UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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THURSDAY,
NOVEMBER 29, 2007

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The meeting convened at 8:00 a.m. at the Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, Maryland, CLYDE W. YANCY, M.D., Acting Panel Chairperson, presiding.

PANEL MEMBERS PRESENT:

CLYDE YANCY, M.D, Acting Chairperson
RICHARD L. PAGE, M.D., Voting Member
JOHN C. SOMBERG, M.D., Voting Member
EUGENE H. BLACKSTONE, M.D., Consultant
JEFFREY A. BRINKER, M.D., Consultant
JOHN W. HIRSHFELD, M.D., Consultant
VALLUVAN JEEVANANDAM, M.D., Consultant
NORMAN S. KATO, M.D., Consultant
WARREN K. LASKEY, M.D., Consultant
DOUGLAS MORRISON, M.D., Consultant
SHARON-LISE NORMAND, Ph.D., Consultant
MARCIA S. YAROSS, Ph.D., Industry Representative
KAREN R. RUE, Consumer Representative

FDA PARTICIPANTS:

JAMES P. SWINK, Panel Executive Secretary
BRAM ZUCKERMAN, M.D., Director, Division of Cardiovascular Devices
HEATHER L. AGLER, Ph.D., Division of Cardiovascular Devices
ASHLEY BOAM, Branch Chief, Interventional Cardiology Devices, Office of Device Evaluation
DANICA MARINAC-DABIC, M.D., Ph.D., Chief, Epidemiology Branch, Office of Surveillance and Biometrics
HESHA DUGGIRALA, Ph.D., Office of Surveillance and Biometrics
ROBERT P. FIORENTINO, M.D., M.P.H., Division of Cardiovascular Devices
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SPONSOR PARTICIPANTS:
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PETER FITZGERALD, M.D., Ph.D., Stanford University
GARY C. JOHNSON, Vice President, Regulatory Affairs, Clinical Research, and Quality Assurance, Abbott Vascular
MITCHELL W. KRUCOFF, M.D., Professor of Medicine/Cardiology, Duke University Medical Center, Director, Cardiovascular Devices Unit, Duke Clinical Research Institute
STUART POCOCK, Ph.D., Professor of Medical Statistics, London School of Hygiene and Tropical Medicine
MURTHY SIMHAMBHATLA, Ph.D., Vice President and General Manager, DES, Abbott Vascular
GREGG W. STONE, M.D., Professor of Medicine, Columbia University Medical Center, The Cardiovascular Research Foundation
KRISHNA SUDHIR, M.D., Ph.D., Director, Abbott Vascular
ROSEANN WHITE, Abbott Vascular

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Panel Vote.....507

Adjourn

P-R-O-C-E-E-D-I-N-G-S

(8:02 a.m.)

CALL TO ORDER

CHAIRPERSON YANCY: Good morning. My name is Clyde Yancy. I am Medical Director of the Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas and Chairperson of today's panel deliberations. I would like to call this meeting of the Circulatory System Devices Panel to order.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this panel during one of the open sessions, please provide your name to Ms. Anne Marie Williams at the registration table. If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to FDA, please arrange to do so with Ms. Williams.

I note for the record that the

voting members present constitute a quorum, as required by 21 CFR Part 14. I would also like to add that the panel participating in the meeting today has received training in FDA device law and regulations. If you have electronic pagers, PDAs, or cell phones, please place them on a silent mode so that they will be minimally intrusive.

Mr. Swink, the Executive Secretary for the Circulatory System Devices Panel, will make some introductory remarks.

CONFLICT OF INTEREST AND DEPUTIZATION TO VOTING MEMBER STATUS STATEMENTS

EXECUTIVE SECRETARY SWINK: I'll now read the conflict of interest statement. "The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

"With the exception of the industry representative, all members and consultants of

the panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

"The following information on the status of this panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC, section 208, and section 712 of the Federal Food, Drug, and Cosmetic Act are being provided to today's participants and to the public.

"FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws. Under 18 USC, section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for that 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 discussion of today's meetings, members and consultants of this panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 USC, section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, and royalties, and primary employment.

"Today's agenda involves the discussion of a pre-market approval

application for the XIENCE V Everolimus-Eluting Coronary Stent System sponsored by Abbott Vascular, a subsidiary of Abbott Laboratories.

"The system is indicated for improving coronary lumenal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions with a length of equal to 28 millimeters with reference vessel diameter of 2.5 to 4.25 millimeters.

"This is a particular matters meeting, during which specific matters related to the PMA will be discussed. Based on the agenda for today's meeting and all financial interest reported by the panel members and consultants, conflict of interest waivers have been issued in accordance with 18 USC, section 208(b)(3) to Drs. Jeffrey Brinker, John Somberg, and Clyde Yancy. A waiver has also been issued in accordance with section 712 of the FD&C Act for Dr. Yancy.

"Dr. Brinker's waiver involves his employer's interest in a sponsor study. His institute received less than $100,000 in funding. Dr. Brinker has no personal involvement in the study.

"Dr. Somberg's waiver entails his employer's interest in the sponsor's study. His institute received less than $100,000 in funding. Dr. Somberg has no personal involvement in the study.

"Dr. Yancy's waivers address personal consulting arrangements with a competing firm to the sponsor and an unaffected unit of the parent or of the competing firms. He receives an annual fee of less than $10,001 for these arrangements, which are unrelated to today's agenda.

"The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in waiver documents, which are posted on FDA's Web site at

www.fda.gov.

"Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Office, which is in room 6-30 of the Parklawn Building.

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

"Marcia S. Yaross, Ph.D., is serving as the industry representative, acting on behalf of all related industry, and employed by Biosense Webster, Incorporated, a Johnson and Johnson company.

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

their exclusion will be noted for the record.

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

I will now read the employment to temporary voting status. "Pursuant to the authority granted under the Medical Devices Advisory Committee charter of the Center for Devices and Radiological Health dated October 27th, 1990 and as amended August 18th, 2006, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting on November 29, 2007: John W. Hirshfeld, Valluvan Jeevanandam, Norman S. Kato, Warren K. Laskey, Douglas A. Morrison, Sharon-Lise Normand, Jeffrey A. Brinker, and Eugene H. Blackstone.

"For the record, these individuals are special government employees and/or consultants to the panel under the Medical

Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. In addition, I appoint Clyde W. Yancy, M.D., to act as temporary chairperson for the duration of this meeting."

This was signed by Daniel G. Schultz, Director for the Center for Devices and Radiological Health, and dated November 16th, 2007.

A few more general announcements. Transcripts of today's meeting will be available from Neal Gross and Company. Information on purchasing these videos of today's meeting can be found on a table outside of the meeting room.

Presenters to the panel who have not already done so should provide FDA with a hard copy of their remarks, including overheads. I would like to remind everyone that members of the public and the press are

not permitted around the panel area beyond the speakers' podium and are not permitted to talk with the consultants.

The press contact for today's meetings are Karen Riley and Peper Long. And I request that reporters wait to speak with FDA officials until after the panel meeting.

Thank you.

CHAIRPERSON YANCY: Good morning again. At this meeting, the panel will be making a recommendation to the Food and Drug Administration on the pre-market approval application, PMA, P070015 for the Abbott Vascular XIENCE V Everolimus-Eluting Coronary Stent System.

The XIENCE Coronary Stent System is indicated for improving coronary lumenal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions less than or equal to 28 millimeters with reference vessel diameter of 2.5 to 4.25 millimeters.

PANEL INTRODUCTIONS

CHAIRPERSON YANCY: Before we begin deliberations on this PMA under the auspices of that proposed indication that we just read, I would like to ask our panel members, who have generously given their time today, and other FDA staff seated at this table to introduce themselves.

We will start with Dr. Zuckerman. Please state your name, your area of expertise, your position, and affiliation. Thank you.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

MEMBER BRINKER: Hi. Jeff Brinker, interventional Cardiologist, professor of medicine and radiology, Johns Hopkins University.

MEMBER HIRSHFELD: I'm John Hirshfeld. I'm an interventional cardiologist at the University of Pennsylvania.

MEMBER KATO: Norman Kato, cardiothoracic surgery, private practice, Los Angeles, California.

MEMBER NORMAND: Hi. Sharon-Lise Normand, professor of health care policy and biostatistics, Harvard Medical School and Harvard School of Public Health.

MEMBER SOMBERG: Hi. John Somberg, professor of medicine and pharmacology, Rush University, Chicago, Illinois.

EXECUTIVE SECRETARY SWINK: James Swink, Executive Secretary.

MEMBER LASKEY: Warren Laskey. I'm Chief of Cardiology at the University of New Mexico.

MEMBER PAGE: Rick Page, cardiologist, electrophysiologist. I'm head of cardiology at the University of Washington in Seattle.

MEMBER BLACKSTONE: Eugene Blackstone, full-time clinical research, head clinical research, Department of Thoracic

Cardiovascular Surgery at Cleveland Clinic.

MEMBER JEEVANANDAM: Valluvan Jeevanandam. I'm the Chief of Cardiothoracic Surgery at the University of Chicago.

MEMBER MORRISON: Good morning. I'm Doug Morrison. I'm an interventional cardiologist in private practice.

MEMBER YAROSS: Marcia Yaross, Vice President, Clinical Quality, Regulatory, and Health Policy at Biosense Webster in Diamond Bar, California and industry representative to this panel.

MEMBER RUE: Karen Rue with Griswold Special Care. I'm from Lafayette, Louisiana. And I'm consumer representative.

CHAIRPERSON YANCY: Thank you.

We will now proceed with a brief post-approval studies update from the FDA.

POST-APPROVAL STUDIES UPDATE

DR. MARINAC-DABIC: Good morning, ladies and gentlemen, Mr. Chairman, Dr. Zuckerman, distinguished members of the panel.

My name is Danica Marinac-Dabic. I am the Chief of Epidemiology Branch at the Office of Surveillance and Biometrics. And this is the unit that is in charge of the review and oversight of the post-approval studies program.

During the past couple of years, the CDRH has made significant commitment of resources to enhance the post-approval studies program, with the major goals to enhance scientific vigor of post-approval studies, establish and maintain accountability for the post-approval study commitments, build post-approval study information management system, build bridges between the post-approval studies knowledge, and pre-market device evaluation, and also to increase the transparency with the public.

Today I would like to give you, our expert advisory panel, an update on the most recent developments in the CDRH post-approval studies program followed by a brief overview

of the current status of the ongoing cardiovascular post-approval studies.

The new CDRH post-approval studies program encompasses design, tracking, oversight, and review responsibilities for the studies mandated as a condition of approval. The program helps ensure that well-designed post-approval studies are conducted effectively, efficiently, and in the least burdensome manner.

During the last several years, CDRH fundamentally changed the processes by which we handle post-approval studies. The main changes had occurred in the oversight, tracking, and review of post-approval studies.

We also issued the guidance document to the FDA staff and the sponsors of medical devices. We also developed and released the post-approval studies Web page and initiated post-market updates to the panel. And, finally, we developed a comprehensive approach to engage other public

health partners in this post-approval studies program.

In 2005, the oversight responsibility was transferred from the Office of Device Evaluation and Office of In Vitro Diagnostics that historically handled the post-approval studies to the Office of Surveillance and Biometrics. And all the post-approval studies review functions were integrated into the medical device epidemiology and surveillance program within the OSB.

We developed an electronic tracking system for post-approval study commitments. This system represents CDRH commitment and determination to ensure that all post-market commitments are fulfilled.

This system is based on the post-approval study time lines incorporated into study protocols and agreed upon by the sponsor at the time of the approval. So all the reporting requirements can convey to the

sponsor -- and this is based on those deadlines -- the due date and the tracking systems are built.

Over the last two years, the epidemiology staff had been gradually integrated into PMA review teams. To advance the least burdensome approach, the epidemiology staff has committed significant resources towards early dialogue with manufacturers to give early input regarding our expectations on post-approval studies and also to help the sponsors by working interactively with them to develop well-designed post-approval studies during the pre-market phase.

Our gaol is to finalize by the time of the approval at least an outline of the post-approval study protocol. And very often we finalize the full study protocol at the time of the device approval. We also agree at that time on the study time lines. And, as I said, those study time lines are built into

the tracking system.

If the advisory panel is convened for that device, then the epidemiologists are part of the FDA presentation team. So we will hear a little bit about the post-approval studies and our assessment and what post-market considerations for post-approval study are. These are the pre-market changes that had occurred during the last couple of years.

As far as the post-market review practice and upon the device approval, the epidemiologist assumed the lead responsibility in the review of the interim and final reports, again the function that was historically residing in the Office of Device Evaluation. However, we keep the PMA review team informed and engaged. And although we serve as the lead reviewers on those submissions, we make sure that the information is being fed back to the pre-market.

The concept of epidemiology lead

and the post-market team availability is envisioned to couple the epidemiologic expertise in observational studies of the Office of Surveillance and Biometrics with the product-specific technical expertise from pre-market and post-market experts to facilitate knowledge sharing within the CDRH.

As I had mentioned, the CDRH had issued post-approval studies guidance documents late last year. And we did one minor revision in August of this year.

In addition to our internal tracking system, the CDRH had also launched the publicly available Web site with general information on all post-approval studies that were initiated post-2005, when the OSB received a lead in oversight responsibilities. And this link on the slide is a link to that. I hope that some of you may already have seen the information that we proudly present to the public.

I am not going to go into a lot of

detail about this study, the definitions, but just to illustrate that we have clear objective criteria by which we evaluate the reporting status of post-market commitments.

And these are our reporting status definitions that are available on the Web site and also in our guidance document. These are also the study status definitions that range from protocol-pending to protocol-overdue, study-pending, study-on-time, overdue, terminated, or completed.

We generally give the sponsor six months to finalize the protocol unless the protocol is approved at the time of the approval, after which we will mark the protocol overdue on the Web site.

We certainly view this -- and this is how it looks like. These are some of the elements that are available on the Web. And, as you can see, there is the information about the PMA number, applicant's name, device name.

We recently added the category of

the medical specialty and also the date the PMA approval is there. We extract directly from the approval order the brief description of the post-approval study protocol. And also we make sure that the public knows when the protocol was approved.

And then the final category is defined as a study status where we mark how well the sponsor has complied with the reporting requirements and how well the study is progressing.

We certainly view this as an opportunity, not only for this Web site to serve as an incentive for the sponsors to comply with their post-market study commitments but also our opportunity to celebrate and to advertise the best practices of the sponsors in their reporting requirements and the progress of the post-approval studies.

And, again, this is another important initiative that we started earlier

this year. We instituted two types of panel updates. One is going to be the general post-approval studies update that we just started presenting today.

This is the very first session that we are presenting this, but we also have the specific post-approval studies update that we started in January when we invited the sponsor of a specific medical device and had the opportunity to present to the panel the progress of their post-approval study followed by the update presentation. And we have some discussion time for the panel. Again, we started with this in January this year. And we have another panel update on a specific ob/gyn device later this year.

And, as I said, the post-approval studies program can be only successful if there is effective partnership between the FDA, industry, and other stakeholders. And toward that effect, we convened the first workshop on the post-approval studies. It was

co-sponsored by the FDA and Food and Drug Law Institute earlier this year, in May.

And we will continue dialogue with all of the stakeholders because we believe that without their support, the program will not be able to transform as quickly as we would like it to be.

Now, let's just examine quickly what happened with regard to the cardiovascular studies since 2005. Since 2005, there was a total of 21 cardiovascular PMAs and supplements approved with post-approval studies. Since some of the PMAs had more than one post-approval study commitment, there is a total of 27 post-approval studies initiated post-2005.

I would like also to say that, in addition to these studies, we also received 36 other pre-2005 studies that we just assumed the responsibility for in April this year. So we do not have all of the updates on all of them, but I hope that by next year in my

presentation, next presentations, I might be able to share some information about those studies as well.

These are just the cardiovascular devices post-approval studies, just a quick overview slide. Again, you can see that as far as the distribution of the study designs, most of the studies are observational. And this doesn't come as a surprise since the post-approval study is a distinctive post-market tool to be used to study continued safety and effectiveness of approved medical devices when used in a broader population under longer-term use outside of the highly controlled settings of pre-market clinical trials.

And, again, I'm very proud to present this slide that shows that all of our studies and all of our sponsors are compliant with regard to the reporting status. You can see that five studies already for which we received the final report. There are 18

studies for which we received the report on time. And for the remaining four studies, a report was received after the due date, but we have it in house. And we mark it "Overdue. Received" on our Web site.

As far as the progress of the studies, again, the vast majority of the studies are on time. We have some studies that are completed, as you can see. And also there are protocol-pending studies, mostly those that were approved in 2007, for which we did not finalize the post-approval study protocol yet. And there are also some study-pending, which means that protocol was approved but the study had not been initiated yet.

As far as how we present to the panel, really, this slide clearly shows that since 2005, there has been an increased number of post-approval studies presentations to the panel. I'm talking here about pre-market panel presentations that range from one out of

9 in 2005 to 6 out of 6 in 2007. This includes today's and tomorrow's presentations. And you will here Dr. Duggirala presenting today on behalf of the Epidemiology Branch.

And this is our vision. To conclude, I just would like to say that, you know, we would like to see that all important post-market questions are addressed by post-approval studies, that studies are realistic and founded on good science.

We would like also studies to be timely, accurate, and provide useful information, based on which we might base some of the regulatory actions if needed.

Also, we certainly would like to have reports that are clearly identified and effectively track. And we are committed to keep our stakeholders apprised.

I cannot stress enough how important it is for us to maintain and cultivate our cooperation with our pre-market colleagues because they are the technical

experts for the product. And we bring the epidemiologic expertise in the study design.

If we proactively address all of these issues in a timely fashion during pre-market, we predict that we will have less enforcement options.

Just for your information, this is the Epidemiology Branch. And the current staff that is involved in cardiovascular devices are marked in blue. You will see there are three epidemiologists, one team leader, a branch chief, and the three project managers that handle post-approval study commitments with regard to cardiovascular devices.

Again, the post-approval studies transformation, vision, and goals present high expectations of us and of the stakeholders. Heightened expectations often bring heightened concerns about burdens, workload, perceived fairness, and added value. It is up to us and our stakeholder to discuss them openly,

responsibly, and collaboratively.

We understand the concerns, but we have to put them into larger contexts of asking and answering the right post-market questions. We welcome an exchange of ideas on diverse methodologies that may be cost-effective, innovative, and productive. We value all analytical approaches and data sources that will give us high-quality answers to the right post-market questions.

Thank you.

CHAIRPERSON YANCY: Thank you very much. Obviously this information is important as increasingly we rely upon the repository of information from post-marketing studies to help us understand the impact of the technologies that we are considering.

Are there any questions for the speaker that you just heard?

(No response.)

CHAIRPERSON YANCY: Great.

1ST OPEN PUBLIC HEARING

CHAIRPERSON YANCY: We will now proceed with the open public hearing portion of this meeting. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making.

To ensure such transparency of the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation.

For this reason, FDA encourages you, the open public hearing, our industry speaker, at the beginning of your written and oral statements to advise the Committee of any financial relationship that you may have with the sponsor; its product; and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

There is no one that has signed up for this session. However, if there is anyone in the audience who would like to speak, we would appreciate hearing from you.

(No response.)

CHAIRPERSON YANCY: Since no one is coming forward, we will proceed with today's agenda. Please note there will be a second opportunity as there is another open public session in the afternoon.

We will now proceed to the sponsor presentation. Whomever speaks first, if you can help me with the nomenclature, that would be great, the XIENCE V Everolimus-Eluting Coronary Stent System.

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

We will begin with the sponsor presentation. Thank you.

MR. JOHNSON: Thank you, Mr. Chairman.

SPONSOR PRESENTATION

MR. JOHNSON: The proper name is the XIENCE V Everolimus-Eluting Coronary Stent.

CHAIRPERSON YANCY: Thank you.

MR. JOHNSON: Sure. Good morning. My name is Gary Johnson. I am Vice President of Regulatory Affairs, Clinical Research, and Quality Assurance for Abbott Vascular.

And on behalf of the employees of Abbott Vascular, our physician investigators, and the patients enrolled in our clinical studies, I would like to thank the panel

members and the Food and Drug Administration for this opportunity to present the XIENCE V Everolimus-Eluting Coronary Stent program.

During today's presentation, we will cover a number of topics. First, I will do a brief introduction. Then Dr. Murthy Simhambhatla from Abbott will review XIENCE V design goals.

Dr. Leslie Coleman from Abbott will summarize our preclinical animal studies. Then Dr. Gregg Stone from Columbia University, who is the PI of the SPIRIT III clinical trial, will review the results of three randomized clinical trials: SPIRIT FIRST, SPIRIT II, and SPIRIT III.

Dr. Stone will be followed by Dr. Mitchell Krucoff from Duke University, who is the co-PI for XIENCE V U.S.A. post-approval clinical study. He will review a combined safety analysis and our integrated post-approval clinical strategy. Finally, Dr. Krishna Sudhir from Abbott will close and

summarize our presentation today.

In addition to the presenters, we also have several consultants with us today: Professor Stuart Pocock from the London School of Hygiene and Tropical Medicine; Dr. Alexandra Lansky from CRF, who served as the angiographic core laboratory; Dr. Peter Fitzgerald from Stanford University, who served as the IVUS core laboratory; and Dr. Renu Virmani from CVPath International. We also have Mr. Ron Van Valen with us from Novartis today.

The purpose of our presentation today is fourfold. First, we want to review XIENCE V design goals and provide a detailed understanding of the major design characteristics and why they were selected.

Second, we want to review the breadth and depth of our preclinical animal studies and vessel healing evaluations. Third, we want to demonstrate the XIENCE V clinical data in its totality establishes a

reasonable assurance of safety and effectiveness based on valid scientific evidence.

And, finally, we want to review the XIENCE V post-approval clinical strategy that augments our pre-approval clinical data and is effectively powered to evaluate low-frequency events.

We are seeking an indication for XIENCE V which is consistent with other drug-eluting stents. The proposed indication is for improving coronary lumenal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions with lengths less than or equal to 28 millimeters and with reference vessel diameters of 2.5 millimeters to 4.25 millimeters.

We are seeking approval for five diameters of stents, 2.5, 2.75, 3.0, 3.5, and 4.0 millimeters. These diameter stents will be available in six lengths: 8, 12, 15, 18, 23, and 28 millimeters. These diameters and

lengths will be available in both a rapid exchange and over the wire delivery system. All stem sizes have consistent drug dose density of 100 micrograms per centimeter2.

There are three major design components of XIENCE V coronary stent system: the stents and delivery system, which are based on the approved Multi-Link VISION and Multi-Link MINI VISION coronary stent systems; the drug matrix, which is a fluorinated copolymer that has previously been approved on other vascular application devices; and the drug, everolimus, which is manufactured by Novartis Corporation.

Everolimus under the brand name Certican has received two approvable letters from FDA for organ transplant indication. Novartis has also granted FDA rights to reference their IND and NDA to support XIENCE V PMA review. XIENCE V stent has received regulatory approval and is currently marketed in 64 countries outside of the United States.

To put our regulatory and clinical activities into perspective, I wanted to provide a brief regulatory history. Abbott Vascular worked collaboratively with FDA in late 2004 and early 2005 to develop a SPIRIT III pivotal clinical trial design.

At the time of initiation at the SPIRIT III clinical trial, in May of 2005, FDA agreed that a trial design and the supporting clinical data from the XIENCE V clinical program would provide adequate assurance of safety and effectiveness for the XIENCE V system.

During that process, FDA reviewed the everolimus safety, pharmacology, toxicology, and ADME studies and identified no concerns. FDA considers everolimus to be a well-characterized and studied drug; therefore, not a new molecular entity, or NME.

Since everolimus was not an NME, the requirement for 2,000 treated patients in clinical studies typically required for a

drug-eluting stent with an NME did not apply to the XIENCE V program.

The XIENCE V's clinical program will be overviewed in detail today. It is a comprehensive, integrated pre-approval and post-approval program that includes over 16,000 patients. It includes four pre-approval clinical studies, for which you will be presented today, and six ongoing or planned clinical studies, which will be reviewed in more detail later in the presentation.

In summary, the pre-approval clinical studies in their totality have demonstrated the following. All the trials have met their pre-specified primary and powered major secondary endpoints. They have demonstrated non-inferiority and superiority in late loss or bare metal stent. They have demonstrated non-inferiority and superiority in late loss over an approved drug-eluting stent. They have also shown non-inferiority

in target vessel failure compared to the TAXUS drug-eluting stent. And, additionally, all of these trials will have long-term follow-up after five years.

The ongoing and planned clinical studies in their totality are designed to include real-world patients, their power to effectively detect low-frequency events of .5 percent, their design to support label expansion to more complex patient subsets. And these studies will also have long-term follow-up after five years.

In addition to our planned analysis, in response to the panel's comments in December, we have also performed a safety subset analysis of all available two-year data from SPIRIT II and SPIRIT III.

Results of this analysis are consistent with the one-year data from SPIRIT II and III as well as the three-year data from SPIRIT FIRST. The results of this will be presented in more detail later in the

presentation.

So, with that brief introduction, I would now like to turn the podium to Dr. Murthy Simhambhatla to review the XIENCE V design.

DR. SIMHAMBHATLA: Good morning. Work on the XIENCE V system began at a time when the first iteration of drug-eluting stents were already on the international market. It was our design objective to develop a second generation drug-eluting stent by integrating well-categorized, well-tested, and proven components into a system capable of assuring a high level of safety, effectiveness, and deliverability.

We made a decision early in the design process to use the Multi-Link VISION and MINI VISION systems as the platform for XIENCE V. The Multi-Link VISION and MINI VISION stents are the number one selling bare metal stents globally and in the United States. This is a proven and well-tested

system.

The Multi-Link VISION stent is flexible and has thin struts, characteristics that we believe are particularly important in a DES era, by assuring a high level of conformability to the coronary vasculature and potentially a greater extent of endothelial cell coverage. The Multi-Link VISION stent is also proven to be highly deliverable, a characteristic that we wish to preserve, even after putting a drug coating on the stent.

A second design objective was to develop a thin, biocompatible drug coating. We felt that a thin coating would minimize the total cross-section of the coated stent strut and that by doing so, you could not only potentially facilitate the extent of endothelialization but also minimize the potential for flow impairment of side branches traversed by the stent struts.

In order to develop a thin biocompatible drug coating, the system had to

be effective at low drug loading. The polymer had to be stable. Particularly in the local in vivo milieu, the coating had to be uniform and conformal to minimize the potential for plated adhesion to the stent surface. And the drug release had to be controlled and compete over time in order to reduce the potential for persistent vascular effects related to the drug. And, finally, the system in totality had to exhibit good hemocompatibility and vascular compatibility.

Shown here are the four components of the XIENCE V system, as previously described. The platform is a Multi-Link VISION stent and stent delivery system. The drug is everolimus. And the drug-carrying matrix is a fluorinated copolymer. I will now discuss each of these components in turn relative to our design objectives.

The Multi-Link VISION stent, which is the platform for XIENCE V, is based on cobalt chromium technology. This technology

allows us to develop thinner struts without compromising radial opacity or radial strength. The thin struts also allow for good flexibility and conformability and in combination with the delivery system result in a low system profile. And, finally, the delivery system itself has been optimized and minimized vessel injury outside a stented segment by reducing the amount of balloon overhang outside the stent.

Shown here are in vitro flow data by Julio Palmaz and his colleagues. These data indicate that the extent of endothelial coverage is related to the barrier to flow. In particular, these data indicate that the extent of endothelial coverage is compromised for obstacle thicknesses exceeding 100 microns. Based on this result, this group postulated that endothelial coverage may be imputed for thicker thin struts.

It is in this context that we believe that the progression toward thinner

thin struts is important. Shown on the left are the scanning electron microscope cross-sections for the first iteration of drug-eluting stents, for which the strut thickness is significantly greater than 100 microns. Shown on the right is the cross-section for XIENCE V stent with a strut thickness of 81 microns.

Also of note is the dark outline of the polymer coating around the bright stent struts. Shown on the left are the outlines for the first iteration of regulating stents where the coating thickness varies from 13 to 20 microns. The coating thickness for the XIENCE V stent, on the other hand, is approximately eight microns.

We tested the deliverability of the XIENCE V system extensively in our synthetic coronary artery models that simulated tortuosity and simulated lesions. In these three-dimensional models, we demonstrated with the deliverability of the XIENCE V system for

the smallest and largest stent sizes were equivalent to the MINI VISION and VISION bare metal stents, respectively.

The drug everolimus is a proliferation signal inhibitor that acts in the late G1 phase of the cell cycle to inhibit cellular proliferation in a reversible manner. Everolimus belongs to the same family of synthetic macrolide compounds as sirolimus. And both these drugs have IC50 values in a similar range for the inhibition of smooth muscle cell proliferation.

We studied a wide range of drug doses in porcine coronary arteries from 100 micrograms per centimeter2 to 800 micrograms per centimeter2. We observed sufficient drug effect at 100 micrograms per square centimeter with no evidence of toxicity of medial necrosis at 800 micrograms per centimeter2.

The lowest effective dose of 100 micrograms per centimeter2 was there for selective clinical development. With this

dose, we had an eight-fold safety margin given the absence of toxicity of medial necrosis with the 800 microgram per centimeter2 dose in our porcine models.

The amount of drug on the XIENCE V stent is significantly reduced relative to other limus-eluting stents. In particular, the amount of drug in the XIENCE V stent is reduced by 41 percent relative to Cypher. This is notable given that the IC50 values for both everolimus and serolimus are in a similar range for the inhibition of full muscle cell proliferation.

We, therefore, achieved a key design objective of effectiveness with reduced drug loading. And this will be demonstrated later in the clinical presentation.

The XIENCE V polymer selection and coating design were optimized for the controlled elution of everolimus over time and for the complete release of drug over time. Approximately 80 percent of the drug is

released by 30 days. And substantially all of the drug is eluted by 820 days.

XIENCE V coating design comprises a primer and matrix system. In the expanded view on the right, the stent strut is shown in white. The drug-carrying fluoropolymer matrix is shown in blue. And a thin primer layer is shown in red. It is the function of the primer to ensure good adhesion between the drug coating and the thin strut.

This system does not have a top coat. In our experience, this system allows for better manufacturing control and drug release than a top coat system for such thin coatings. This system also allowed us to optimize the adhesion of the coating to the stent strut while minimizing unwanted adhesions to the delivery balloon.

The drug-carrying matrix is an ultra pure copolymer comprised of vinylidene fluoride and hexafluoropropylene monomers. This polymer has been used in approved

cardiovascular, neurologic, and ophthalmic sutures.

The ratio of the vinylidene fluoride and hexafluoropropylene allows us to optimize the coating elasticity in order to prevent the coating from cracking upon stent expansion and coating toughness to ensure the durability of the coating during the act of stent delivery to the target lesion.

This polymer is one of the most stable entities chemically because of its durable carbon carbon backbone and the covalent carbon fluorene bonds. And this stability confers to this polymer a high degree of stability in vivo as well as biocompatibility. And, finally, this polymer has good hemocompatibility.

Shown here are micrographs of the XIENCE V system, illustrating its coating integrity. The coating was designed to minimize webbing, bridging, and strut-to-strut contact in the crimped state. It was also

designed to maintain the coating integrity after simulated use, stent expansion, and fatigue testing.

A key design objective for the XIENCE V system was to assure a level of hemocompatibility that was at least equivalent to the bare metal VISION platform. We tested hemocompatibility in accordance to ISO10-993 and showed in an un-hecronized ex vivo shunt study that the amount of polymers accumulated on the XIENCE V stent was less than that on the bare metal VISION stent. We, therefore, surpassed our objective of ensuring equivalent hemocompatibility to the bare metal stent.

We also studied the vascular response of the XIENCE V system and XIENCE V copolymer extensively in porcine models and demonstrated that all the way out to two years, the polymer response is equivalent to the VISION bare metal stent. We have also studied the vascular response of three times the amount of polymer on the stent and have

found the response equivalent to the bare metal vision stent.

So, in summary, the XIENCE V system is built on the proven VISION stent and stent delivery system. The VISION stent is flexible and has thin struts. It is also a deliverable stent.

We have also developed a thin, biocompatible drug coating that is effective at low drug loading. The polymer is stable. The coating is uniform and conformal around the stent struts.

The drug release is well-controlled and complete over time. And, finally, the system exhibits good hemocompatibility and vascular compatibility.

I will now turn over the podium to my preclinical colleague, Dr. Leslie Coleman.

DR. COLEMAN: Good morning. I would like to present to you an overview of the XIENCE V preclinical program. The clinical program consisted of an extensive

assessment of the biocompatibility of the XIENCE V system and assessment and characterization of the pharmacokinetics of XIENCE V, a comprehensive safety assessment, and an assessment of the endothelial cell response to XIENCE V.

The biocompatibility of the XIENCE V system was demonstrated through numerous in vitro and in vivo studies. All studies were conducted in compliance with applicable guidelines, and all studies passed.

The pharmacokinetics of the XIENCE V was characterized in a porcine coronary artery model. And, as you can see in the graph, the graph on the left demonstrates that the XIENCE V released everolimus in a consistent and controlled manner, with complete drug release by 120 days. And we believe that it's very important to have complete release of the drug from the system in order to allow for vessel healing.

These release kinetics translate

into effective arterial delivery, as you can see on the right graph, where we have controlled release of everolimus to the target tissue or the stented artery over time. This has allowed for the presence of everolimus during the first several months following stent implantation consistent with the peak cellular phases of neointimal hyperplasia.

The clinical pharmacokinetics of XIENCE V were studied in several substudies within the SPIRIT II and SPIRIT III clinical trials.

Results from all P-K substudies were consistent across geographies and showed limited systemic exposure of everolimus up to a total dose of 588 micrograms. And at all times the amount of systemic everolimus correlated with the number of stents implanted into the patient.

Importantly, systemic exposure to everolimus was well below the minimal therapeutic blood level of three nanograms per

ml that must be maintained at a steady state when everolimus is delivered orally to prevent organ transplant rejection.

We conducted a comprehensive safety assessment of the XIENCE V system. This entailed 35 animal studies. We evaluated the system in two species. And we have data on the XIENCE V system extending from 28 days out to 2 years.

We chose to evaluate the XIENCE V in two animal species in order to account for any species-specific responses. And we evaluated the XIENCE V system in numerous configurations, including single stents, which we did evaluate in two species, again with data out to two years. We evaluated the response to overlapping XIENCE V stents, also in two species.

And then, as mentioned previously, we conducted studies to understand fully the safety margin of the system by evaluating a maximum dose system that has eight times the

amount of everolimus on the system as well as polymer-only systems, ranging from 1X polymer out to three times the amount of polymer on the system. And we have evaluated these polymer systems out to two years.

From a safety perspective, our goal was to establish effective drug delivery with rapid vessel healing. We defined vessel healing by the following four criteria that we should have a smooth muscle cell rich neointima incorporating all stent struts as rapidly as possible. There should be minimal persistent fibrin, minimal long-term inflammation, and a rapidly endothelialized lumen.

These are representative histologic images of XIENCE V as compared to a VISION bare metal stent at numerous time points from 28 days out to 2 years. The bar graph below demonstrates the inflammatory scores over time, again comparing XIENCE V to VISION metallic stents from 28 days out to 2 years.

Inflammation is scored on a scale of zero to four with a score of zero to one being considered background in this particular model, in the porcine model.

As you can see, the neointimal response to XIENCE was similar to a VISION metallic stent. And there is minimal long-term inflammation. From 180 days out to one year and then to 2 years, the neointimal response is stable.

At higher magnification, one can appreciate the cellular composition of the vessel wall in response to a XIENCE implant. The bar graph demonstrates fibrin over time. And, as we would expect, there is peri-strut fibrin at 28 days consistent with peak drug elution. But as the system elutes the drug, there is minimal to no fibrin consistent with elution of the drug and no longer drug being detected in the tissue. Again, the neointimal response is stable from six months out to two years, consistent with a healed vessel.

Endothelialization in the porcine model was complete at all time points evaluated. To summarize the safety response, during the active phase of drug elution, we did observe that there was a fully endothelialized lumen, there was neointimal coverage of all stent struts with peri-strut fibrin, consistent with drug elution, inflammation comparable to VISION metallic stent and no mineralization, no medial necrosis, demonstrating the overall lack of vessel toxicity.

At 180 days and beyond, the phase at which there is no longer a drug detected in the tissue, the vessels were again fully endothelialized and largely in a quiescent, healed state. And so these findings we believe are consistent with vessel healing.

So, to conclude the safety assessment, we have demonstrated safety in two animal models with data out to two years. We have met the goal of our DES safety program by

demonstrating these parameters, that there is a neointima incorporating all stent struts, minimal fibrin, minimal long-term inflammation, and a rapidly endothelialized lumen, consistent with vessel healing.

We have also been very interested in understanding the endothelial cell response to a XIENCE V system. As such, we have conducted several novel research studies in collaboration with Dr. Renu Virmani in order to understand the endothelial cell response to a XIENCE V stent in comparison to a metallic VISION stent as well as other commercially available drug-eluting stents.

All of these studies were conducted in a rabbit model, which allows us to really differentiate the endothelial response to various stent platforms.

And as part of these studies, we conducted an assessment, an in-depth assessment, of the endothelial cell coverage by qualitative and quantitative means through

scanning electron micrograph evaluation. We also looked for the presence of specific endothelial cell markers through both confocal microscopy and molecular evaluation.

This I chose representative scanning electron micrograph of the lumenal surface of stents that have been cut longitudinally following 14 days in a rapid vessel, iliac vessel.

And, as you can see, if we look at the XIENCE V, we have good endothelial cell coverage of the stent surface. And it's somewhat similar in coverage as the VISION metallic stent. And there is greater coverage as compared to the other commercially available drug-eluting stents.

We quantified the endothelial cell coverage. And the data is demonstrated here. And in order to assess coverage, we looked both above the stent struts as well as in between stent struts.

And when we look over the stent

struts, you can see that there is significantly greater coverage with the XIENCE V stent as compared to other commercially available drug-eluting stents. And the XIENCE V stent has similar coverage to a VISION metallic stent.

In order to understand endothelial cell integrity and functionality, we looked for the presence of two specific biomarkers. We looked for expression of platelet endothelial cell adhesion molecule, which is a membrane glycoprotein that is constitutively expressed by endothelial cells. And we also looked for production of vascular endothelial growth factor, which we believe should be down-regulated with complete endothelialization.

The expression of PECAM is demonstrated here. This was evaluated by immunohistochemical means. And the chemical expression is shown here. And, consistent with the endothelial data that I just showed,

there is significantly greater expression of PECAM on the part of XIENCE as compared to other drug-eluting stents.

In terms of VEGF production, we looked for both protein levels as well as gene expression. And the data shown here are from two different sets of experiments. And the data is consistent with one another.

We do see that the levels of VEGF expression for XIENCE are similar to a VISION metallic stent and less than the other drug-eluting stents. And we believe this is consistent with endothelialization.

So, to summarize, XIENCE V demonstrated rapid re-endothelialization compared to other drug-eluting stents. And XIENCE V demonstrated enhanced endothelial cell function. And, to conclude, we do believe that rapid endothelial cell coverage and function are consistent with vessel healing.

I would now like to introduce Dr.

Gregg Stone, who will speak to you about the SPIRIT clinical program.

DR. STONE: Thank you, Leslie.

Good morning. My name is Gregg Stone. I'm an interventional cardiologist at Columbia University Medical Center. And I am here to discuss the preclinical investigational pathway that has been undertaken for the SPIRIT program of the XIENCE V stent.

I have also represented in the past Boston Scientific as the principal investigator of the pivotal TAXUS IV trial that led to approval of that device in the United States and have also been the principal investigator of the United States TAXUS 5 and TAXUS 5 ISR trials.

I currently receive research support from both Abbott Vascular and from Boston Scientific, which are the manufacturers of the two stents that I will be discussing in this presentation and which were pitted

against each other in the SPIRIT II and SPIRIT III trials. And I also do work with other device companies that manufacture devices that I won't be discussing today.

This is the second time of four you are going to see this slide describing the 16,000 patients that will be enrolled, have been rolled, and will be enrolled in the pre-approval and the ongoing and planned clinical studies for the XIENCE V stent.

And I am going to be specifically describing the results of four different studies. These of these were randomized trials: the SPIRIT FIRST trial, the SPIRIT II, and SPIRIT III, and then the SPIRIT III 4.0-millimeter stent registry arm, which was part of the SPIRIT III randomized trial.

So if we first look at the SPIRIT FIRST trial, this was the first in-human use of the XIENCE V stent. This trial was performed at a time when one could still compare a drug-eluting stent versus a bare

metal stent. And this compared the XIENCE V stent versus the otherwise similar bare metal VISION stent.

This was a relatively simple randomized controlled trial in single de novo lesions. It was performed in 60 patients in 9 sites in Europe. Again, relatively short focal lesions with a reference vessel diameter of three millimeters and a lesion length of up to 12 millimeters were enrolled in this study and then randomized one to one to either the XIENCE V Everolimus-Eluting Stent versus an otherwise identical multi-length VISION bare metal stent.

Again, this was prospective. This was single blind and randomized. Angiographic and intravascular ultrasound was performed or intended to be performed at six months and one year in all patients with clinical follow-up performed at regular intervals up to five years.

I will be emphasizing the primary

and the major secondary endpoints for these studies. The primary endpoint was angiographic in-stent late loss at 180 days, with a major secondary endpoint of intravascular ultrasound-determined percent volume obstruction; that is, tissue growth within the stent.

At 180 days, this trial, of course, was underpowered to look at clinical events. Both of these endpoints looking at the degree of neointimal growth within the stents over time were powered for superiority. That is, the XIENCE V stent had to be better than the bare metal stent. And the principal investigator was Patrick Serruys from the Thorax Center.

What I will be doing for all of the data that I will be showing is I will be only showing you p-values when it was either a primary endpoint or a powered secondary endpoint. Otherwise we will be displaying the results as either differences or relative

risks with confidence intervals, which should be considered secondary analyses or exploratory.

Here you can see the primary endpoint of this trial, SPIRIT FIRST drug-eluting stent, versus bare metal stent looking at in-stent late loss. That is, from the time of the immediate post-procedure to six months later, how much tissue actually accumulated at the worst spot within the stent as determined by quantitative coronary angiography?

And you can see there was a marked reduction in the amount of late loss from a mean of 0.85 millimeters with the VISION bare metal stent to 0.1 millimeter with the XIENCE V stent, an 88 percent reduction, which was highly statistically significant.

When one looks at the major secondary endpoint of percent volume obstruction, this now looks with a more sensitive intravascular ultrasound method,

looking at the percentage of tissue growth now on a volumetric basis within the stent margins that were occluding the illumene, if you will.

You can see that, similarly, there was a marked reduction in the percent volume obstruction from almost 30 percent of the stent being filled with tissue with the VISION bare metal stent. And this was reduced 72 percent to an 8 percent volume obstruction with the XIENCE V stent, again highly statistically significant.

Now, I did mention that this trial was underpowered for clinical events, but, of course, these patients were followed clinically. And we have data now out to three years on the patients that were enrolled in the XIENCE V stent versus the VISION stent in SPIRIT FIRST.

You can see that, importantly, there were no cardiac deaths in either arm. Other events were relatively low in frequency, especially in the XIENCE V arm, in these

patients followed out to three years.

I will point out that there were trends towards reduced target lesion revascularization. This is the purest clinical surrogate of drug-eluting stent efficacy. This means ischemia leading to a repeat procedure due to restenosis, either at the lesion itself or at the margins out five millimeters from the lesion; the composite endpoints of major adverse cardiovascular events, which I will describe further later; and target vessel failure, also tended to be reduced with the XIENCE V stent, but, again, we weren't powered to show differences for this trial. And, perhaps most importantly, there were no cases of stent thrombosis out to three years in this small study with either the XIENCE V stent or the VISION bare metal stent.

So the conclusions from the SPIRIT FIRST trial were that this trial met both its pre-specified primary and major secondary

endpoints, demonstrating superiority of the XIENCE V stent compared to the bare metal multi-link VISION stent in reducing late loss and percent volume obstruction.

We now entered a phase in clinical development where most physicians were using drug-eluting stents for the majority of patients with coronary artery disease. And it no longer became feasible to compare drug-eluting stents to bare metal stents.

So now we will be looking at studies comparing the XIENCE V stent to the otherwise widely utilized paclitaxel-eluting TAXUS stent. So this is DES versus DES. And the first such study, which was designed in Europe, was the SPIRIT II randomized controlled trial.

This was a more challenging study in which high-risk patients were enrolled. Patients were enrolled with up to two de novo lesions, rather than one, with a maximum of one lesion per epicardial vessel. And the

lesions were also more challenging. They could be in smaller vessels or larger vessels, ranging from 2.5 to 4.25 millimeters and, probably even more importantly, much longer, up to 28 millimeters in length.

A total of 300 patients were enrolled in this trial at 28 sites outside the United States. And patients were randomized three to one to either the XIENCE V Everolimus-Eluting Stent or the TAXUS Paclitaxel-Eluting Stent. So this was also a prospective, single-blind, randomized trial.

Angiographic and intravascular ultrasound follow-up was performed or intended to be performed at 180 days in all patients and 2 years in approximately half the patients. Clinical follow-up was performed at regular intervals up to five years.

Now, the primary endpoint for this 300-patient trial, in which a DES was compared to a DES, was angiographic in-stent late loss at 180 days. And this trial was powered to

demonstrate the XIENCE V compared to TAXUS was first not inferior and then if it met that endpoint to test whether or not it was superior in terms of reducing in-stent late loss.

The powered secondary endpoint was angiographic in-segment late loss at 180 days. And this was powered for non-inferiority. And Patrick Serruys at the Thorax Center was again the principal investigator.

This shows now for the first primary endpoint the angiographic patient flow at 6 months of 300 randomized patients. Six-month angiographic follow-up was completed in 92 percent. And Europe is very good with angiographic follow-up.

And if we look at the primary endpoint of in-stent late loss, one can see that not only was the XIENCE V stent shown to be non-inferior to the TAXUS stent in terms of late loss, but it was also highly statistically superior with a marked 69

percent reduction in late loss, from 0.36 millimeters with TAXUS to 0.11 millimeters with XIENCE V.

And I will just remind you this compares to 0.8 to 1 millimeters with bare metal stents. So this expanded scale, you still see this marked reduction in late loss with XIENCE V compared to the otherwise leading TAXUS stent.

When one looks at in-segment late loss, this now looks not only at the biologic efficacy of the drug-eluting stent device; that is, what is going on within the margins of the stent; that is, in-stent late loss, but also takes into account the five-millimeter edges. And this can look at balloon stent mismatch issues, drug diffusion effects, and other such effects. And this is more the whole lesion itself.

And you can see even considering in-segment late loss, while the trial was only powered for non-inferiority, you can see there

tended to be a 53 percent reduction in in-segment late loss, from 0.15 millimeters with TAXUS to 0.7 millimeters with the XIENCE V stent.

Looking at the intravascular ultrasound measures, again, of percent volume obstruction, this is the most commonly relied upon IVUS measure. You can see that there is a statistically significant 66 percent reduction in volume obstruction from 7.4 percent with TAXUS -- and, again, this usually compares to about 30 percent with the bare metal stent -- down to 2.5 percent with the XIENCE V stent. So the DES is doing what it is supposed to be doing in terms of inhibiting tissue regrowth.

Now, if we look at the clinical outcomes, at one year -- and this trial, again, was not powered for clinical endpoints, but, of course, it's important to look at how the patients did -- you can see the 12-month clinical follow-up, which is the data that we

currently have from this trial and has been completed in 99.3 percent of the patients.

First, looking at safety endpoints, stent thrombosis has been adjudicated by both the pre-specified per-protocol definition and then by now the widely used Academic Research Consortium definitions; that is, definite or probable ARC stent thrombosis. And one can see that the rates of stent thrombosis out to one year were low with the TAXUS stent -- that's the red -- and also very low with the XIENCE V stent.

If one looks at cardiac death, there was zero percent cardiac death at one year with the XIENCE V stent versus 1.3 percent with the TAXUS stent. There was a numerical trend towards less myocardial infarctions with XIENCE V compared to TAXUS. And there was a borderline statistically significant reduction in target lesion revascularization.

Again, this is clinical restenosis.

These are real procedures due to recurrent ischemia, recurrent angina, recurrent symptoms requiring rehospitalization for repeat either angioplasty or surgery. So 6.6 percent with TAXUS and 1.8 percent with XIENCE.

As a result, when we start looking at composite measures of safety and efficacy -- and I am not a big fan of these composite measures because you can obviously have the components going different directions. So it's important to look at the components.

But the first composite measure that we often look at is MACE. And this is cardiac death, myocardial infarction, or target lesion revascularization which is relatively specific to the stent itself.

And here you can see that for the first time in a randomized trial, we actually saw a significant reduction in MACE with one drug-eluting stent versus another from 9.2 percent, which is a relatively low number, actually, with the TAXUS stent for this type

of lesion and patient mixed, but reduced to 2.7 percent with the XIENCE V stent.

Now, the next component that we can look at of what can happen in terms of repeat vascularization is what we call target vessel revascularization remote; that is, remote from the target lesion. This could be new lesions that occur in the side branches, from guide catheter trauma, from a new distal lesion, progression of disease.

We wouldn't expect a drug-eluting stent to either prevent this or to improve upon it. And you can see these two drug-eluting stents had similar rates of TVR remote.

So if we look at the second composite measure of target vessel failure, which is somewhat more of a general measure now looking at cardiac death, MI, TLR, or TVR remote. You can see, of course, this will always dilute out a little bit of the ability to see the difference between two devices.

And that's what we see here.

Nonetheless, you could see a trend towards a 51 percent reduction in target vessel failure with XIENCE compared to TAXUS, 9.2 versus 4.5 percent.

Thus, the conclusions from SPIRIT II are that the SPIRIT II trial met its pre-specified primary endpoint, demonstrating superiority of the XIENCE V stent compared to the TAXUS stent in reducing in-stent angiographic late loss.

So this brings us now to the pivotal United States-based SPIRIT III randomized controlled trial, which was designed in concert with FDA to support this pre-market approval application of the XIENCE V stent versus the TAXUS stent, again DES versus DES. And, as you'll see, this trial was designed in very similar fashion to SPIRIT II.

So, once again, we took patients with up to two de novo lesions with a maximum

of one lesion per epicardial vessel, with very similar reference vessel diameters and lesion lengths, as in SPIRIT II, an RVD of 2.5 to 3.75 millimeters and lesion lengths up to 28 millimeters. This actually matches the labeling of the TAXUS stent for use in the United States.

And this was a much larger study, randomizing 1,002 patients at 65 United States sites. Patients were randomized two to one to the XIENCE V stent compared to the TAXUS stent.

This again was a prospective single-blind, randomized trial. Angiographic and intravascular ultrasound was performed at eight months in pre-specified subsets of patients. And I'll describe this for you coming up.

Clinical follow-up was intended to five years at regular intervals in all patients. And that's ongoing. The primary endpoint for this trial was angiographic

in-segment late loss at eight months. So we have now extended from in-stent late loss, which is easier to show because that's just looking at big differences within the stent, to now in-segment late loss, which is a more comprehensive measure taking into account what goes on at the edges, where the drugs might not be able to get to.

So, looking at this more comprehensive measure at eight months and this trial is powered, again, for sequential non-inferiority and superiority testing of XIENCE V versus TAXUS.

The first 564 patients enrolled into this trial were entered into the angiographic follow-up cohort with the patients after that enrolled in a non-angiographic follow-up cohort. There were no statistically significant differences in the baseline characteristics of the patients intended for angiographic follow-up versus those who weren't.

Now, the major secondary endpoint, which was actually also a co-primary endpoint because both endpoints were required to be met for regulatory approval, was the first time we have actually looked at a clinical endpoint. And that was ischemia-driven target vessel failure.

So this is this general measure of safety and efficacy at nine months, cardiac death, myocardial infarction, or target vessel revascularization that consists of target lesion or vascularization or TVR remote.

With 1,002 patients, this trial is powered for non-inferiority. And that was the regulatory burden that had to be met. The trial was not powered for superiority for target vessel failure. And it was my honor to be involved as the principal investigator of this study.

Now, in addition, we also wanted to look at the safety and efficacy of a 4.0-millimeter stent. And we often treat

large vessels with drug-eluting stents. Right now we have to take the currently available 3.5-millimeter stents, put them in, expand them with a larger balloon to get them up to 4.0. There is not currently an approved four-millimeter drug-eluting stent on the United States market.

So what was worked out in concert with FDA to evaluate this since we couldn't randomize it to another 4-millimeter drug-eluting stent was to take within these patient populations the appropriate lesions that were eligible for a 4-millimeter stent -- and that's a reference vessel diameter of 3.75 to 4.25 millimeters -- and to do a small registry, basically just to see if the results were consistent with the XIENCE V stent and at least not inferior to the results of the TAXUS stent in the remainder of the randomized SPIRIT III trial.

So this was a prospective single-blind 4.0-millimeter registry compared

to the concurrent TAXUS control arm from SPIRIT III with angiographic follow-up at 8 months in all patients intended with clinical follow-up ongoing to 5 years. And the primary endpoint that was agreed upon for regulatory approval was angiographic in-segment late loss at eight months powered for non-inferiority to TAXUS from SPIRIT III.

So if we first look at these primary angiographic endpoints, this is the randomized trial, the first 564 patients. And you can see that at 8 months, angiographic follow-up was completed in 77 percent of patients.

Usually in the United States, we get about 75 to 80 percent. And, in fact, we have powered this trial for 75 percent angiographic follow-up. If one extends this out to another one month, then we are up to 82 percent angiographic follow-up, but this is the official formal window, with 77 percent.

This was the primary endpoint of

SPIRIT III in-segment late loss at eight months. And, once again, one can see that not only was the XIENCE V stent compared to the TAXUS stent -- not only did it meet the primary endpoint of non-inferiority, but it was also highly statistically significant superior in terms of reducing in-segment late loss across the entire lesion and at the edges from 0.28 millimeters with TAXUS to 0.14 millimeter with XIENCE V, a 50 percent reduction p-value of 0.004.

When one looks at the four-millimeter stent, you can see that, again, the late loss was 0.17 millimeters with this, which was shown statistically to be non-inferior to the 0.28 millimeters to the TAXUS randomized control trial. You can look, however, at the confidence intervals of the difference. And you can see that it does not overlap unity. So this actually was a reduction.

Now, if we go back to the

randomized control trial and first look at IVUS measures, we can see the IVUS once again supports on a volumetric basis what we saw on a spot analysis with the angiogram. And that is first looking at a slightly different endpoint of neointimal hyperplasia volume.

This is the amount of tissue that grows within the stent margin over the eight-month follow-up period. You could see that 21-millimeter3 of tissue on average grew within the TAXUS stent versus 10.1-millimeter3 in the XIENCE V stent, a statistically significant 52 percent reduction. And if one looks at, again, percent volume obstruction, you can see similar types of findings, a 38 percent reduction, from 11.2 percent down to approximately 7 percent, with TAXUS versus XIENCE, respectively.

Now, importantly, intravascular ultrasound is a very powerful tool that allows us not to look at only the tissue inside the stent but to look at abnormal vascular

responses. And what we like to see with a drug-eluting stent is that it inhibits tissue growth but doesn't do anything abnormal to the vessel wall. By angiography, we didn't see any aneurysms or ectasia in the study, but ultrasound is more sensitive than that.

What we can do is look at the external elastic lamina volume. This is actually the size of the entire vessel by intravascular ultrasound. And what one can see is when one looks at the XIENCE V stent patients in media after implant to eight-month follow-up by ultrasound, you can see that there is no growth in the vessel. It basically stays where you left it.

When one looked at the TAXUS stent, we see what we have seen in other trials. And that is an expansion or positive remodeling of the vessel. So the stent doesn't change, of course, over time, but the vessel actually is positive remodeling or expanding outward.

And when we want to see after this

how this translates into the most concern that we have of incomplete stent apposition, which is acquired during follow-up -- that means a stent that was well-implanted initially at the end of the procedure but the artery, which presumably from vascular toxicity is positive remodeling, so it pulls away from the stent. This is a concern that, at least anecdotally, has been related to stent thrombosis.

We can see that with both stents, this was actually quite low. It occurred in 1.1 percent of XIENCE V patients and 2.3 percent of TAXUS patients. So what we have seen here by looking at angiography and what is supported by IVUS is a stent that leads to larger lumens compared to the other drug-eluting stent without positive remodeling; that is, without vascular toxicity, and without a risk of late acquired incomplete apposition.

Now let's look at the clinical follow-up in SPIRIT III of the 1,002

randomized trials. Nine-month follow-up was completed in about 98 percent of patients and 12-month follow-up in approximately 97.4 percent of patients. And this was the co-primary endpoint of the trial; that is, target vessel failure at nine months.

Again, this was powered for non-inferiority. And the XIENCE V stent was shown to be non-inferior to the TAXUS stent for the co-primary endpoint, the first time a clinical endpoint has been pre-specified, target vessel failure from 9.7 percent with TAXUS to 7.6 percent with XIENCE V, a relative risk reduction of 21 percent, but you can see the confidence interval does cross the line of unity, so not statistically significant from superiority testing.

We now have follow-up to all of the patients out to one year in the SPIRIT III trial. And these are the hazard curves. Again, we have got TAXUS in red and XIENCE V in blue.

You can see here that there tends to be less target vessel failure in the XIENCE V arm compared to the TAXUS arm, 11.1 percent versus 8.5 percent, a relative 25 percent difference, but the p-value is .8. But this trend -- and I will get back to this -- is due to what tends to be less peri-procedural non-Q-wave myocardial infarctions very early on, with then what tends to be a little bit less ischemic target lesion revascularization later on.

This comes out, actually, more so when one now looks at the more stent-specific composite endpoint of major adverse cardiovascular events. Again, this is cardiac death, myocardial infarction, or target lesion revascularization that is right at the site of the stent and at the edges of the stent.

Here you can see the difference again in peri-procedural non-Q-wave MIs. And then you do see the curve spread over time, as I will show you later, because of less target

lesion revascularization with XIENCE V stent such that at the end of one year, we actually see, just like we saw in SPIRIT II, a significant 43 percent reduction in major adverse cardiovascular events with one drug-eluting stent versus the other TAXUS stent. So 5.9 percent with XIENCE V, 10.2 percent with TAXUS. And this is a fairly striking 43 percent reduction.

So here are all the one-year result endpoint event rates. One can see again stent thrombosis, both per-protocol and by the ARC definitions, infrequent in both groups and no different; cardiac death, also infrequent in both groups and not different; overall myocardial infarctions out to one year, somewhat catch up.

And you can see 2.8 percent with XIENCE V, 4.1 percent with TAXUS. Target lesion revascularization in this trial, of course, very underpowered for this endpoint, tended to be numerically less with XIENCE V

compared to TAXUS, so overall major adverse cardiovascular events.

And this is now using binomial numbers, slightly different than what I showed you at the hazard curves. This is a relative risk but a 42 percent reduction confidence interval, .37 to .90, 10.3 percent with TAXUS reduced to 6 percent with XIENCE.

This trial, with more complex lesions and patients, actually had a significantly higher rate of the noise, if you will, additional revascularizations outside the target lesion but similar between the two stents, as one would expect. And, therefore, when one looks at TVF, it somewhat dilutes the ability to see differences compared to MACE. Nonetheless, you see this numerical trend, not statistically significant for a 24 percent reduction in TVF with XIENCE compared to TAXUS.

Thus, the conclusions from SPIRIT III was that the pivotal United States-based

SPIRIT III trial met both its pre-specified primary and major secondary or co-primary endpoints, demonstrating superiority of the XIENCE V stent compared to the TAXUS stent in reducing angiographic in-segment late loss and non-inferiority with regard to the nine-month endpoint of target vessel failure.

Now what I am going to do is present to you data from a true patient-level pooled meta-analysis of the SPIRIT II and III trials. So what is the rationale for doing this? With the time that the SPIRIT III trial was designed, the regulatory burden that was agreed upon with the FDA for approval of the XIENCE V stent was the demonstration of non-inferiority for angiographic late loss and target vessel failure compared to TAXUS. That required randomization of 1,002 patients.

But since that time, interest has shifted to examination of lower frequency safety and efficacy endpoints, such as death, myocardial infarction, stent thrombosis, and

target lesion revascularization. Neither SPIRIT II nor SPIRIT III was powered to examine the rates of these endpoints.

Thus, at the request of FDA, to provide more power to examine infrequent events, we have combined SPIRIT II and SPIRIT III in a true patient-level pooled meta-analysis. And this is very valid to do compared to some other meta-analyses because in SPIRIT II and SPIRIT III, patients with similar inclusion and exclusion criteria were randomized in two consecutive randomized trials, XIENCE V versus TAXUS. And follow-up has now been completed to one year in both trials.

So this summarized is the patients enrolled in the study, again similar inclusion and exclusion criteria, up to two de novo lesions with a maximum of one lesion per epicardial vessel. The reference vessel diameter was 2.5 to 3.75. And the lesion lengths were up to 28 millimeters.

There were 3 patients of the 1,302 that I described in SPIRIT II that did receive 4-millimeter stents, but that is really the only difference between these 2 randomized trials.

So 1,302 patients, 1,506 lesions. We have more power to look at low-frequency safety events and efficacy events, 892 randomized to XIENCE V, 410 randomized to TAXUS. These were two consecutive prospective single-blind trials with similar inclusion and exclusion criteria.

Now, importantly, we actually asked Abbott that we at the Cardiovascular Research Foundation, which is affiliated with Columbia University Medical Center, that we wanted to perform this analysis unhindered, if you will, by industry. So we asked them to provide both complete databases from the SPIRIT II and SPIRIT III trial for this unrestricted academic analysis. And we pre-specified the endpoints.

This is very similar to what we did for all the CYPHER and TAXUS trials that were published approximately six months ago in the New England Journal. We pre-specified superiority testing on all endpoints, but also all of these analyses should be considered exploratory and hypothesis-generating.

These are the baseline characteristics of the 892 XIENCE V patients and the 410 TAXUS patients. And they're very reflective of what we saw in both trials individually. In general, they were well-matched between the two groups.

The mean age, as you can see, was about 63 years. Approximately 30 percent of the 1,300 patients were women. And a relatively high proportion, about 28 percent, had diabetes mellitus, otherwise relatively similar to what we have seen in most of the versus DES trials.

With the one unique feature that all of the previous trials with TAXUS and

CYPHER only allowed a single lesion and a single vessel, we had 16 percent of the patients that had 2 lesions and 2 vessels randomized to either XIENCE versus TAXUS.

When one looks at the vessels that were enrolled in these patients, they were distributed throughout the coronary tree with about 42 percent of them being in the left anterior descending artery. And when one looks at quantitative coronary angiography, it was very closely matched in the 2 groups, about 2.76 millimeters, so relatively small vessels, and lesion lengths about 14.4 millimeters, so moderately long lesions. And this is 1,506 total lesions.

Now, first if you look at the 30-day outcomes -- and this is where we first start to really see differences that may become clinically important -- at 30 days, there were no cases of cardiac death in either SPIRIT II or SPIRIT III, but there was a statistically significant reduction in

1 myocardial infarctions from 2.9 percent with
2 the TAXUS stent versus one percent with the
3 XIENCE V stent, a 66 percent reduction. Thus,
4 the composite endpoint of cardiac death or MI,
5 of course, had the exact same numbers since
6 there were no cardiac deaths.
7 Now, we don't expect many TLRs at
8 30 days with any sort of stent, and there
9 weren't many, similar with the 2 stents.
10 Thus, both major adverse cardiovascular events
11 and target vessel failure were actually
12 improved at 30 days with the XIENCE V stent
13 compared to the TAXUS stent.
14 Now, we don't know in detail why
15 this was, but, actually, this is not
16 surprising. I was actually the first one to
17 point out that in TAXUS V, we do have a higher
18 rate of peri-procedural myocardial infarctions
19 with the larger strut stent that we had tested
20 in that study. And presumably it's the
21 thinner stet strut and the more adhesive
22 polymer that has less bonding, webbing, et

cetera, that is potentially less thrombogenic that leads to less side-branch compromise and perhaps other events that leads to an enhanced safety profile at 30 days.

Now, these are not only small, tiny myocardial infarctions. When we look at the level of the myocardial infarction as estimated by the peak CPK less than five, which we could consider small MIs, versus five to ten, which you might consider moderate sized MIs, versus greater than ten times the upper limits of normal, which are large MIs and nobody would argue are prognostically important, you can see that the XIENCE V stent compared to the TAXUS stent tends to reduce the levels of all sorts of MI, small, moderate, and large.

Now if we go to the one-year outcomes in these trials, first, I will show you the lower-frequency safety events. This is stent thrombosis with a pre-specified protocol definition. And one can see almost

identical rates of stent thrombosis out to one year with these two devices: 0.8 percent with TAXUS, 0.7 percent with XIENCE.

When we used the ARC definite or probable definitions, again, this is what most people are using right now, you can see that, again, out at one year, there is no difference in stent thrombosis between the 2 devices: 0.8 percent with TAXUS and with XIENCE V.

If we look at all-cause death at one year, all-cause death is infrequent. And there is no difference in all-cause death, 1.8 percent with TAXUS and 1.3 percent with XIENCE. What you are going to see in all of the next series of slides is that while these low-frequency safety events tend not to be different, you will see that they do tend to benefit or favor the XIENCE V stent, at least in terms of lower numerical rates of adverse events, which is reassuring.

So if we look at cardiac death at one year, one percent with TAXUS, zero percent

with XIENCE V, of course, low frequency, still not statistically significant but reassuring, when we look at MIs, I showed you that the 30-day MI rates were statistically significant.

And the curves stay roughly parallel since that time, so overall MIs out to one year, 4 percent with TAXUS, 2.3 percent with XIENCE, a relative 44 percent reduction with a borderline p-value of 0.08.

Thus, looking at our pre-specified endpoint of cardiac death or myocardial infarction at one year, again, you can see that it tends to favor the XIENCE V stent, 2.7 percent versus 4.5 percent with TAXUS, a relative 40 percent reduction, but the p-value is .10.

Now, if we look at efficacy measures, this is where it starts to also become revealing because we actually do see a statistically significant reduction in target lesion revascularization or clinical