as we all know, angiography is not really a standard either, and first of all, there is inter-observer subjective variation and how one calls a percent stenosis, and then there is the very physiologic issue that a borderline stenosis is 70 percent, which is where your threshold was. It may or may not really be hemodynamically significant.

Even the gold standard, and I realize there are limitations in what else you could use but, nevertheless, were the angiograms interpreted at a central core lab, was there use of a quantitative angiographic package determining stenosis, and perhaps most importantly, since SPECT in most cases was done beforehand, although I realize in some cases it was not. But if it was done beforehand, it was the clinical read as well as your central read, could the angiographers, who had given you this interpretation of the angiogram if it wasn't central, would they have known the results of the SPECT, because then you wonder really how independent the standard is from one of the tests that is supposed to be based upon that standard.

DR. WALOVITCH: The angiography was quantified using a standardized package and a cerebral vascular research lab, Dr. Lansky, in New York, they did all the

angios.

With regards to the SPECTs, the SPECTs were 80 percent of the time were more prior to the angio data.

DR. LINCOFF: So, the reads were all central reads for the angio.

DR. WALOVITCH: They were all central reads for the angio, and they were all central reads for the SPECTs and the ECHOs.

DR. HARRINGTON: Emil.

DR. PAGANINI: Most of the other questions I had were already asked so I won't repeat them. But one question I do have, it was stated in one of the discussions that the patients with COPD tended to be those patients that you might get the best benefit from having a contrast enhanced ECHO, and yet you are asking for COPD to be one of your label restrictions. But some of the data that you had was based on COPD mild to moderate, which may have improved the sensitivity and specificity.

Would you care to comment on that sort of almost dichotomous statement?

DR. WALOVITCH: Dr. Picard.

DR. PICARD: I would like to comment on it because of my experiences with the other contrast agents and the

current way we use them in light of the warnings that had been placed last year.

I think some of it is the adjective that you use in front of the word COPD. I think that what we are talking about here is all patients with COPD, whether it's a mild form or a more severe form, typically, are patients who we have difficulty with imaging. So we, as you saw in the contraindications, certainly include moderate to severe. COPD as a contraindication and we wouldn't want to use this agent in that group of patients. But certainly in the mild and mild to moderate COPD where there is a problem with image quality, we would be using this agent.

DR. HARRINGTON: Does that answer your question, Emil?

DR. PAGANINI: Well, I guess I am a little bit concerned about--you know, we are talking about how certain drugs are being used in ECHO enhancement that haven't really been approved, and so I am sure that if you have a population that is very hard to read, but enhancement will make it easier, that you are going to start to see a lot of off label and, if that is the case, that might be a reason for studying that subgroup of populations that might, in fact, be used as an off label, not that you would want to

make it as a label issue, but at least you want to get some sort of a handle on it.

The same issue as with CKDs that I had before, that subpopulation of comorbidities that tend to come to these type of tests, have not really been represented well in these studies to date.

DR. HARRINGTON: Let me ask Dr. Dittrich and then I will go to you, Jim.

DR. DITTRICH: I would only point out that the purpose to avoid those patients with chronic obstructive lung disease is because of the dipyridamole so there is already a prespecified reason not to treat those people. It is unlikely that off label or out of label use will accrue when dipyridamole or the adenosine agonists are being used but that is really a safety issue.

I think there are many years of experience with dipyridamole that suggests that that has not expanded regardless of the imaging agent outside that category.

DR. HARRINGTON: Dr. Neaton.

DR. NEATON: I just want to make certain I just heard something correctly. Did I understand you to say in response to the question that SPECT was generally done before the angio?

DR. WALOVITCH: Yes.

DR. NEATON: Because I saw it in 33, all the angios would have been done before SPECT.

DR. WALOVITCH: Not in all cases, no.

DR. NEATON: The inclusion was a recent angio--

DR. WALOVITCH: No, the inclusion was they had to have had or have been scheduled for an angiogram.

DR. NEATON: So that some of the angios were done before SPECT and some afterwards?

DR. WALOVITCH: Twenty percent or less were done before, 80 percent afterwards in the 33. In the 32, they were all done afterwards.

DR. NEATON: Okay, and the results of the angio were unknown when it was done beforehand.

DR. WALOVITCH: Correct.

DR. HARRINGTON: I think that was Dr. Lincoff's question. He was trying to get at core laboratory information.

Dr. Fox.

DR. FOX: Thank you, Mr. Chairman.

There is an element to the benefit-risk assessment that hasn't gotten a lot of conversation this afternoon that I would like to raise, and that is around ionizing radiation

exposure.

Dr. Picard, in his presentation, made reference to this and other members of the sponsor's team have made cross-reference to this. On Slide CC-19, there is a reference to Thompson and Cullom, J Nuclear Cardiology from 2006.

I went back and looked at that article. It's a review, it is not particularly extensive, but it seems to be a bit more of an opinion piece. But it does raise I think some interesting controversies around the lack of agreement about how to accurately measure dosimetry. I mean I am no nuclear physicist but I know we have got some very experienced nuclear people around this table today.

Given the fact that the target population or some important subpart of the population is likely to have a fairly large cumulative exposure to ionizing radiation during their disease journey, repeat caths, repeat scans, et cetera, I wonder if we can have some discussion around people's opinions about the radiation exposure risk and how that might figure into a benefit-risk assessment of this potential product.

DR. HARRINGTON: Jonathan, that is a great question that we are going to actually address during the

question period, is the performance and some of the issues of the comparator. So, if it is not a specific question for the sponsor, I would like to hold it. But I do want to have the discussion, because it has been highlighted as an issue, the risk of ionizing radiation, and we do have some experts around the table.

DR. FOX: It is more a question for the panel than for the sponsor.

DR. HARRINGTON: Perfect; so let's hold that.

I am going to go to Dr. Fleming, Dr. DeMets, Dr. Tatum, Dr. Neaton, and then I will see if we can't wrap this up in the next few minutes for questions for the sponsor, and then if anyone has questions for the FDA, although we have involved them along the way, then, we will get to the questions.

DR. FLEMING: I have a safety question for the FDA, so I will put that off, it sounds like, Mr. Chairman, and I will ask the two quick efficacy questions first and come back to the safety question when you saw it is the right time.

So, for the sponsor, two quick efficacy questions. On page 132 and 133 in the briefing document, you try to summarize why this is an important advance, and at the top

of page 133, you say that for AI-700 ECHOs, there is an increased sensitivity for detecting CAD with increasing severity of disease.

Are you saying that increasing severity of disease is a correlate or are you saying it's an effect modifier? To be specific, are you simply saying that as severity of disease gets higher, the sensitivity will go up, or are you saying that as severity of disease gets higher, the relative efficacy of this contrast ECHO will be enhanced relative to alternative diagnostics?

DR. WALOVITCH: We are saying the former. Slide on.

DR. FLEMING: Okay. I don't need to go on. The latter would have been of real interest, the former is just a correlate, it's just an association.

My second question. The second question is: Before the break, I had referred to the FDA's presentation of Study 21 where in Study 21, there is some evidence to contrast the contrast ECHO against a placebo, a non-contrast ECHO, and in that experience, the success rate was 73 percent against 68 percent.

I refer to that as a modest difference. But if this had been what we would have seen in a big trial with

400, 500 patients, and it would have been statistically significant increase from 68 percent to 73 percent, would that be a clinically meaningful and important advance?

Was I dismissing that difference too readily, that if you can increase 68 percent success rate with non-contrast ECHO to 73 percent, is that a clinically important advance?

DR. WALOVITCH: Dr. Senior, do you have a perspective on that, or Dr. Dittrich?

DR. DITTRICH: It is difficult to answer, but I have to point out again, and you acknowledged as well, these are small numbers, and I know you are extrapolating--

DR. FLEMING: I am asking a different question. I am completely taking off the table the numbers saying if this had been based on a large experience so that the estimates are reliable, is this a clinically important advance.

DR. DITTRICH: In that case, I will leave it to the panel members to answer, but I will make the comment again, because I think it is entirely inappropriate to evaluate--

DR. FLEMING: You are not going where I am going. The Chairman has given me limited time. My question is

simply, what difference do you need to see, what true difference, in truth, what true difference is clinically important?

DR. DITTRICH: Well, then, I will answer as a cardiologist and ECHO cardiographer that that would vary depending on the pretest probability of disease in the patient I am evaluating.

DR. FLEMING: So, let's say it's in this context of about 50 percent, and you could achieve a 68 percent with non-contrast ECHO, is an improvement to 73 percent, as 21 suggests could be true, is that important?

DR. DITTRICH: It could be.

DR. HARRINGTON: Tom, I think some of the ECHO cardiographers around the table are chomping to get in on this discussion, so let's ask them.

DR. SACHDEV: This is an important question because if I am looking at Study 21 correctly, the comparison was between the contrast agent and placebo using a vasodilator stress.

I thought Dr. Picard said that you need very high dose vasodilator to get wall motion. So, without a contrast agent, using only placebo, how do you get a sensitivity and specificity, can you explain that, please?

DR. DITTRICH: You are exactly right. That is one of the key components of that study that makes it unhelpful in this discussion.

DR. SACHDEV: This is not a valid comparison at all, right?

DR. DITTRICH: Correction.

DR. SACHDEV: You cannot get a sensitivity and specificity from a placebo.

DR. DITTRICH: And I will make the point again, that it is not regarding the numbers or any projection that Dr. Fleming had that again, these were acquired with technology from early 2000, 2001, 2002, at a time when the company was developing its skill in using the microspheres with technology that is now obsolete, and that is why I am a little impassioned about making sure that there is no over-assessment of this used.

DR. HARRINGTON: Dr. Teerlink had a comment.

DR. TEERLINK: I will kind of agree with Howard and saying that I think the technology issues are a major issue. However, if one wants to take into account that study, if anything, you have really critically disabled the placebo group, and so the fact that they are so close together, actually, in my mind, argues against any

additional benefit. However, I am personally not interpreting it that way, because I will say that the technology has advanced markedly since 7 years ago.

DR. HARRINGTON: John, I was hoping you were going to answer Tom's question. You run an ECHO lab. What is clinically meaningful? That is what Tom is asking us. It is 5 percent, 6 percent, 10 percent? That's what you are asking, right, Tom?

DR. FLEMING: Yes.

DR. TEERLINK: I guess 5 percent for me would be on a lower limit.

DR. HARRINGTON: So, your judgment is that 5 percent difference when we are talking a starting rate of around 67, 68 percent is not that meaningful to you?

DR. TEERLINK: It's on the lower limit of what would be meaningful to me.

DR. SACHDEV: I think it's important to determine whether or not that 68 percent is a real number. Dr. Senior, how can you do perfusion or how can you make a diagnosis when you don't have a contrast agent?

DR. HARRINGTON: Go ahead, Bob, while he's getting up there.

DR. TEMPLE: Well, isn't that the question, it's

what do you get for giving the contrast agent. So, the conversation here can only be based on 21, which everyone knows is too tiny and nobody thinks it's reliable. But are we hearing that you think the answer to that question needs to be known; that is, do you have to know how much better the ECHO with contrast is than the ECHO without contrast to make a sensible judgment? Is that what you all are saying or asking?

DR. FLEMING: I am setting the stage for a non-inferiority margin discussion later today.

DR. HARRINGTON: I think that is exactly the question that is going to arise, Bob, during the question period.

Dr. Senior, did you want to comment?

DR. SENIOR: Well, I think without contrast you can look at wall motion abnormality anyway. You can look at wall motion without contrast. And with contrast, what you get is you see a better assessment of wall motion and then you see perfusion, too.

So, yes, you can make a comparison between the two, because essentially on one you are looking at wall motion, on the other, you are looking at wall motion in a better way with perfusion.

DR. DITTRICH: Could I amend that? First of all, could you show the slide on quality change. I have two slides that we would like to give and may add some perspective away from 20, 21, and this is related specifically to contrast versus non-contrast.

I need the slide that describes the change, well, I can talk about it, we change from approximately 27 percent of patients at baseline, non-contrast, in this study. To give you a perspective, these were patients who were recruited without regard to image quality at baseline.

Actually, they couldn't have acardia, as we call it, in the stress ECHO lab. You had to be able to see a heart, but you didn't have to have any minimum amount of endocardial seen.

When we did that slide up, again, we had 27 percent of ECHO patients who had poor acoustic window quality at baseline, 99 percent became evaluable. Now, keep that point in mind and then we want to show just an assessment, taking a 27 percent baseline poor quality. Slide up.

[Slide.]

Let's now pretend we are doing a test of AI-700 ECHO and SPECT in 100 subjects with a 50 percent disease

prevalence, and who would go on to further diagnostic testing based on a 99 percent evaluable.

Now, we are taking all comers so how in theory would the population who aren't having contrast performed, and if we look at that, we would now add, and we are taking instead of 27 percent, half of that, 15 percent in whom you would either guess wrong or you wouldn't be able to do the test, and you would now move 65 percent instead of 50 percent who would incorrectly have the need for an angiogram or go on to other testing.

It is a simulation which basically says it does matter and we don't have those data that we can present. But, in fact, given the data from the Phase 3 on acoustic window quality, you could predict differences similar.

DR. HARRINGTON: Thank you.

Bob, did you want to make a comment? Than, I am going to go to Dr. DeMets, Dr. Tatum, Dr. Temple.

DR. MATTREY: Just a quick comment about the quality of instrumentation. It has improved dramatically since the 2000s. But if I were able to predict, I would say it improved the non-contrast quality to a lesser degree than the contrast quality.

So, the advance since the early 2000s is the

ability to recognize bubbles from non-bubble signals. So, both would have improved, but the improvement in the contrast performance is dramatically different.

DR. HARRINGTON: Thank you.

David.

DR. DeMETS: Thank you. The question that I am struggling with is in a non-inferiority design, there are a whole bunch of assumptions that have to more or less be true. So you can do it the way it's intended.

One of those is, of course, you have the right control or comparative arm, and I have no doubt that the SPECT is the right comparator. But it also depends on how well you apply it. In other words, you can have a great drug and you have terrible compliance, and that would not be an adequate comparator.

What I don't understand, I don't know enough about this field, is whether this particular modality in this setting, in this population, is applied in a way that the results we get are as good as we could expect or they are not. My interpretation of what I have read so far is that maybe it's less than--it's disappointing from what we would expect.

I am trying to understand, maybe the sponsor can

comment, whether this is the best application in this population that we could expect or it's less than we hoped for.

DR. HARRINGTON: David, that is one of our questions, as you know, but I would like to have the sponsor give us their perspective and then I will ask the other members to hold their comment until we get to the discussion.

DR. WALOVITCH: Slide on.

[Slide.]

We believe that the quality control for SPECT was done throughout the trial duration. The SPECT core lab, as I have indicated, was the ASNC Certification Lab for accreditation of nuclear laboratories throughout the United States. We had a pilot study where the trialists had to demonstrate proficiency in both ECHO and SPECT in order to be able to go into the pivotal trials.

Our imaging guidance was similar to the American Society of Nuclear Cardiology guidance, and the core lab was a quality control center in which they eliminated studies that weren't done in accordance with guidance, and they were not part of the intent to treat population.

The cardiologists were blinded to all information

that may explain the results, and as I have indicated, the people that we have had doing this all have greater than 10 years experience, are board certified nuclear cardiologists, and are experts in the field of nuclear cardiology.

So, I think we have done what would be considered appropriate comparative studies. These were gated and they also had quantification. I don't know if I have anything else to tell you about the quality of the SPECT, but we believe that the results of SPECT in this trial are the results of this patient population in a blinded read environment.

DR. HARRINGTON: Again, this will be a topic we are going to get some of the feedback from the experts around the table. Thank you.

I think I have Dr. Tatum unless we had already gotten to your question earlier.

DR. TATUM: My question is for the FDA.

DR. HARRINGTON: Now, I want to take a few minutes, if there are remaining questions--I know we have engaged the FDA some, but if there are remaining questions specifically for the FDA before we get to the questions--so Tom, you had indicated you had a question and James, you have a question.

DR. FLEMING: Safety is obviously a critical part of benefit to risk, and the direct evidence we have about safety for a product at hand is especially important.

But if it is thought that there are class effects that are potentially important and there is a lot of evidence about safety with other members of a class, it is important to factor those in.

I wasn't part of these earlier discussions that we were alerted to at the very beginning of today, that have led apparently to Black Box warnings for ultrasound contrast agents specific to serious cardiopulmonary reactions or acute inflammatory responses.

So, could you enlighten me to what extent are those insights and decisions relevant to our assessment of safety for this product

DR. RIEVES: Yes, sir. In general, we anticipate that there are some important class effects here. That is based not only on the very limited clinical data that we have here, the pattern of these reactions, the hypotension, that sort of thing, being very similar to a number of the reactions that we have had reported in the post-marketing experience for the approved agents but also in the animal data.

The animal data are very compelling for hypotensive responses in pigs, for example. So, given the clinical with the animal, as well as just the nature of the products, that alone, we do anticipate that what we are regarding as class effects and class labeling for safety would apply here at a minimum.

DR. FLEMING: So that, in essence, if this product were approved, then, based on the data here, as well as the totality of data you have available for the class, it is very plausible, if not likely, that there would be a box warning for these reactions?

DR. RIEVES: Yes, sir, we do anticipate that.

DR. HARRINGTON: Dr. Tatum.

DR. TATUM: This comes back to your question that we have been kind of bouncing around about the diffusion of this, how it would be used, how it would go into practice.

I don't have any answer to this question. I know that in other things that we have brought or discussed in the past, there has been more effort by the FDA to get reproducibility studies that are really quite robust, more so in drug development where you are actually going with heated measures type things and looking at variability.

But how would you approach one like this where you

are looking at the possibility that it is going to be used diffusely, it is going to be a screening trial, there is probability of marked variability, reader variability, but also acquisition variability, and reproducibility?

How do you see this fit? I mean is what we have here sufficient or are you thinking that we need something more in that line?

DR. RIEVES: I can opine on that. That is really one of the main reasons we brought it here, because we are particularly concerned about the safety aspects for a screening tool. The nature of this is a screening tool. So, we anticipate that it would be relatively widely used.

But at the same time, given some of the evidence, safety concerns, we are torn between, for example, the consideration of a risk evaluation mitigation strategy, what we are referring to as RIMS.

A RIMS for a diagnostic imaging agent or screening tool, I think one has to question the logic behind that in terms of the diagnostic benefit to be gained from that.

So, we have not resolved that issue but we have major reservations. I think I can speak for the team in saying that we have major reservations about using a risk mitigation strategy, if you will, to try to contain our

concerns over safety at this time.

DR. HARRINGTON: Bob.

DR. TEMPLE: My assumption, again, little experience in this, is that what you would accept as a risk would depend on what you got as a benefit. For example, if you could avoid 100 percent of fruitless angiograms, you know, that showed nothing, you might find this risk worth it, because they are not benign.

So, that is why it still seems very important to me to know what it is you get for this thing, because you can do an ECHO, and that is sort of free of any risk, and here you now inject something and there are potential problems with it. You know, you have to decide how bad they are, but the question comes back to me what have you gained, how much.

You could also ask how site-dependent it is and other interesting questions like that. But I don't know, Dwaine, did that sound right?

DR. RIEVES: It does. We are challenged by non sequiturs of sorts, a screening tool that takes apparently very sophisticated training to read at the same time of what appears to be notable safety concerns, relatively limited database. It creates a real challenge.

We recognize the convenience factor, we all appreciate that and think that would be great advance. But, on the other hand, these other constraining, the safety, the technical expertise that is required, the effort that would need to go into a risk containment, a risk mitigation strategy is a real challenge I think for a screening tool, a diagnostic with this level of performance characteristics that we are seeing today.

So, our acting consensus is one of special concern regarding this.

DR. TATUM: Can I ask a follow-up question? Do you think a computer assisted diagnosis system, similar to what is used in SPECT, applied to this could be informative and helpful and useful?

I realize they have to be approved and the whole thing.

DR. RIEVES: This gets into opinion and everyone has opinions, but I think it gets at what Dr. Flack was also trying to emphasize, the challenge in interpreting these images, and if there is some way to more quantitatively make the interpretation simpler, then, I think we would all find that much more palatable.

DR. HARRINGTON: Other questions for the FDA?

Dr. Rieves, I have a quick question for you. How widely used are the currently available contrast agents, do you have a sense of that?

DR. RIEVES: Oh, contrast agents, gadolinium--

DR. HARRINGTON: The currently available ECHO contrast agents, how widely are they used? What level of experience does the FDA have with them?

DR. RIEVES: Oh, these agents have been on the market for 20 years so it's a mammoth experience.

DR. GOROVETS: Are you talking about ultrasound or--

DR. RIEVES: Or contrasts in general?

DR. HARRINGTON: I am talking specifically about cardiac ECHO and contrast agents on a yearly basis.

DR. RIEVES: Oh, ultrasound contrast agents, I am sorry, I thought you were talking about radio pharmaceuticals. The contrast agents are much more limited. I think we are talking about 10 years--correct me on this--but we have run the numbers on this. There is very limited--we are in the hundreds of thousands.

At a recent advisory committee, some estimates have put it worldwide exposure I want to say up to a million or so, but this is just off the cuff figures. As compared

to a gadolinium and other agents, it is very tiny but, on the other hand, estimates are about a million worldwide exposure.

DR. HARRINGTON: Yes?

DR. RAMSEY: Are you planning for a break here? I just wanted to make a comment.

DR. HARRINGTON: I am actually going to look around the table and see if people want to get up and stretch their legs, but forge ahead if possible.

DR. RAMSEY: I would like to make a brief comment. When I listen to all the statisticians I am absolutely overwhelmed. I have to take a course, but that's another story. I did my own little analysis.

We just finished the Radiologic Society of North America, and at that society meeting, knowing I was coming here, I went to all of the ultrasound booths and talked to all of the people there and, of course, many of them come worldwide and use these ultrasound contrast materials in other countries to great effect.

In addition to talking to them, and listening to the way they use it and apparently without great concerns, I then spoke to Dr. Barry Goldberg, who has been very active in ultrasound from the very beginning, and I asked him if we

need this contrast material and how should I vote, and he said, you know, that we absolutely do need these available and that they are very helpful and, in fact, the last meeting we had of this committee regarding ultrasound contrast agents, he said following that meeting he got together with a group of other people and they are now forming a society for use of contrast agents and ultrasound, and he personally felt it was very vital to have these available.

As a corollary to that, I am going to show my ignorance, is this contrast available in other countries besides the United States, is it being used now?

DR. HARRINGTON: Dr. Rieves, do you know, or does the sponsor need to answer that?

DR. RIEVES: The sponsor can confirm, but I don't think it is marketed anywhere in the world.

DR. HARRINGTON: They are confirming that.

If there are no further questions for the FDA, Bob asked if he could ask a question of the sponsor. So why don't we do that, and then let's turn our attention to the questions.

Are people okay with forging ahead or do people need a break? Do people want to forge ahead, try to finish,

or do you want to take five minutes?

Let's have Bob's question, question down here, and then let's take five minutes, and then we will forge ahead.

Go ahead, Bob.

DR. MATTREY: I just wanted clarification regarding the mechanical index. I noticed Dr. Senior, you showed flash destruction. I would assume those were above 1.

DR. WALOVITCH: The high MI flash destruction was at 1, we did not exceed a mechanical index of 1 in the trials. The real-time perfusion imaging with the power modulation was at 0.3 so most of the time we were imaging at an MI of 0.3 or below, and for the flash, it was at 1.

DR. MATTREY: How does that compare to other micro bubble based agents in terms of the flash mechanical index? I am trying to understand, because you made the statement that your practical is more resistant to ultrasound, which means you would need a higher mechanical index to achieve destruction I would assume.

Then, you made the statement there were no PVCs found. I just want to clarify in my mind that you have looked at the PVCs and related them to the flash.

DR. WALOVITCH: Regarding PVCs, in earlier trials

when we brought the mechanical index above 1, we saw a correlation with PVCs. But if you keep the mechanical index at 1, you won't induce PVCs with AI-700.

DR. MATTREY: Thank you.

DR. SAHAJWALLA: I have a couple of questions. One was I know you want to compare apples to apples. So Persantine, we wanted to compare ECHO Persantine with SPECT Persantine but, in clinical practice, if the patient is able to, then, we prefer to do an exercise SPECT rather than a Persantine SPECT. So why would they not have been asked to compare with exercise SPECT also unless they are going to put on the label that this is to be used only in patients who cannot exercise?

DR. HARRINGTON: The current label, as I understand it, that is proposed, Dr. Rieves, is that this is specifically indicated for people undergoing pharmacologic stress.

DR. RIEVES: Right, that is what we envision. The wording is not exactly that, but that's I think what we all envision.

DR. SAHAJWALLA: The other question was regarding particles like in patients with cardiac shunts, is there a like a risk for stroke? In the animal studies that they

have done, they have injected only 1.4 times the normal dose. But sometimes conceivably, you could inject more, you know, if like the technical setup fails.

So, have they studied it with the larger than 1.4 times the normal dose in rats or other animals?

DR. HARRINGTON: So, two questions of the sponsor, one of which is comment on the shunt question, and how those patients were excluded or plans to exclude them, and secondly, I think the question is are there animal data on very large doses of the drug to understand toxicity.

Is that essentially the question?

DR. SAHAJWALLA: Yes.

DR. WALOVITCH: We didn't study any patients with shunts. If they had a history of a PFO, they were eliminated. There was no specific agitated saline study to eliminate those patients. There were occasionally patients who did have shunts in the trial. They tolerated dosing well.

With regards to the preclinical studies why don't we show--slide up.

[Slide.]

This was the inner carotid injection study where we injected the total dose right into the carotid artery and

the findings that we saw. The only findings were clinical findings at 1.8 x the clinical dose, and they are listed here.

There was no histological or morphological abnormalities noted in the brain tissue upon evaluation. That is the only data we have with direct injection of the material to the brain.

DR. HARRINGTON: Does that answer your question? Great.

Why don't we break and let's just keep it really to five minutes, because the questions are going to take some work. So, come right back.

[Break.]

FDA Questions to the Committee

DR. HARRINGTON: I want to start quickly because we have some people who may need to depart early, and I would like to get through the questions into the voting phase.

We have two questions, then, a vote. Based on that vote we have a fourth area of discussion. As is frequent with FDA, it is tiered questions with multiple pieces to it. This is really for the panel, and this is where we need to have our discussion.

The group has been bringing up these issues throughout the day. Again, this is not a voting question, this is discussion all leading us to the vote. So, here is the question.

Question 1. Please discuss the extent to which the Phase 3 data provide persuasive evidence of diagnostic efficacy.

Talk specifically about consistency between the studies. Issues regarding the comparator, in this case, SPECT. The final question is what is the added value of AI-700 to non-contrast echocardiography.

This is really looking at the Phase 3 data and how people have viewed what we have heard today in the context of or in the issue of diagnostic efficacy.

Dr. Lincoff was quick to raise his hand. We will start with you, Mike, followed by you, Tom.

DR. LINCOFF: First, I would like to address the question of whether or not this provides incremental benefit over non-contrast ECHO. I think my approach is a little bit different. They both use ECHO, but I think they are really two different tests.

By using contrast here, and the sponsors have said themselves that in the interpretation of the images, wall

motion was not used or was not coded for, so this was really a perfusion test. What they did is they transformed ECHO, which was a structural test, to a perfusion test for at least this particular issue.

So, it seems to me that the correct comparator was indeed SPECT, which is another perfusion test, and we have to make our decisions based upon relative efficacy, and if we believe that they are not inferior equivalent, then, whether or not there are other advantages perhaps in this system of this approach that would render worth taking the potential risks associated with that.

So, I think that the first issue is we don't really need, it isn't relevant to compare to non-contrast today, because they look at different things. Yes, they delineate wall structure, et cetera, but the real issue is perfusion.

As for the consistency, I personally don't have a problem with ongoing evaluation of performance of readers and at a point in time saying, you know, we see a systematic problem, that we are going to change that and take it from there.

The changes between the two studies in terms of the sensitivity I think is a reasonable evolution and

assuming that can be modeled in practice I think it is a realistic finding and useful in terms of looking at non-inferiority.

DR. HARRINGTON: Some of the issues that you have brought up, Mike, that we have to return to, you feel that SPECT is a reasonable comparator. One of the issues we will have to address, and we have experts around the table, is was SPECT used appropriately, critical question in non-inferiority particularly. So we have to come to that issue.

The consistency issue, as I suspect we will have some disagreement around the table as to how people view that. So, you have brought up the starting points.

Tom, this may be the time to begin the non-inferiority discussion.

DR. FLEMING: I think I will get into that.

My sense about this is there are, as we look at AI-700 ECHO with perfusion and wall motion, there are relevant contrasts, relevant comparisons to SPECT, which is the perfusion alone, to the non-contrast ECHO and to the unbiased coin.

In essence, what this question is asking us is what is the persuasiveness of efficacy. My global sense, as I was mentioning before break this morning, is that it seems

disappointing that this procedure isn't suggesting to at least being better than SPECT since it's, in fact, using perfusion and wall motion, and that it in very, very weak data from the 21 trial is suggested to be only modestly better than non-contrast ECHO.

So, my sense about Part C is that the data are really too limited but I think that is a significant shortcoming because I do think it's relevant to understand its relative efficacy against both SPECT and non-contrast ECHO.

In terms of the focus of where the data are in 32 and 33, obviously, those data are giving us an important insight about this agent against SPECT. As we had many discussions in 32, it fails on sensitivity, and 33, it fails on specificity.

The issue that I want to get at is there, however, has been an indication that it wins on accuracy, and I am not persuaded by that, and that leads to the non-inferiority discussion.

DR. HARRINGTON: So, let's have it.

DR. FLEMING: So, essentially, the sponsor in my view provides essentially no justification for their non-inferiority margin of 0.83. In Appendix 8 of their document

they say, "Any specified NI margin will be arbitrary and based on limited relevant clinical and statistical information." To me, that is a scientifically very dangerous approach to non-inferiority.

Non-inferiority is clearly indicated and justified by the ICH guidelines and by extensive research in the literature and application.

Margin needs to be evidence based, preserving a substantial fraction often stated to be half of the effect of the active comparator, and based on clinical judgment meaning that a margin, a non-inferiority trial doesn't establish you are at least as good as, or you are similar to, it only rules out you are unacceptably worse than. Therefore, the margin has to be sufficiently rigorous that anything at the margin or less would be an acceptable loss of efficacy.

I do think there is an evidence-based approach here. So let's suppose we started off by saying, and this is for accuracy, let's suppose we were trying to preserve at least half of the effect of SPECT just against a coin flip.

Well, SPECT here in 32 and 33 has a 68.3 percent overall pooled estimate of efficacy with two standard errors being it's at least 64.7. 64.7 is 14.7 percent above a coin

flip at 50. Half of that is 7.3. To me, that is the biggest margin that I could possibly justify, 7.3.

7.3 divided by 68.3 is 0.1. So, basically, that's a relative margin, not a 0.83, but 0.9. So, basically, if you are simply saying I want to preserve at least half the effect against a coin flip, then, the most lenient margin I could allow is 0.9.

Now, from the clinical relevance side, and this is where I was trying to get some independent assessments, clinical relevancy, if you use 0.9 for a margin, you are saying if it's 68.3, I can have as much as a 7.3 percent absolute reduction without that being really clinically important. That is clinically acceptable.

Well, John, when pressed, said 5 might be the lower limit of what is clinically acceptable, we would have to argue that when you get up to 7.3, it is still in the clinically acceptable range.

That is a discussion that we could have, and obviously, that depends on benefit to risk, so that depends also on safety issues and other considerations. But, generally, it would seem that the most lenient margin for accuracy that I could see in this setting would be 0.9. But it might not be even possible to justify that in the

following sense.

Is it adequate here to establish superiority to a coin flip, or do you actually have to be superior to non-contrast ECHO, which I think I am hearing from FDA is the case.

Well, now, here is where we are in trouble. What does non-contrast ECHO do if a coin flip is 50 percent? Let me just say modestly it's 55, and according to the 21 date, it seems like it would be better than 55.

Well, now, 64.7, 55 preserving half the effect, now you are down to a margin of absolute 4.8, relative risk 0.93, which by the way, if you had a 0.93 margin you would be saying it's okay to lose 5 percent, which John is saying is on the edge of what he would say would be okay.

If, in fact, though, the non-contrast is 60, now you are looking at an absolute 2.5 percent to preserve half the effect or relative risk margin of 0.965.

Consequences, if we take what I think is a lenient margin, a 0.9 here, the first trial 32 fails. Two of the three readers clearly don't meet that.

The second trial makes it, two of three do make that. If you are using 0.93, it is barely 1 of 3 against 2 of 3. If you are using the 0.96 margin, accuracy fails for

all 6 readers, all 3 readers in both trials.

So, I do think there are evidence-based margins that you can justify or you can formulate in this setting. It would be at the most lenient would be 0.9. The 32 trial does not meet that criterion.

DR. HARRINGTON: Before I open it up to the rest of the panel, Dwaine, did you want to make a comment?

DR. RIEVES: Actually, I think Dr. Fleming elaborated on it, and it is why that third bullet is down there as added value. Remember, to be clear that we all understand with AI-700, they did interpret wall motion plus myocardial perfusion. They do have wall motion there.

So, comparing it to non-contrast ECHO in our mind is relevant. The case report forms were just not designed to collect the contribution of wall motion versus perfusion.

DR. HARRINGTON: To tease those two issues apart as Mike Lincoff brought up earlier this morning.

Go ahead, Bob.

DR. TEMPLE: This sort of goes to what Mike was talking about. If I understand it, the idea here is to predict what the result of an angiogram is going to be, and I don't care whether they do it by wall motion or perfusion. I just care whether they do it, and the hypothesis is I

suppose that if you have both wall motion measures and perfusion measures, you are likely to do better, which is not particular shown.

But I had a question for Tom also. You are comparing how they did compared to your coin flip, which you are saying is supposed to be 50 percent or thereabouts. How do you factor, then, in the comparison with the comparator with the SPECT, how do you do those two things?

DR. FLEMING: Well, the SPECT is--so, in this case, we have a bonus that we don't usually have in clinical research, and that is, if you are willing to say it's good enough to preserve at least half the effect of SPECT against a coin flip, we actually know what the coin flip result is, and here it is 50 percent.

So, we know what SPECT is, and so we just use the very traditional. We know that SPECT is at least 64, we know it's at least 14.7 percent better than a coin flip, preserving half the effect using a traditional approach, gives us the margin of an absolute 7.5, which is a relative 0.9.

It is more complicated, though, if you say wait a minute, this agent has to preserve more than half of how much SPECT is better than a coin flip. It has to preserve

more than half of how much it is better than non-contrast, and that would be logical if what you were saying here is this agent needs to not only beat a coin flip, it actually needs to beat a non-contrast ECHO.

So, if your view is it has to not only beat a coin flip, it has to beat a non-contrast ECHO, then, then we are back into the classical, it's really hard to be rigorous because I don't know, because non-contrast ECHO wasn't part of the study.

But if I am pretty cautious and just say non-contrast ECHO just increases you from 50 to 55, then, the margin then would tighten to 0.93.

DR. TEMPLE: The other thing I guess you have to think about all the time is that doing SPECT is harder because you have to go to particular places. There is radiation exposure, stuff like that, so somehow that would get factored in.

DR. HARRINGTON: Well, that's a direction--before I get to you, Jim--that I wanted to pursue with you, Tom. The notion that one has to preserve a non-inferiority, half the benefit of, say, active versus placebo, which is what we talk about in the drug side of things, is a convention but not necessarily a hard and fast rule.

Here is a case where we have an imaging technology that does have this issue, as Jonathan brings up, of ionizing radiation, this one does not. It does have some cost issues, which are different here, and which may spare patients multiple tests.

For example, it is rare that you get SPECT alone in this group of patients. People typically get rest ECHO plus a SPECT. Perhaps now having just one test is a better step forward.

So, how do you weigh that as you start to think about the establishment of the margin?

DR. FLEMING: So, that is very valid and this gets into an inexact science. But very important for us to consider, because in the end, everything is benefit to risk, and the issue of preserving half the effect, people frequently point out that could be cautious although it, in fact, might not be cautious enough.

One does need to consider relative safety and tolerability issues, and so the safety discussion that we are going to get into is an important part of this.

Preserving half the effect, in my sense, is somewhat of a middle ground. But, essentially, to justify a margin, even preserving half the effect, I would think you

have got to be arguing that there is a reason that I want to enter into an alternative approach.

Why am I going to give up half of the benefit that I already have with SPECT? Why am I willing to give that up? Well, non-inferiority ideally is motivated because this new approach will be much more convenient, safer, et cetera, et cetera, so I need to hear that to justify that I don't have to have superiority, to justify non-inferiority, preserving half the effect is okay.

If we can say this is substantially safer, then, one can justify a margin that would be somewhat larger. On the other hand, if there are worries about safety here, one would argue why aren't you having to show superiority, which is preserving 100 percent of the effect.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: Also, if you follow that thought and say this is an onerous procedure, I would just as soon avoid it, it becomes more important I would have said to know how it compares with the non-contrast ECHO, which, of course, we don't have a lot of data on.

DR. HARRINGTON: Yes, which is the question that Dr. Sahajwalla brought up earlier this morning.

Go ahead, Jim, and then I will pepper Tom a bit

more.

DR. NEATON: Maybe just two points. First, on the non-contrast, I put less weight on 20 and 21, and maybe we can come back to that in later discussion, because of how that target population was chosen, which I think is very, very important to keep in mind.

These were people with MRI versus healthy controls. But coming back to Tom's point where the logic I think, you know, is typical Tom, very flawless and helpful.

I still am a little uncomfortable with the truth in 32, so I put more weight personally on 33, and I just wanted to put that out there in terms of how other people feel about this, because 32 is comparing SPECT versus SPECT plus history and other stuff. So it's kind of a setup for SPECT in my mind, whereas, 33 is primarily comparing the two of them against the angio.

So, when I look at the data, I mean I realize there is a dilemma here in terms of how you kind of mimic the kind of target population that ultimately will want to receive this, and there is a lot of artificiality to these designs that we can talk about later.

But in terms of the risk ratio or the ratio of the accuracy, and sensitivity and specificity, I put a little

bit more weight on 33 for that reason.

DR. HARRINGTON: Because in 32, as you rightly point out, in fact, a much smaller percentage of the patients had an angiogram, and a lot more of the truth was defined on the clinical characteristics. So that is bothersome to you.

DR. NEATON: Well, it is not only that, as I understood it, it's the clinical characteristics plus SPECT.

DR. HARRINGTON: It's all the information that was available.

DR. NEATON: Right.

DR. HARRINGTON: Tom, do you want to comment on that?

DR. FLEMING: I understand Jim's point. I think they are both important studies, and it has been noted that 32, though, might match the patient population more, similar to what would be approached in the real world.

By the way, I understand Jim's point, too, about 21 and 22 being taken with great caution. That is not helping the situation, though, that just means that we essentially really have minimal to no evidence to understand how non-contrast ECHO compares to contrast ECHO.

DR. HARRINGTON: Does it bother you, Tom, to have

the same level of non-inferiority margin given that the truth was defined so differently in the two studies?

DR. FLEMING: Well, that is a great point, too. Non-inferiority margins, we often treat them as though there is a single answer to be applied across the board. Non-inferiority margins are very specific to the nature of the active comparator, the endpoint, and how trials are, in fact, conducted.

DR. HARRINGTON: Dr. Fogel.

DR. FOGEL: I was listening to Tom and I am always amazed about how much of an insight I get whenever I listen to him. You are comparing a coin flip and how much better we have to do over a coin flip. But, in everyday real life, every physician, after listening to the history, doing a physical, getting an EKG, and whatever, they have a pre-test probability of how likely it is to have coronary artery disease.

So, in my mind, after listening to you, it makes me wonder. We have to have a higher level of standard, of more than just a coin flip. But, at the same time I have to balance that, hey, I am avoiding ionizing radiation, I am avoiding invasive angiography to a certain percentage, and I guess it's cheaper.

So, I guess I am wondering how do you balance the increase over a coin flip with a pre-test probability of a physician with a patient versus what you are going to avoid, which is possibly cancer in 20 years with radiation or some complication of the invasive angiography.

DR. FLEMING: And those are very valid issues. Essentially, what we are doing here is we are measuring benefit to risk against the active comparator, which is against that, and the approach is unless you show you are superior to establish efficacy by non-inferiority, you have to argue how much worse could I be.

You point out correctly, SPECT, while it is not perfect, provides an important advance over a coin flip, because it is reducing the level of morbidity, et cetera, that someone would have to undergo if you didn't have at least a SPECT screen.

For that rationale, the concept of non-inferiority is saying how much are you willing to give back. To say I am willing to give back half against a coin flip is, to my way of thinking, a huge give back.

It would seem, and supported by your arguments, that if anything, maybe you want to give back not half against a coin flip, but half against a non-contrast ECHO or

something along those lines.

But then you are getting margins that are even greater than 0.9. So, the most lenient that I can think of here, both from the perspective of preserving half the effect against a coin flip, realizing that--I mean why is non-inferiority done? It is done because we realize what we already have is importantly better than nothing. Then, why should you be willing to give up a lot of that if you have already acknowledged that it's important?

You need to protect the public against giving back too much.

DR. FOGEL: You want to protect against the drift.

DR. FLEMING: And biocreep is another consequence with overly lenient margins.

DR. HARRINGTON: So, let's go to Bob and then to John.

DR. TEMPLE: The way the conversation is going, SPECT is sufficiently onerous that we might accept something that was considerably inferior to that if we thought it was useful, all of which suggests that the more relevant comparison is with non-contrast ECHO, and that is how I understood what some people were saying.

If that is true, then, it is troublesome that you

don't know what the effectiveness of non-contrast ECHO is. By the way, do we know what the effectiveness of SPECT is? I mean is there good data to say how much better that is than anything else?

DR. FLEMING: We don't know what it is.

DR. TEMPLE: When you do non-inferiority, you have a rigorous description of what the benefit of the control is, which is lacking here. We are working entirely on what I would have called--what we are calling in our various guidance M2, the acceptable loss of effectiveness when we don't know what M1, the true effect of the control is.

It is a little different from the usual non-inferiority--

DR. FLEMING: We don't know what M1 is against non-contrast ECHO, you are absolutely right. We know what it is against a coin flip, because we know in these sets of studies, 68.3 against 50.

DR. TEMPLE: You can say what it is at a minimum, it is pretty modest for SPECT 2, pretty modest.

DR. HARRINGTON: Dr. Tatum, did you want to comment on that?

DR. TATUM: Well, there is a lot of data as to the benefit of using SPECT. I mean there is prognostic data,

there is outcomes data, there is years and years of data that can go down to telling you what the probability of an event is going to be over a period of a year, five years, a combination of all the information put together.

I think you have to put that in perspective, and that is something we would expect we would still get here, but you don't have that data at this point in time.

Again, it comes back to that issue of finding significant disease or significant vessels versus the burden of ischemia, function, and the other parts that come together at the same time.

DR. TEMPLE: Let me ask one follow-up question. How much do you learn from SPECT compared to what your best possible history and all that stuff gave you? I mean that is in some ways another question.

Coin flip is one question. But another is--I mean I guess I was struck in the second study, in the 33 study, that all of those people were definitely going to have an angiogram, and they all did. Somebody thought they needed it.

The sensitivity, nonetheless, was about 70 percent or something like that. I am not in this business, but that worries me. That means that of those people who somebody

thought enough of to want to do an angiogram, a fair number of them were missed, and then if you followed that advice of the test, you wouldn't have tested them. Wouldn't that make you feel bad?

DR. HARRINGTON: Correct.

DR. TATUM: That is another thing I keep hearing around the table, is that we are going to prevent a number of caths. In point of fact, non-invasive testing isn't perfect, actually leads to caths that probably should not have been done to begin with, too.

So, let's get on the other side of that question, and going back to your question, if I started with a population that has a 95 percent probability of disease, I shouldn't be doing a non-invasive test to find out if there is disease present. I have got a whole different set of questions.

If I am dealing with a population that is 10 or 15 percent, I have got a totally different thing. I happen to be dealing with one here that is 50-50, which is probably the most difficult one to actually deal with, and I am looking for additional information in that particular group.

DR. HARRINGTON: Bob, for me, there are two major issues here that we are struggling with, one of which is Dr.

Tatum is indicating that we use SPECT and we have several decades worth of experience for all sorts of things. We use it for prognosis, we use it for lesion localization, we use it to help guide revascularization.

We use it for a lot of things. But we are in a little bit of an artificial situation here where we are only using it to ask a very specific question, which as Dr. Picard pointed out, is really only part of the clinical question.

So, we want to be cautious and that the artificiality of the situation doesn't make us ignore the fact that we have got a lot of other information on SPECT, several decades worth, which gets to the importance of not giving up even in the artificial situation.

The other side is that as you know well, in the whole imaging world, we have almost no well done randomized, controlled clinical trials which actually use the imaging modality to then help us in clinical decisionmaking and measurement of real clinical outcomes, and that is a problem.

If you look, for example, at the ACCHA guidelines on imaging, less than 4 percent of the imaging guidelines are Class IA. Why is that? What is a IA? A IA is well

done, randomized, controlled clinical trials.

So, we have got some issues here that make the standard pretty tough.

John.

DR. TEERLINK: You actually just hit on one of my assumptions that actually, there is no data to describe how these diagnostic tests that I am aware of affect outcomes in terms of our decisionmaking and things, which is why I think Tom's comments are particularly salient, because we don't have anything else to really fall back upon.

Other assumptions are that there is this concept that this will potentially reduce multiple tests, but, in fact, I would say, you know, patients will still get the full ECHO and be billed for the full ECHO, and that will still be done as a separate test, so you don't pull them together.

I don't think you are going to get cost savings or study savings in that regard. There may be some convenience savings on the patients' part because then you will do the full-blown trans-thoracic ECHO and then do the stress testing. I don't think we are going to save that.

There is also, as you were saying, no evidence in terms of saving invasive tests at all, either from these

studies or from clinical experience. In fact, if anything, it may increase studies.

The question is will it increase useful studies, will it do so in a way that makes an important--because there are clearly studies, caths out there that we aren't doing that we probably should be doing, is there any evidence that this will provide or capture more of those patients, and I don't see any evidence from these studies to direct that.

We are also being asked to make this tradeoff between, you know, everybody is mentioning ionizing radiation, which I don't know, and I would love to hear somebody who knows or has a sense of what is that real risk that everybody is talking about. My sense is that it is relatively low risk, and we are comparing that to trading off to complement activation and episodes of hypotension, which are real risks that we have seen.

DR. HARRINGTON: Let's stop there because I think that is a critical question. We have heard multiple people today, Jonathan brought it up, the sponsor brought it up, avoid ionizing radiation.

We have got several nuclear cardiologists around the table. Help us out. Has that risk been quantified?

What is the risk? Can you give us some data that will help the Committee put it into context? Okay. Dr. Tatum.

DR. TATUM: There is no data. There is lots of opinion, and we heard that there were opinion pieces and there are emotions, and there is political--but from point of fact, we really don't have data.

There is theory, and you could believe that the multiple gene hits maybe would lead to some cancer. But, if you even look at the people who have had therapy, the signal is pretty weak.

Now, where it really is an issue is in the use of CT right now. I don't think everybody is going to agree on this, in the use of multi-slice, now up to 312 slice CT, on a routine basis, particularly in the oncology population even, I think is very problematic. But we are talking magnitudes of difference here.

In the pediatric population, there is no question, we should not be doing that.

DR. HARRINGTON: Dr. Fogel.

DR. FOGEL: I have actually done a lot of looking into it in the pediatric population, and it has come up with some additional data in the adult population, not necessarily with nuclear. But, in terms of cath and in

terms of CT scan, it is clear, based on atom bomb survivors that are extrapolated, and indeed there are tradeoffs--I understand when you combine it with that. But the data that we have in terms of workers in the nuclear industry, and workers and atom bomb survivors, it is clear that all the experts say that estimates are that especially at the age of initial exposure, gives you an increased relative risk.

Even in patients who are--and I actually have the paper somewhere around here--even in patients who are 50, 60 years old, you still have a 3, 4, or 5 percent increase in mortality in cancer rate per gray as you go up.

If you have an exposure to 2 milliseverts versus 4 milliseverts, it actually doubles, and there is a study that was done that came out of Israel, that followed patients who had cardiac cath and followed them for 20 years, and their relative risk of malignancies especially melanomas and lymphomas are actually triple or quadruple what was normally expected.

So, although there isn't a lot of data for some of the nuclear, there is clearly a ton of data with cath and with CT that show even in adults, there is a significant risk that needs to be avoided.

DR. TEERLINK: How many chest x-rays is this

worth? My sense is that the nuke's dose is probably an order of magnitude less than a cardiac cath easily. So then, if it's an order of magnitude less, then, your 2 to 3 time risk with a cardiac cath goes down quite significantly, I don't know. I mean the studies on cardiac cath were done longer times ago when our dosage in cardiac cath was much higher. I think everything has gotten safer.

How many chest x-rays is a typical nuke study equal to? Just to provide some kind of basis.

DR. FOGEL: A chest x-ray is 0.2 milliseverts on average, and I don't know, what is a nuclear, a typical nuclear? A CT scan angiography is about 100 times that.

DR. HARRINGTON: Dr. Sahajwalla, do you have some data on this?

DR. SAHAJWALLA: I think it's around 15 milliseverts or so nukes test, and like a CTA can be between 6 to 12 milliseverts. I don't know what a cardiac cath radiation dose is.

DR. HARRINGTON: Does the sponsor have some data?

DR. WALOVITCH: Slide on.

[Slide.]

It's around 10 milliseverts for a Technetium 99m sestamibi. That is the first bar graph.

DR. FOGEL: Compare that to a chest x-ray, which is 0.2 milliseverts.

DR. SENIOR: It's about 10 to 12 effective dose milliseverts for Technetium rest and stress, and if you go to CT angio, it's about 6, well, angiography is about--I don't think it's more than 12.

DR. FOGEL: No, it's about half that.

DR. SENIOR: So, it's less, coronary angiography is less.

DR. HARRINGTON: That is very helpful. The other thing for the panel to remember, particularly the non-cardiologist, these studies are frequently done multiple times in patients over the period of several years. So people should keep in mind the lifetime dosing here, as Dr. Tatum points out, we don't have all of this quantified but there is growing concern that it's sizable. We will leave it at that.

John, do you have another question?

DR. TEERLINK: In terms of the rest of the questions, the consistency between the studies, Mike kind of addressed the issue of consistency as in reader consistency, and I was actually looking at consistency between the different results of the studies.

Thirty-two is of a more screening population study, which seems to be more appropriate for this study, yet it fails on the very marker that we would be most interested in, which is the sensitivity.

Yes, I agree there is a poor truth standard. But, just because it's a poor truth standard, doesn't mean we should give it a pass and say okay.

Thirty-three, I am not sure whether the difference between 32 and 33 is driven by the differences in patient selection, the retraining, or some other agent.

In terms of the SPECT comparator performance, I would be interested in hearing from our nuclear colleagues whether you feel that the SPECT performance in the study is something that we can use as a reasonable comparator.

In terms of the added value to non-contrast, I think this is very important because this is actually clinically what is going to happen. Clinically, you are going to have places that do stress, that do dobutamine stress ECHO, and switch from dobutamine stress ECHO to Persantine ECHO with the contrast agent.

I think it is a very, very relevant comparator and I want to reinforce that I think Study 21 provides absolutely no information, no useful information, because

dipyridamole is the stress agent. So it crippled the non-contrast study to look at the way most stress ECHO is done was with dobutamine.

It is not really providing a comparison at all between the current standard approach and this new approach. So I don't find it informative at all.

DR. HARRINGTON: I suspect that is going to be an issue when we come back in Question 4 about what other studies. My read of this, as well, John, is that the places that would be likely to adopt this are the folks who did stress ECHO, and currently, we don't have any information as to the incremental value of this relative to contemporary stress ECHO.

Mike go ahead.

DR. LINCOFF: But the unmet medical need, if there is one, isn't necessarily to replace stress ECHO unless it is just to get better images. I mean if we are worried about reducing radiation, if we are worried about improving availability, if we are worried about reducing cost, we are not going to do any of those things from switching from stress ECHO to contrast ECHO.

DR. HARRINGTON: That was part of my point.

DR. LINCOFF: If there is a niche for this

product, it is replacing SPECT even though it may be logistically difficult. But you might think that places that have been using SPECT for years will certainly have the capability of doing ECHO, and if this were an acceptable stress test, they may start to use that.

So, I don't think we can just say that this is never going to be taken up in SPECT hospitals or SPECT centers and therefore, that is not the comparison, because I don't think there is much of an incremental benefit over dobutamine ECHO except perhaps if there is a safety difference in avoiding dobutamine.

Where I see the difference is SPECT, and that is a comparison. I think there is also the fairness factor here, I mean they went into these with an a priori I assume discussion at some point saying use this as a comparison.

DR. HARRINGTON: We did hear that, and correct me if I am wrong, Dr. Rieves, but we did hear that the FDA recommended SPECT as the comparator in Phase 3, is that an accurate reflection of the discussions?

DR. RIEVES: That's correct, yes.

DR. HARRINGTON: Dr. Tatum.

DR. TATUM: After the last meeting, I was very interested because we had asked the same question, how much

contrast is being used, ECHO contrast media. So I was talking--and some of the ECHO cardiographers can answer this--I asked some of the people that were here why was it not more used in the general practice, and I was told it was too complicated, and it was logistical issues, that you needed a different level of expertise when you are using contrast, it wasn't available, and therefore, the use in the general practice was extremely low.

Did I get the right information?

DR. HARRINGTON: Some of the ECHO cardiographers, Dr. Sachdev, do you want to comment?

DR. SACHDEV: I think other people can comment also but, in general, I would guess it is used in only 5 to 10 percent of patients, and that is variable between bigger institutions and smaller labs.

But the reason that you bring that up, did you bring that up because of the difficulty in setting up these studies?

DR. TATUM: We are talking about something that could be diffused broadly to lots of existing ECHO labs that are out there, many of which are in private offices and that would be the huge advantage, people wouldn't have to come to certain centers and this kind of thing.

But at the same time I am understanding there is a barrier to that implementation which has to do with the level of skill that is required using contrast.

DR. SACHDEV: I would agree with what Dr. Picard said earlier, that when people first start to do stress ECHOs, everybody in small labs has ECHO machines, and the capability is there to set this up. It does require some training but I think it is really meant to replace thallium or, you know, nuclear imaging, and people have nuclear labs set up for financial reasons, for feasibility reasons, for other reasons. But anybody with an ECHO lab and interest in the ability to get the necessary training can set up this kind of a study.

DR. HARRINGTON: Go ahead, John.

DR. TEERLINK: So, yes, the contrast was a little more difficult to use. To address Mike's earlier comment actually, dobutamine ECHO is pretty easy to do. So the people who would have replaced SPECT, you know, there is already, those people who could replace SPECT with an easier to use one-day, one-stop shop, that we already have that with dobutamine ECHO.

So, in fact, I think a lot of that transition has already occurred, and I think what we have seen is, in fact,

there are other factors driving who does what that are independent of those issues.

The increased availability of some of the windows and all that may drive a little more. But the thing that is going to be largely replaced is dobutamine ECHO if this goes, first of all, because you get just better opacification.

I, as an ECHO cardiographer, will grant the need for something to allow us to see better, and I am very enthusiastic about that concept. We need something like that. The question is, is this the thing that we need to replace dobutamine ECHO even though it was tested against SPECT, because it is not going to replace SPECT practically, in a meaningful way.

DR. HARRINGTON: Mike and then Bob.

DR. LINCOFF: I will keep this quick because I don't want to belabor it, but I think part of the reason that people use SPECT rather than dobutamine is that there is much less inter-observer, there is much less level of skill required for reproducibility with SPECT.

That is not to say you don't use skill to use SPECT. But you are reading an ECHO, I think there is much more of an effect of the training of an echocardiographer.

So, if you had a technique that had better visualization, that you could read more reproducibly, read from an observer to observer, I think you might see a replacement.

DR. TEERLINK: Do you see evidence that this actually changes any comparison to stress ECHO? Did you see that this was better than stress ECHO in terms of inter-observer or inter-observer readability?

DR. LINCOFF: No. All I am saying is that many people who would use SPECT rather than dobutamine do so because it is going to be easier to read the SPECT.

DR. HARRINGTON: I think that was Dr. Tatum's point earlier today when he asked the question about computerized algorithms to read the scan. I am assuming that is the genesis of your question.

DR. TATUM: That is part of it. I have tried to get ultrasound involved in oncology for a long time, and I have spent a lot of money trying to do that. The problem always comes back to how do we control the reproducibility from dimensional measurements to angles you are taking, and everything else, and many people looking at fixed type systems. But that has always been the issue and that was my question coming back to reproducibility.

Using the same image set is one thing, going back

and redoing the test, do you actually get the same information and how variable that is, is another whole piece to the equation.

DR. HARRINGTON: Bob.

DR. MATTREY: I just want to throw in my two cents worth. I am not a cardiologist, and my guess for the lack of penetration to the level you are expecting with contrast ECHO is, number one, they are not approved for perfusion imaging, and number two, they are only going to be used when the non-contrast study is suboptimal or at least justified why you need to use contrast study.

So, if you put the transducer on somebody's chest, you don't see enough detail to do your stress ECHO, you may then seek the aid of a contrast material. But that is strictly for myocardial edge detection.

This agent is for perfusion, so one does not know how that will impact the utilization. So, it's a little bit different.

DR. HARRINGTON: John.

DR. FLACK: What this discussion has boiled down to for me is that the non-contrast ECHO, I don't think there is any doubt at least from a non-imager's perspective from where I sit, that this contrast is better in part because

you can't even calculate the sensitivity and specificity if you are throwing away results and can't get them, and now you can get images here 99 percent.

So, I would say that that would indicate to me that you get better pictures, get better outcomes in the sense of being able to read something.

The flip side of that, though, is the difference between SPECT and this, I am convinced after listening to the discussion that the margins were too generous here, and giving up that much didn't make any sense.

I think the question for me is what you might give up with this kind of highly operator-specific test and ability to pick up disease, are you giving up too much in relationship to what you might be getting on the safety side.

To me, that is the question with the test and SPECT, and the consistency between studies I think is a nightmare trying to figure out why there is not consistency between the studies, because you may have an MI from a very small lesion that is never going to give you ischemia on any kind of testing because it ruptures and you get a plug in there to close your vessel off, you don't have any collaterals around it.

Yet, you may have a lesion that gives you ischemia that is big, that doesn't ever really rupture, and it is sort of like EKG and echocardiography. You can trot in far left ventricular hypertrophy from both of them, but they are basically kind of telling you different information on the same organ.

These two versions of the truth, to me we are really looking at two different versions of reality, and quite frankly, I don't like very much that hodgepodge version, because it has got everything in the kitchen sink in there and all kinds of underlying pathophysiology that I wouldn't expect one test to pick up.

DR. HARRINGTON: Tom, let me ask you, along the lines of your calculations for non-inferiority, did you also do the power calculations with the more stringent non-inferiority boundaries, the kind of studies that you would be talking about in terms of size to help people understand what that might look like?

DR. FLEMING: I did first pass approximations, that is what I have done. But, essentially, it depends somewhat on whether you think it is not just what you want to rule out. Let's say you used what I consider the most lenient margin that I could possibly justify, which is 0.9,

so you are allowing a relative 10 percent reduction, so about a 7, 7.5 percent absolute reduction.

If the alternative hypothesis is that you are really the same, the studies would probably have to be about twice as large as what these are. However, if your view was that you are actually hoping by developing a procedure that is simultaneously addressing perfusion and wall motion, that you could be just slightly better, not enough better that it is plausible you could show you are superior. But, if you are 1 or 2 percent better, then, you can rule out that you are 7 percent worse with sample sizes similar to what we are dealing with here.

DR. HARRINGTON: So, if your point estimate favored you--

DR. FLEMING: Well, if truth favors you very slightly, then, your probability of being sufficiently favorable to rule out you are 7 percent worse is high even if sample sizes aren't a lot different from what they have had.

DR. HARRINGTON: My timekeeper is reminding me that we need to summarize some of the issues here. I think Dr. Rieves and others, we have had a pretty robust discussion around this first question. Let me see if I put

in some context with you.

I think I am hearing from the group with some exception that the group is troubled a bit by the consistency between the studies, that this definition of truth which varies between the studies is problematic, failing therefore on some of the different endpoints of sensitivity and specificity as has been pointed out by Dr. Mucci, is bothersome to some, not to everyone, and that is the general sense I am getting from the group.

Would people just with a simple head nod, it seems to be what people are indicating. With the comparator, I think there are a lot of issues that have been summarized. Dr. Tatum all day has been troubled by whether or not SPECT got a fair test. Is that an accurate comment?

Others seem to be less troubled by that. But I think, largely led by Tom's elegant discussion, there is some question about whether or not the non-inferiority margin is appropriate in this indication. People seem to be generally agreeing with that.

The last part I think is particularly challenging is that I think people do question not if there is added value. But whether or not we have enough information to state that there is added value of this contrast agent to

standard non-contrast echocardiography that would include dobutamine stress because it hasn't been studied.

Is that a fair assessment? Okay. Let's go to Question 2.

Now, we are going to flip the coin and go to the safety side of the equation. What the FDA would like us to discuss is the extent to which the Phase 3 data provide persuasive evidence of safety, and they would like us to comment on these three issues: the rate and nature of acute reactions necessitating AI-700 discontinuation; the safety database size, the single arm study, the stress confounder. This is the dipyridamole issue and the inability to tease out the confounding of the dipyridamole, and then finally, something we haven't talked about a lot today, this notion that the white count goes up, the CRP goes up, complement activation goes up, what do people think about that.

So, the safety side of the question. Does somebody want to kick us off? I knew I could count on you, John.

DR. FLACK: I will try to be brief here.

What I find very difficult in looking at the safety data is we are constantly trying to figure out what would the expected rate of complications be in a population

like this, knowing that this is not a well population.

I think the proximity, though, of some of the physiologic effects, which if extreme enough can become adverse events, convinces me that it is more than just a population, that there is an issue with using this contrast agent.

I am bothered by it. It is not benign, and clearly there would have to be limitations and restrictions on who this is given to, and I would kind of worry about who is responsible for it, is it the price of doing the test, doesn't know much about the patient, or is it the doctor ordering the test who is probably not going to be nearly as familiar with the contraindications.

I don't think you can adequately make an assessment. But I think there are some pretty disturbing signals in the data for screening tests from my vantage point, even considering the sickness of the population.

Finally, the biomarkers, it looks like there is activation of complement and there are blood pressure reductions, and at least for a period of time, there are some fairly notable physiologic effects, and this got a little bit more down side than many screening tests that I would be comfortable with.

DR. HARRINGTON: So, you are following up on Dr. Rieves' comment, this discomfort around the fact that this is designed as a gatekeeper, perhaps not enough safety information for you in that role?

DR. FLACK: Yes.

DR. HARRINGTON: Okay. Let's go to Emil.

DR. PAGANINI: Very quickly on all three. The first, the risk has to be balanced against the benefit. So, whenever you are talking about risks of safety, you really want to look at benefit. I don't think we really defined a fairly substantial and clear-cut benefit, therefore, any risk is higher than what would be justified.

The larger group, you need to look at a larger group and include a lot of the folks that were excluded before, specifically, again renal, thinking that the only reason the heart exists is to send blood to the kidneys.

DR. HARRINGTON: Strike that from the record.

DR. PAGANINI: No, please, keep it in the record. The larger group would have to include some subgroups that were eliminated like CKD-3 and higher, and also a better understanding of effects of inflammatory mediators and what that does to different organs, not just the kidney, recognizing that there are some other organs in the body.

Finally, I think the whole issue of these mediators and biomarkers need a better review than what we have received. I think a review of any type of extracorporeal exposure or exposure to non-biologic materials and what that does to mediate a response needs I think to be a little bit better flushed out especially since we are talking about class issues here.

Those would be my three comments.

DR. HARRINGTON: Good comments.

Mike?

DR. LINCOFF: Although we are calling this a screening test, it is not like drawing a PSA. This is a population of patients who we are doing stress tests on because they have signs and symptoms of ischemic heart disease.

So, this is a high risk population of patients in whom we take risk in doing a stress test, we take risk in doing dobutamine, we take risks in giving dipyridamole, and these risks are relatively small. But that's why there are physicians there. So it is not untrained personnel. We are doing these studies in a high risk group of patients with expert personnel.

Assuming there is benefit--and that is not what

this question is. But, assuming there is benefit, I think there is some tolerance for risk in this population, and what we have seen are events that do seem to follow a theme and also seem to follow a theme that is consistent with some of the other contrast materials related to hypotension and maybe bradycardia and maybe some of the same mechanisms.

But, at least in the 1,000-plus patients that have been evaluated thus far, have not been severe to the extent that they have been irreversible, required extraordinary means to overcome.

Now, in the larger population, there may be those rare events. But that is always the situation we are in when we have 1,000 patient pre-approval, and we don't know what is going to happen when it's rolled out.

I think that at least for what is a reasonable database at this stage of development, I haven't seen alarming things although I have seen things that indicate that this isn't a drug that one gives with an inexperienced group.

I am concerned about different populations, not as much the kidney, but the whole unstable ischemic group of patients and the concern that somebody may be tempted to use this in the setting of reperfusion for acute MI, et cetera.

I mean there is a whole other group of patients that, in fact, came up with other types of contrast materials, there, we have no experience, and if this drug were approved, I think there are going to have to be extraordinary means to try to prevent this from being used outside the population that has been tested unless new data comes along.

Finally, with regard to the inflammatory markers, certainly, inflammatory markers in the long-term have prognostic value. But we don't know what it is short term, and these have been very transient, minor--they have been relatively minor elevations.

They may, in fact, link to the mechanisms that we are seeing for some of the side effects. But whether or not they have other prognostic value beyond what we actually see in the events I think is very speculative, and not something that I would consider a major factor.

DR. HARRINGTON: Mike, let me just push you a little bit. Are you saying that this is a group of patients, and I agree with you, that we would be usually willing to takes some risk on, because the underlying disease that we are trying to find out if it's there is a risky disease so we are willing to take some risks?

Do 1,000 patients' worth of information quantify

for you with enough certainty that you are comfortable in terms of maybe using a diagnostic agent like this?

DR. LINCOFF: One thousand patients without one event--

DR. HARRINGTON: One person with non-palpable blood pressure?

DR. LINCOFF: We know what that means. It means somebody got very bradycardic. But we deal with that, we frequently deal with that. We didn't have a patient that you couldn't get out of it. Certainly the possibility exists that you would in a larger population. But, in 1,000 patients, we didn't have, although they are called SAEs, when I was a cardiologist, as any cardiologist dealing with this group of patients would really consider a severe reaction.

DR. HARRINGTON: But I think what you are also saying is that if a diagnostic like this were to be used, it would need to be really carefully monitored in terms of the setting in which it is used until we got more experience with it, because there are a lot of untested issues here, no ACS patients, no CKD patients, not a lot of really old people, a lot of other issues.

DR. LINCOFF: Absolutely, and we are seeing

relatively noncomplications in a relatively healthy group of patients. The external validity beyond that population is completely unknown, and I am not dismissing the findings, But I am saying in this population with a reasonable first pass at a number of patients, it looks reasonably reassuring.

DR. HARRINGTON: On the safety, and I have got three prominent statisticians here, let me ask, should we be bothered by the fact that this is not a randomized clinical trial, or is this study design informative enough that we should get over our hangup on the need for randomized clinical trials?

DR. NEATON: I am bothered by it, and I don't put much confidence in the literature base controls that were cited, and I think it's disappointing that the sponsor didn't take advantage of the setup that they had, at least potentially randomize the order of SPECT and ECHO, and the fact that we have no side effects on ECHO or SPECT when it is given the day before or something like that is kind of a real limitation.

I don't understand why you couldn't do some randomization here.

DR. HARRINGTON: David.

DR. DeMETS: I am not thinking that we need to have a two-armed study, but I think the randomization order would have given us better reassurance. There could be a sequencing effect that we don't understand. That would at least have been one way to strengthen the studies that we saw.

DR. HARRINGTON: Do you want to add to that?

DR. FLEMING: So, single arm makes sense when two criteria hold. One, when you have a very clear sense of what would happen in the absence of your agent, and, two, where what you are really concerned about is something that is odds ratio, relative risk increases of 10 or more, as I always say with rotavirus, intersusseption occurring at a rate of 10-fold more, I could see that in a single arm or in a pharmacovigilance program, or PML on Tysabri in Crohn's disease and MS, where the relative risk is 1,000, I don't need a randomized to compare, a single arm experience is fine.

But when I care about increases that are of an order of magnitude of a relative risk of 2, if that would really matter, it is very difficult to sort that out as to what is due to the treatment versus what is due to selection factors in patients.

In this setting, there is a level of reassurance from the experience, and I certainly agree with Jim and Dave that it would have been much more enlightening if we had had some element of randomization. But, in this setting, without seeing any immediate life-threatening or fatal occurrences in 911 people, the rule of 3 basically, we can be somewhat comfortable in this type of population that the true rate isn't more than 3.3 per 1,000.

The down side is rates lower than that could be very problematic in benefit to risk in this diagnostic, and we don't have the ability to sort that out.

DR. HARRINGTON: Go ahead, Bob.

DR. TEMPLE: I don't think this is a single arm trial. It's a nonrandomized crossover as other people have said. But there are multiple arms. It is just you might have gained from randomizing the order.

DR. HARRINGTON: Go ahead, Mike.

DR. LINCOFF: I can understand wanting comparison if you had outcomes, efficacy outcomes, but here we are talking about safety with an event rate that looks to be about 1 percent.

So, if we did randomize to look at the relative risk of these events, what would the sample size have to be

to put a reasonable confidence interval around a difference or lack of difference with an underlying event rate of less than 1 percent? I mean is that even feasible?

We are talking about a mega-trial for a diagnostic agent.

DR. HARRINGTON: Any takers on Mike's comment?

DR. NEATON: I think that would be true for the serious adverse events, but it would not be true for some of the more common ones that were cited here in terms of hypertension and the other reactions.

DR. HARRINGTON: Let's talk a little bit more about the study design, because the sponsor spent a fair bit of effort explaining to us about the dipyridamole issue as a confounder. What do people think about it, how do we help in the assessment of the adverse events with the dipyridamole in the middle there?

Are people content? I thought they went through great effort showing us the time relationship, when the events occurred. They tried to give us some sense in the briefing document of what other dipyridamole studies looked like.

I mean are we happy with the explanation of a lot of these side effects may well be attributable to the use of

dipyridamole?

DR. TATUM: If you looked at the last slide that actually was showing the progression, what you saw is, in fact, during the pharmacologic infusion, the way that works is 4 minutes as we said, the peak is at 7.

You had a very low number. It was when the second dose was given, you got an additive and significant increase. To me, that is kind of bothersome. So what is going on there is really questioned.

I really feel like, you know, dipyridamole has side effects, there is no question about it, and it looks to me like this is an additive, and they are kind of moving in the same direction, which is an issue.

There is a little dichotomy problem here I am having trouble with. We talked about the specific population we are talking about here. But there have been conversations about the screening trial, diffusion, and other things, and that is where I am having some discomfort because my concern is I think pharmacologics are overused anyway.

So, if we begin to put out a pharmacologic in this fashion, are we going to stop doing the real test, which is the treadmill test, which is the best test, because it is

going to be easier, more available and easier to do, does that, in fact, have a safety issue at the same time.

Again, in looking at this, and looking at the flow patterns, I think there is an additive effect here, not that it is huge, but it sure looks like it's moving in the same direction.

DR. HARRINGTON: But is it fair to say that we--but we don't know, it's--

DR. TATUM: We are back to that same question. We needed a trial in which we were able to tease those two parts out, and we don't have that information, or we may have some of that information, that would be a question.

If in the trial where they were done separately, can we get at that information or at least is there enough to look at it to say should we design a trial to actually look at that particular issue.

DR. HARRINGTON: David, I saw you shaking your head. Do you want to comment? Did you agree with Dr. Tatum in terms of the confounding issue, the dipyridamole, or do you want to add something to this?

DR. DeMETS: I have nothing to add, but I think there is an inherent confounding that is, with the data we have, would be tough to tease out. I don't see any way

around it.

DR. HARRINGTON: Dr. Day.

DR. DAY: I raised the confounding earlier today and I just wanted to say I am still concerned. But there are two ways to look at it.

One is to reverse the order of the two tests as Dr. Temple was talking about, and the other way is to do t he AI-700 twice without anything added, and we will talk about that later, but I am saying there are multiple confoundings. There may also be a confounding of elapsed time and other things, as well. So it is just very difficult to know about the adverse events here.

DR. HARRINGTON: Go ahead, Dr. Fogel.

DR. FOGEL: I was always under the impression that this agent would always be used with dipyridamole or another vasoactive substance that would have similar side effects. So, whether it's dipyridamole or the combination of the dipyridamole and the agent or just the agent alone, I guess I don't see the point why it really even matters since you are always going to be using it in combination together, or at least that's the indication. So it seems that trying to separate it out seems artificial.

DR. HARRINGTON: You are saying it's part of the

package, so you have to accept what comes with the package?

DR. FOGEL: Right, everything including the side effects of dipyridamole plus whatever side effects that might be due to the AI-700.

DR. HARRINGTON: So, trying to tease it out is in some regards an academic exercise, but doesn't really--

DR. FOGEL: Yes.

DR. DAY: I don't think it is entirely because when they are put together in the package that is going to be in clinical practice, these people have already gotten it by itself before. So I don't think it's totally cleared the body, and there are two doses. It's with the package later, but by itself first so I don't think it's entirely academic although I do take your point.

DR. HARRINGTON: Bob, go ahead.

DR. TEMPLE: Well, had there been--it's easy to say this now--had there been an arm that was just the ECHO with dipyridamole but without the contrast agent, then, you would be able to know just what to attribute to the contrast agent, and that would be informative.

DR. HARRINGTON: Mike, did you want to weigh in?

DR. LINCOFF: That would have been the SPECT arm had you separated them in time as somebody had pointed out

earlier, which in retrospect might have been a nice design.

DR. HARRINGTON: The final thing I want to probe would be it before we get to the vote is the inflammatory markers. I think it was Mike that said, you know, this is short lived, we don't have a lot of information about whether or not this is important for a couple of minutes, a couple of hours, okay, it's there, more data needed, don't get too worried, is that oversimplification, Mike, or is that pretty accurate? Good enough.

Does anybody want to weigh in on this? Does this complement activation, the CRP, the white cell count, does this bother anybody? Is this something we should discuss further? Go ahead, Emil.

DR. PAGANINI: It bothers me, if that is what you are asking me.

DR. HARRINGTON: Yes, I am asking.

DR. PAGANINI: I don't know what it means. I think Mike's point that it is short term, short lived, that's fine, but I have no idea. There is no data here on any long-term outcomes. The only data I can show is stuff that had the similar response to non-biologic exposures way back in the past on extracorporeals, and that has shown to have some long-lasting effect in that it created a

prolongation of acute kidney injury, it created a worsening of CKD.

So, I mean there are some things that are long lasting that we don't have, so to say, well, gee, it got better within 15 to 30 minutes, so what, is I think an oversimplification. Something happened, it was a clear response, and it did get better, thank God, luckily, that's good, so gee whiz, thanks, that's it, close the door, and on to the next, I don't think so. I would like to find out why the hell it happened.

DR. HARRINGTON: Mike, and then I am going to go Dr. Sachdev, Bob, and then Dr. Tatum.

DR. LINCOFF: At the risk that--I don't want to seem cavalier about this, but I do recall, and I can't find it, and hope maybe somebody who authored these documents, one of the document actually talked about the magnitude of the rise in the markers with that particular example, that dialysis membrane, and it was my recollection, perhaps I am wrong, but it was much higher in terms of magnitude.

Yet, we don't look for this, and a lot of other things, we don't look for it, a lot of drugs, a lot of things we do. So we don't know. It is not that we don't know what the consequences of his particular rise, we don't

know what the consequences are of all the unknown rises, because we don't know what other things we do to cause transient rises in these inflammatory markers.

So, because it was measured, without any clear consequences, it is something that is interesting and we should look at it and perhaps try to study it further, But I don't think that that is a criteria for being concerned in this isolated fashion particularly given the magnitude, which was very small, in fact, my recollection is that they didn't even exceed the upper limits of normal for many of these markers.

DR. HARRINGTON: Dr. Sachdev.

DR. SACHDEV: That was exactly my point. One could ask what do nuclear agents do to complement activation. These people are on all kinds of medications, what do combinations of drugs do to this type of biomarker analysis, and in the setting of patients having chest pain who you are doing a stress test with exercise, a stress test with exercise have risks, these people have coronary disease, and you are doing a test with trained personnel, with resuscitative equipment there. So I don't see many of these issues as being clinically significant, and it is definitely not prohibitive for use of these things.

DR. HARRINGTON: Good comment.

DR. MATTREY: I would just like to comment about the kidneys. I am sorry I don't know much about the AI-700 relative to kidneys, but I have done lots of studies on kidney flow, kidney perfusion with ultrasound contrast agents that are microbubble based. There is no effect.

Now, I don't think all agents cause complement activation, but I am not privy to that data. I know the agents I have used have not had complement activation. The particulate load is I think not an insignificant potential to explain many of the symptoms, the fever and the pyrexia is likely related to macrophage activation.

I don't know about the complement and its relationship to that, but I don't believe that the kidney is a big deal, and I can't imagine if they have monitored kidney function that the blood pressure is related to kidney issues. I am not worried about the kidney from my perspective. I think this is a particulate effect, they have a surface activity on the surface of their bubble that is causing complement activation that is not a class reaction to all microbubbles.

They do have a slightly higher particulate load than other microbubble agents, particularly at the dose that

is used, which is about 2.8 ml for a 70 kilo person, but that is my perspective on the AE. I think it is particles and their particle has something on the surface that is causing the complement activation, maybe the negative charge, I don't know. But those are the issues.

DR. HARRINGTON: Dr. Tatum and then Dr. Fogel.

DR. TATUM: Yes. One of the things I did get a look at was nano-based contrast agents that have been in use and also some are experimental. Among those that are in use, I found no elevation in markers or complement. However, in the experimental you mentioned those that have negative charges are pretty much universally causing complement activation. So that would make sense.

The thing that I was a little bothered by is that the particle components are actually eliminated from the body over a period of days or up to a week if I understand, and everything was stopped at 72 hours so that there is no evaluation of what is happening long term to these particle components, probably nothing. But again we have no data on that particular piece.

DR. FOGEL: I am not an adult cardiologist, I am a pediatric cardiologist. But, having done a quick literature search, there seems like there are a number of papers in the

literature that look at complement activation and increasing complement components in both myocardial ischemia and myocardial infarction.

So, obviously, I am not saying that that can totally explain this, but it has to enter into the fact that we can't certainly pin this on just the agent, and that we have to say that it's at least in part due to the patient population that we are studying.

DR. HARRINGTON: Fair comment. Dr. Rieves.

DR. RIEVES: To just be sure we are on the same level, these are not bubbles, these are porous spheres, these are more rigid. The marketed agents are microbubbles. But this is not a bubble.

DR. TATUM: Would anybody comment on the CRP?

DR. HARRINGTON: I think that Dr. Fogel's point and Dr. Sachdev's points are very accurate. We don't know. There is data that ischemia by itself will cause a rise in both thrombotic, as well as inflammatory, markers. We don't know necessarily the relationship between the rise of those things and subsequent outcomes.

It does appear, as Mike has pointed out, to be relatively time limited. I think we are in an area where we don't have a lot of information.

DR. HARRINGTON: I think we have had a good discussion. Dr. Rieves knows about safety and covered the three key areas that you wanted us to cover. I suspect we are going to come back to some of those in the vote.

So, this is a voting question. The question is does contrast enhancement of rest/stress echocardiography with AI-700 provide sufficient diagnostic benefit to justify the risks associated with the product?

Let me just review for you how we are going to vote. We don't have the electronic voting material today so it will be by show of hands, and we will first take the Yesses, and what I want you to do, when I call for it, is to raise your hand, keep your hand raised while we get a count, and then we will go around the room and ask you to say your name and how you voted.

We will then do the noes, we will repeat that. We will do the abstains, we will repeat again the same basic format, and then we will have a discussion about why you voted and what I will do is I will start at one end and go around the room so everybody can say their piece.

Don't feel as though you have to repeat something, just refer to another speaker if, in fact, they made your remark. So, again, the yesses, the noes, abstains, and then

discussion.

Any questions before we do that?

Okay. Does the contrast enhancement of rest/stress echocardiography with AI-700 provide sufficient diagnostic benefit to justify the risks associated with the product?

Everyone who would vote Yes, please raise your hand and keep it up. Raise them high so we can see.

[One hand raised.]

DR. HARRINGTON: Okay. Let's go around and state your name and how you voted into the microphone.

DR. RAMSEY: My partner just warned me that I would be the first one that would have to make a comment.

DR. HARRINGTON: All I need is your name and--

DR. RAMSEY: Ruth Ramsey. I vote Yes.

DR. HARRINGTON: Okay. We will come back to the discussion.

Did anyone else raise their hand? Okay. So, now the No's, people who would vote No to this question, raise your hand.

[Hands raised.]

DR. HARRINGTON: Okay. So, let's start with you, Dr. Lincoff. Say your name into the microphone and how you

vote.

DR. LINCOFF: Michael Lincoff. No.1

DR. SAHAJWALLA: Maya Sahajwalla. No.

DR. PAGANINI: Emil Paganini. No.

DR. FINDLAY: Steve Findlay. No.

DR. DeMETS: Dave DeMets. No.

DR. FOGEL: Mark Fogel. No.

DR. TATUM: Jim Tatum. No.

DR. TEERLINK: John Teerlink. No.

DR. FLEMING: Thomas Fleming. No.

DR. HARRINGTON: Robert Harrington. No.

DR. FLACK: John Flack. No.

DR. SACHDEV: Vanda Sachdev. No.

DR. GEVA: Tal Geva. No.

DR. NEATON: Jim Neaton. No.

DR. DAY: Ruth Day. No.1

DR. KASKEL: Rick Kaskel. No.

DR. HARRINGTON: Okay. The final is all of those who chose to abstain, please raise your hand.

[One hand raised.1]

DR. HARRINGTON: State your name.

DR. MATTREY: Robert Mattrey. Actually, it's not abstaining if I don't have an opinion. It's just I don't

think there is enough data to answer that.

DR. HARRINGTON: Mike, let's start at your end of the table and explain your vote. I don't think, Jonathan, you get to. Let's start with you, Mike.

DR. LINCOFF: Well, I am not as worried about the safety side although there are mild signals. I guess I am influenced by the concerns, the statistical considerations regarding whether or not we have really proven true comparability to the existing standard. I believe the SPECT is an appropriate standard, but I am not convinced that the existing data proves non-inferiority to that standard.

DR. SAHAJWALLA: I am influenced both by the statistical considerations and also by the lack of long-term safety data. That is why I voted No.

DR. PAGANINI: I voted No based on the lack of superiority or even the lack of comparability and concern over the long-term effects and short-term effects of some of the safety issues. Finally, somewhat disappointed that the study itself, which proposes to show both wall motion and perfusion together was not studied as such as an improvement over what exists.

DR. FINDLAY: On balance, following the day's very excellent discussion in which I felt often a non-non-

inferior on the statistical analysis personally, very challenging stuff. But, on balance, I wasn't convinced on the safety or on the benefit versus risk ratio.

DR. DeMETS: Some of my issues were that while I agree that the SPECT is a good standard, it was not clear in my mind that it really was applied in the most effective way.

I would share some of Tom Fleming's concerns about the margin and to me, the issue of sensitivity is the key thing if you are going to use it as a diagnostic, I mean you still have some kind of a sequential testing if you wanted to.

Finally, there is the other issue is that you get a Yes or No answer, and you don't get much information about the degree or severity of the coronary disease.

DR. FOGEL: For me, it was both statistical and design considerations, and the fact that it's ischemic heart disease possibly leading to myocardial infarction, and the results could be devastating.

If it was another disease that might be less severe or fatal, I might have been tilted a different way. But, because we are dealing with heart disease that could kill people, I think it needs to be more of a slam dunk than

it is.

DR. TATUM: I agree with what has been said before. The other thing is I still have a problem with the comparator study and the way it was done. But the other one is that as a point Dr. Rieves pointed out just recently, this is not a bubble, it's a particle, has many characteristics of nanoparticles, and signals were seen in the inflammatory part are very bothersome to me as well as the issue of not having it mono-dispersed completely and what that means. That I think needs to be studied further.

DR. TEERLINK: I agree with what has been said so far, as well as my earlier comments. I would add that I am not as concerned about the safety issues although I think they did need to be more thoroughly investigated. I think there was an opportunity for perhaps post-marketing assessment of some of those safety issues but, nonetheless, the efficacy was not sufficient for me to vote in favor.

DR. FLEMING: In responding to Question 1, I think I have already laid out the essence of my concerns about the lack of consistent and persuasive evidence of efficacy.

I am particularly concerned about the results in the 32 trial in terms of the lack of establishing persuasive evidence of non-inferiority, on accuracy, and on

sensitivity.

My sense is overall that if the results had been trending more favorably as I might have hoped with the concept of perfusion and wall motion being combined in the ECHO, that it would have been very plausible to have obtained results that were trending somewhat positively, and one could have ruled out the loss of an unacceptable amount of efficacy for SPECT. But it is very important in non-inferiority to ensure that when you have made important advances as SPECT is relative to a coin flip, that you are able to reliably rule out meaningful losses of that efficacy.

Everything is benefit to risk, though, as well, and my sense about the risk side is that there are some encouraging aspects in terms of lack of life-threatening and fatal occurrences and yet the sample size here and the nature of the design is leaving us with a fair amount of uncertainty about actual safety.

While it has been pointed out that it would take an extraordinarily large trial to rule out a doubling and a rate of an event that is 1 in 1,000, we can't even be confident about the nature of causality for the SAEs and the discontinuations which are in the rate of a 2 percent

background, and it would have been achievable to have ruled out a tripling in that rate if we had had a design more along the lines of what Jim Neaton had pointed out.

So, it is as much a concern about the uncertainties as it is about the evidence that actually exists that leaves me with a sense that no, these data do not reliably establish favorable benefit to risk.

DR. HARRINGTON: It is my perspective, it is largely, Tom, based around your final comment, is that I felt that there was just insufficient information to prove efficacy. I felt that the efficacy information was, in fact, very inconsistent. I had issues with some of the design of the clinical studies including the lack of any randomization.

I had issues with the non-inferiority margin, and I felt that the inconsistency of the 32 moving to 33 were important enough to take notice and say that perhaps a third study would have helped nail that down.

On the safety side, I also agree with my colleagues that giving a patient population which is potentially so large, a rather limited safety database as we had, while somewhat reassuring, did not address some of the patients that we are going to see who would be treated here

including very old people, chronic disease, et cetera.

So, I felt that the uncertainty on the efficacy side and the limited safety database is what made me vote as I did.

DR. MATTREY: The question asks whether the AI-700 provides sufficient diagnostic benefit to justify the risk associated. The study was not designed to look at benefit versus non-contrast. The study was designed to compare stress ECHO with the contrast material to SPECT.

To me, the discussion between sensitivity and specificity really was balanced by looking at the receiver/operator characteristics, and to me I was convinced that at least they seem to perform comparably according to that data.

So, if you use that as one side of the equation, which is the diagnostic benefit, I would say in my opinion they showed that it was comparable to SPECT. Whether SPECT was compromised or not, I am not an expert in that area.

The AEs I think were not sufficiently evaluated and analyzed to balance the positives and know what that ratio is, and that is where I was uncomfortable deciding one way or the other. So, I don't have a good balance on both sides of the equation.

DR. FLACK: The margin issue was a problem for me, the fact that the designs left too much uncertainty as to whether you are dealing with a problem with the population or a problem with the test itself.

The inability to take more information and to make it perform better than the existing standard may have occurred in part because you are going after non-inferiority and you have these reasonably liberal margins. But, in reality, getting more information, I think the opportunity that was missed here was to really take and develop algorithms and ways of reading that incorporated information that gave you better performance, not inferior performance, and also coupled with that, and just too much uncertainty, and all, I don't think that the case was proven although I do believe that there is a lot in the data that is currently there, that can be exploited to address some of these issues, but it was just not put forward today with enough clarity for me.

DR. SACHDEV: As I mentioned, I recognize the safety issues, but was less concerned about them. I think SPECT was an appropriate comparator. As far as efficacy, I do think that the truth standard or the reference is a problem. I would have liked to see comparison with just

angiography if possible.

I am concerned about a sensitivity in the low 60s for a diagnostic study in a high risk population.

DR. GEVA: I wanted to add a comment to the company, and that is the underlying premise of this technology is certainly worth pursuing. Getting better quality data, combining wall motion and perfusion, the principle is I think worth further investigation.

As far as the overall weight of the evidence that was presented today, the robustness of the test, how it actually performed, that was disappointing in light of the potential risks.

DR. NEATON: Well, I think this is a potentially very useful drug, and I was persuaded to vote the way I did because of the arguments of the widespread availability of ECHO, and it would be widely used.

That concerns me because I think 33 is a good study and I can put some confidence in it. But, like you, Bob, I guess if I had seen another study like that, that replicated it, plus kind of an experimental design to kind of help me with the safety issues, that I think it would be there.

DR. DAY: For efficacy, the main stumbling block

was the word persuasive in the question, persuasive evidence. I thought there was some evidence here and there, but, taken together, it was not persuasive, largely because of inconsistency.

I have already voiced my concerns about the study design and the impact of that and being able to interpret what is going on in the SAEs and the discontinuities, and I think we would want to know more about that, and how all this gets translated out into practice does concern me as well.

DR. KASKEL: I think it's a promising drug and my concerns are echoed around the table with the study design. I particularly think that we need to look at the data regarding other drugs that the patients were on, and also the safety issues with biomarkers.

If controls with normal, quote "endothelial function," unquote, have these risk factors with the CRP and complement, what happens to patients who have abnormal endothelial function that get this potential insult needs to be looked at.

DR. RAMSEY: Ruth Ramsey. I voted Yes. Both supporting what Bob Mattrey said. So I will also second what he said, and say, too, that it is equal to SPECT, which

I thought it was from the data, then, it is better than SPECT because it doesn't use ionizing radiation, and I am very concerned about that, not just for the patients, but for the medical personnel. You can't feel it, you can't smell it, you can't taste it. So ionizing radiation is something that I am concerned about, and it is a cumulative dose over time.

Regarding the fact that it's a newer technique--yes, it is a newer technique, but I believe that there are people out there who are capable of teaching us or whoever is involved on how to read these appropriately and to interpret the data.

Of course, we are making quantum leaps forward in the technology of ultrasound, as well as all other technologies that are out there, so I will stick with my Yes vote.

DR. HARRINGTON: I have been asked to read into the record a final vote, which was 16 No, 1 Yes, and 1 Abstain.

Dr. Rieves, I think as part of the going around to discuss, you have gotten a lot of your information on additional studies. I will just summarize for the group, and, please, when I am done, jump in if I have missed things

that people said.

I think you have heard that in future studies, we should have a better defined non-inferiority margin that is based on evidence. We think the primary endpoint, the FDA statistical reviewer made that comment this morning, and I think that weighed into some of the decisionmaking.

We think the truth standard, several people mentioned this, and I think that is worth, or maybe clarify the truth standard is a better way to talk about that.

The comparative performance, Dr. Tatum and others brought that up several times, probably worth some discussion in future studies.

Some aspect of randomization, I think would be informative for many of us. A larger safety database with perhaps a broader population a la Emil's concerns including patients with, for example, chronic kidney disease would be informative, other comorbidities, and finally, somehow to really nail down what is the incremental value of perfusion plus wall motion with contrast over just wall motion alone I think is a piece of information that the group would find valuable.

Those are the comments I summarize as you all went around the table. Did I miss things that people feel that

the sponsor should hear about so that they have some guidance going forward? Go ahead, Dr. Tatum.

DR. TATUM: Several times it came up we really need a better quantitative method that can be used for assessment particularly by the FDA so some kind of either scoring system that is segmental or something. Computerized would even be better if we could do that.

DR. HARRINGTON: Good comment.

Dr. Rieves or Dr. Temple, do you have final questions for the group?

DR. FLEMING: Maybe one more comment.

DR. HARRINGTON: I am sorry, Tom, go ahead.

DR. FLEMING: I thought that was a great summary. You hit many of the issues. There was one other issue and it is not necessarily a recommendation, but just an issue to be considered, and that is, is there an enriched population, is there the ability to identify a population in which benefit to risk relative to whatever the active comparator would be, SPECT or whatever, could be anticipated to be enhanced.

Of course, with a larger trial, that allows you to explore that, although that is treacherous, because you are probably fitting noise rather than signal. So I am asking

for more than that. I am asking for a theory to be developed if there is, in fact, the possibility to do so, that would give you a sense of where benefit to risk would be enhanced, and if so, could that then be addressed in either the design through eligibility or in the design by allowing more heterogeneity, but then prespecifying specific targeted subgroups.

DR. HARRINGTON: Bob, go ahead.

DR. TEMPLE: I guess my impression is--and again I want to remind everyone how little I know about this--is that if the contrasted test were just clearly considerably better than the no contrast test, then, the fact that it's an alternative to something involving radiation and something involving great difficulty in getting it done, would carry a lot of weight I think. But I would be interested in whether you think that, too.

DR. RIEVES: I think you are exactly right, it would. It's the totality of the data is what we are interested in.

DR. HARRINGTON: Dr. Rieves, do you have any final comment for the group or questions?

DR. RIEVES: No, it has been a great discussion. Review team, any special thoughts, any questions? We really

appreciate it. We have gotten a lot of insight.

DR. GOROVETS: No, it was very helpful, but no additional comments.

DR. HARRINGTON: I want to thank people for taking time out of a busy schedule and travel safely home. Thank you.

[Meeting adjourned at 4:15 p.m.]