29 received the VISION stent. Angiographic follow-up for the primary endpoint at 6 months was approximately 89 percent. At 180 days, XIENCE V had significantly lower observed in-stent late loss compared to the VISION bare metal control.

Similar reductions in other measurements of restenosis compared to VISION were also observed at 180 days. One-year angiography and IVUS follow-up, not shown here but also provided to the panel, showed similar trends.

This is a graph of major clinical endpoints in SPIRIT FIRST with lower observed ratios in the XIENCE arm in blue out to one year and continued lower event rates in the XIENCE arm out to three years. This represents the longest available follow-up in subjects who have received XIENCE stents in the SPIRIT clinical program.

In summary, SPIRIT FIRST met its primary endpoint with lower 180-day in-stent

late loss for the XIENCE stent compared to the bare metal control. Angiographic data demonstrated consistently lower rates of angiographic measures of restenosis versus the control. No stent thrombosis events were observed after three years in this study.

As typical of many feasibility studies, two key limitations of SPIRIT FIRST included small sample size and inadequate power to assess clinical endpoints or safety outcomes.

SPIRIT II was a randomized controlled trial conducted outside the U.S. in 300 subjects with the pre-specified objective of first demonstrating non-inferiority and subsequent superiority of XIENCE V to TAXUS. Subjects could have study stents implanted in a maximum of two de novo native coronary artery lesions, each in a different epicardial vessel, with diameters between 2.5 and 4.25 millimeters, with lesion length up to 28 millimeters.

The primary endpoint was angiographic in-stent late loss at 180 days with a non-inferiority margin of .16 millimeters. The protocol originally planned for four interim looks to test the study hypothesis with control of overall type I error rate using a one-sided alpha of .05. However, as will be discussed, only two of these analyses were performed.

Important secondary endpoints included acute success, other angiographic and IVUS-based measurements of restenosis, composite clinical endpoints, and stent thrombosis.

This table shows key baseline characteristics of SPIRIT II subjects. For the variables shown, there are no statistically significant differences between the two arms at the unadjusted .05 level. In the table headers for this in subsequent slides, N represents the total number of treated subjects and M the total number of

treated lesions.

Pre and post-intervention lesion and vessel characteristics were similar between the stent treatment groups. The differences above are not statistically significant at the unadjusted .05 level.

Successful delivery and deployment of the study stent was measured by clinical device success on a per-lesion basis. Clinical procedure success was measured on a per-subject basis and, by definition, also included freedom from in-hospital MACE.

Both clinical device and procedural success rates for the XIENCE V stent were high. Thirty-day MACE rates were low for the XIENCE V stent.

Angiographic follow-up for the primary endpoint at 180 days was 91.7 percent at the patient level and 91.3 percent at the analysis lesion level.

Based on a completer analysis, SPIRIT II successfully met its primary

endpoint by demonstrating non-inferiority of XIENCE V to TAXUS with respect to 180-day in-stent late loss. Compared to TAXUS, XIENCE also had statistically lower 180-day in-stent late loss.

In SPIRIT II, XIENCE also demonstrated numerical trends towards lower angiographic restenosis endpoints compared to TAXUS, including in-segment late loss, percent diameter stenosis, and angiographic binary restenosis.

Key IVUS results again showed a trend toward lower numerical rates of restenosis as measured by neointimal hyperplasia volume and in-stent volume of obstruction.

Incomplete stent apposition data for SPIRIT II are also presented in this table. Incomplete stent apposition can be assessed by intravascular or ultrasound evidenced, in part, by one or more stent struts separated from the vessel wall.

As shown here, although post-procedure incomplete stent apposition was not uncommon, late acquired incomplete apposition was not observed in SPIRIT II.

Major clinical outcomes for SPIRIT II are shown here. Rates of clinical events and stent thrombosis were infrequent in the XIENCE arms out to one year. However, SPIRIT II was not adequately powered to evaluate all of these clinical endpoints.

In summary, data from the SPIRIT II trial indicates that the XIENCE V stent was superior to TAXUS with respect to in-stent late loss at 180 days. Additionally, there was a consistent trend of lower rates of angiographic restenosis across multiple angiographic and IVUS-based secondary endpoints. However, SPIRIT II was not adequately designed, nor intended to evaluate clinical endpoints, nor lower frequency adverse events. Finally, as will be discussed later, it cannot be ruled out that the interim

analysis in SPIRIT II biased the study conclusions.

The trials that comprised the SPIRIT III study are outlined here. In contrast to the RCT, the SPIRIT IV arm, the SPIRIT 4-millimeter arm, was a single-arm registry in which a 4-millimeter-diameter was evaluated in native coronary arteries of diameters of between 3.75 and 4.25 millimeters. This single-arm design was chosen due to the unavailability of a suitable four-millimeter-diameter control stent to which to randomize.

Finally, there were pharmacokinetic studies performed in volunteers enlisted from the SPIRIT III RCT.

The SPIRIT III RCT was a randomized non-inferiority study in the 1,002 subjects that represented the pivotal U.S. trial in support of the XIENCE V PMA. The objective of SPIRIT III was to evaluate XIENCE, compare to TAXUS, and the treatment of a maximum of two

de novo lesions up to 28 millimeters in length and native coronary arteries with RVDs of 2.5 to 3.75 millimeters.

Two co-primary endpoints were pre-specified. Study success required both endpoints to be met. The angiographic endpoint of in-segment late loss of 240 days was to be evaluated using a one-sided alpha of .025 and a difference of in-segment late loss between the XIENCE and TAXUS arms of no more than .195 millimeters.

The clinical endpoint of ischemia-driven target vessel failure at 270 days was tested using a one-sided alpha of .05 and a difference in TVF rates of no more than 5.5 percent. Together these non-inferiority margins were judged to adequately assess similar clinical performance between these two stent platforms as well as to preserve treatment effect of XIENCE compared to bare metal stents.

Important secondary endpoints are

listed here. And they included standard measures of angiographic and clinical performance previously noted.

This is a diagram of the study design showing the randomization scheme of SPIRIT III. After randomization of the treatment arm, subjects were then assigned to either clinical, angiographic, and IVUS follow-up; group A, clinical and angiographic follow-up, group B; or clinical follow-up only, group C.

Key baseline demographic and clinical characteristics for the SPIRIT III RCT are shown here. The only two variables shown have statistically significant differences between treatment arms at the unadjusted .05 level of prior CABG and unstable angina. Other variables appear to be well-balanced between treatment arms.

Tabulated here are key baseline lesion vessel characteristics. In this table, lesion characteristics are presented for all

target lesions treated. Because treatment of dual vessel disease required each lesion to be in a different epicardial vessel, the number of lesions treated per patient is equal to the number of vessels treated. One can see that in SPIRIT III, approximately 15 percent of subjects were dual vessel treated. None of the differences between the characteristics shown above are statistically significant at the unadjusted .05 level.

Clinical device success rates in the XIENCE and TAXUS arms are comparable at 98.3 and 98.7 percent, respectively. Clinical procedure success was comparable between treatment arms with the rates in the XIENCE and TAXUS arm of 98.5 and 97.3 percent, respectively. Thirty-day MACE and MI rates were low in both the XIENCE and TAXUS arms.

As shown here, the SPIRIT III RCT successfully met its co-primary endpoint of 240-day in-segment late loss as well as its co-primary endpoint of 9-month target vessel

failure. By meeting both co-primary endpoints, the study success criterion was fulfilled.

Target vessel failure and non-hierarchical rates of its component endpoints, of its component clinical endpoints, are shown graphically here out to nine months. Stent thrombosis rates were infrequent in SPIRIT III.

Clinical outcomes out to one year were expected to increase compared to nine months, but no additional safety concerns were noted. Stent thrombosis rates remained infrequent events at one year.

Focusing further on one-year stent thrombosis events in SPIRIT III, we again see low stent thrombosis rates at acute, subacute, and late time points according to the protocol definitions. Using the ARC definite plus probable definition, two additional events are added to the total stent thrombosis rate in the XIENCE arm.

Substantial overlap in 95 percent confidence intervals is noted for the low ARC-defined total stent thrombosis rates, although it should again be noted that the SPIRIT III RCT, like previous pivotal DES trials, was neither designed nor intended to adequately evaluate these low-frequency events.

Secondary angiographic outcomes at eight months are tabulated here. As in SPIRIT III, we again observe the consistent trend towards numerically lower angiographic measures of restenosis in XIENCE compared to TAXUS. And IVUS results at eight months post-implantation continued this trend with additional measures of neointimal hyperplasia volume and percent volume obstruction.

Although XIENCE had numerically higher incomplete stent apposition post-procedurally and out to the 240-day follow-up, late acquired incomplete apposition rates remained low.

The SPIRIT III RCT successfully met both its co-primary endpoints by demonstrating non-inferiority of XIENCE to TAXUS with respect to 240-day in-segment late loss and 270-day target vessel failure.

Angiographic and IVUS results suggest a consistent trend towards lower restenosis in XIENCE compared to TAXUS. The XIENCE V stent had a comparable safety outcome out to 12 months compared to TAXUS.

I would like to discuss some of the limitations of SPIRIT III before moving forward. As in many experimental studies, SPIRIT III was not designed to establish safety and efficacy in specific patient subgroups or secondary clinical endpoints.

Post hoc data analyses and apparent trends towards significance need to be interpreted cautiously when assessing performance in specific patient subgroups or across multiple secondary endpoints.

As we will be discussing in the

biostatistical presentation, 199 subjects at 37 sites were evaluated by unblinded study personnel at their 9-month follow-up visit, representing nearly 20 percent of the total SPIRIT III RCT cohort. However, excluding subjects that were evaluated by unblinded study personnel did not alter the study outcome.

Finally, evaluable angiographic data was available for only 77 percent of subjects randomized to receive 8-month angiography for analysis of the primary endpoint of in-segment late loss, less than the FDA-requested 90 percent follow-up rate.

As noted previously, the SPIRIT III four-millimeter arm was a prospective, non-randomized, single-arm study. Its pre-specified objective was to evaluate XIENCE V compared to TAXUS in the treatment of a maximum of two de novo lesions up to 28 millimeters in length in native coronary arteries with RVDs from 3.75 to 4.25

millimeters.

For the primary endpoint, in-segment late loss at 240 days in the 4-millimeter XIENCE V arm was compared to that of the TAXUS arm in the SPIRIT III RCT. A non-inferiority margin of .195 millimeters was also used, which was the same as that in the SPIRIT III RCT. Again, because a four-millimeter DES was unavailable as an active control, a single-arm approach was chosen for the study. The interim analysis was conducted in 69 subjects enrolled with an adjusted p-value applied to the analysis of in-segment late loss.

Important secondary endpoints include standard measures of procedural and device success and other previously noted clinical and angiographic outcomes.

Key baseline demographic and clinical characteristics of the SPIRIT four-millimeter arm are shown here. Small sample size at the four-millimeter arm

complicates direct comparison to the same variables in the SPIRIT III RCT but, nevertheless, appear to be clinically comparable.

Target vessel and vessel size differed somewhat between the four-millimeter study and the RCT of the SPIRIT III trial, which is not entirely unexpected given that this single-arm registry specifically evaluated the XIENCE stent in larger vessels.

Rates of clinical device and clinical procedure success rates remained high in the four-millimeter arm, are compared here with the TAXUS and XIENCE arms of the RCT.

Thirty-day MACE rates are shown in the table below. Non-Q-wave MIs account for the majority of 30-day major adverse cardiac events in both arms.

The primary analysis in-segment late loss at 240 days in the 4-millimeter XIENCE V arm was compared with that of the TAXUS arm from the RCT with a non-inferiority

margin of .195 millimeters. An interim analysis was planned after 69 subjects enrolled in a 4-millimeter arm had completed their scheduled follow-up and after unblinding of the RCT.

At this analysis, outcomes in 69 subjects were to be compared to the angiographic subjects enrolled in the TAXUS arm or the RCT and a one-sided nominal significance level of .0377. Given this design, the primary endpoint was met.

However, of the 69 subjects enrolled and treated in a 4-millimeter arm, only 49 subjects, or 71 percent of those enrolled, had qualifying follow-up angiograms. This was lower than the 77 percent available angiographic follow-up in the RCT.

Other angiographic results in the four-millimeter arm at eight months are compared here with both the TAXUS and XIENCE arms of the RCT. Although unadjusted for baseline differences, the XIENCE's

four-millimeter stent had comparable results to that observed in the RCT. Finally, although SPIRIT IV allowed for treatment of up to two vessels, there were no two vessel treated subjects in the study.

Target vessel failure and non-hierarchical rates of its component clinical endpoints are shown here. Clinical events at 9 and 12 months were the same. There was one protocol-defined stent thrombosis but no ARC-defined stent thrombosis in the single-arm study. However, the four-millimeter arm was not adequately powered nor intended to evaluate these endpoints.

The SPIRIT III four-millimeter arm successfully met its primary endpoint of 240-day in-segment late loss. Secondary angiographic endpoints demonstrated lower observed rates of restenosis compared to the TAXUS control and were also similar to XIENCE V data from the SPIRIT III RCT.

The SPIRIT III four-millimeter arm

was not designed adequately to evaluate clinical outcomes but for the subjects available for clinical analysis, the results of the XIENCE four-millimeter arm were comparable to those seen in the RCT.

Some of the limitations of the SPIRIT IV study are highlighted here. First, the SPIRIT III four-millimeter arm was non-randomized without a concurrent control. Further, only 71 percent of enrolled subjects had qualifying follow-up angiograms. Finally, the study was not designed to evaluate clinical endpoints but to establish the effectiveness of the four-millimeter platform by demonstrating comparability of in-segment late loss to TAXUS in the SPIRIT III RCT.

Pharmacokinetics of Everolimus eluted from the XIENCE stent was evaluated in three different substudies. Two of the substudies were conducted as part of the SPIRIT III trial. And the third P-K substudy was conducted OUS as part of the SPIRIT II

trial.

The P-K substudies were conducted in three different geographic locales, and the global pharmacokinetic data included a total of 73 subjects. The objective of each substudy was to determine the pharmacokinetics of everolimus delivered by XIENCE V.

The total dose of everolimus received by subjects within the three substudies varied from 53 to 588 milligrams. And the number of stents implanted per subject ranged from one to four.

The following table summarizes the pharmacokinetic parameters of everolimus from these studies. Pharmacokinetic parameters associated with the elution of everolimus from XIENCE V were consistent in all three substudies. In each of the substudies, the highest Cmax values were 2.4, 2.11, and 2.79 nanograms per millimeters. And all values were associated with the highest dose of everolimus administered.

In all substudies, the Cmax value never reached the minimum therapeutic value of 3.0 nanograms per millimeter necessary to be maintained for the effective prevention of organ rejection, which is its proposed systemic indication.

These three studies demonstrated that whole blood concentrations of everolimus increased proportionately to total stent dose. And, in conclusion, Abbott has provided a proper characterization of the pharmacokinetic profile for XIENCE V.

FDA requested post hoc analyses of clinical outcomes for patients in the SPIRIT II and III RCTs. The primary goal for this analysis was to provide improved estimates of the true rates of death, MI, and stent thrombosis in the XIENCE and TAXUS DES platforms, primarily by increasing the evaluable sample size in a post hoc manner.

Subgroup data will be presented on single versus dual vessel treated subjects and

diabetics. Follow-up in the combined analysis is through one year. And since both SPIRIT II and SPIRIT III RCTs are randomized with the same active control and trials were similar in the distribution of patients' baseline characteristics, no statistical adjustments were made for baseline variables in the combined analysis.

The pooled population from the SPIRIT II and SPIRIT III RCTs consisted of 1,302 subjects. Of these, 892 were randomized to XIENCE V and 410 randomized to TAXUS. Although not shown here but previously provided to the panel, baseline characteristics between the pooled XIENCE and TAXUS populations were similar.

The hierarchical composite endpoint of TVF is shown here graphed together with non-hierarchical component rates to its left. In the combined population, XIENCE also had lower numerical rates of clinical events compared to TAXUS. Stent thrombosis rates

remain low in the combined population, up to one year, and will be discussed later on.

This and the following slides contain Kaplan-Meier incidence rates of freedom from clinical events. Here we note similar rates of all death-free survival and in both arms similar Kaplan-Meier estimates of cardiac death-free survival out to one year as well as similar Kaplan-Meier estimates of MI-free survival to one year.

Kaplan-Meier estimates of protocol and ARC-definite post-probable stent thrombosis rates are also similar out to one year in the combined SPIRIT II and III analysis.

Finally, stent thrombosis rates at one year and the combined analysis are tabulated here. The rare frequency of stent thrombosis events makes interpretation of the point estimates difficult. However, comparability of the stent thrombosis rates in XIENCE and TAXUS at 12 months is suggested by

very similar observed stent thrombosis rates, or .0 percent versus .0 percent.

The differences in 12-month definite plus probable stent thrombosis rates seen in SPIRIT III RCT, 1.1 is XIENCE versus .06 TAXUS has become negligible in the combined analysis. That includes additional data from SPIRIT II and a larger effective sample size.

It should also be noted that across these analyses, both TLR-censored and TLR-uncensored stent thrombosis rates were the same since no intervening TLR occurred in subjects who had a stent thrombosis.

SPIRIT II and III represent the first DES studies intended to support a PMA that prospectively allowed treatment of dual vessel disease. Approximately 16 percent of all subjects in the combined SPIRIT II and III population had dual vessel treatment.

Sponsor has provided the following table of clinical endpoints stratified by

single versus dual vessel treatment. Data from that table is graphically represented here. The composite endpoint of TVF is shown in blue, with non-hierarchical component endpoints to its left.

Although robust statistical comparisons are limited in such post hoc subgroup analyses, clinical endpoints appear to trend lower in the XIENCE arms, in both the single and dual vessel subgroups. However, in the dual vessel subgroup, although there were numerically higher observed stent thrombosis rates in XIENCE versus TAXUS, there were not higher observed rates of death, cardiac death, or MI in the XIENCE arm.

Diabetics comprise an important patient population at increased risk for cardiovascular morbidity and morality. Like previous DES trials, diabetic patients were not excluded from the SPIRIT clinical program.

Although there were not pre-specified hypotheses or clinical design

features to warrant a specific label indication for the use of the XIENCE V stent in diabetics, FDA believes that the clinical outcomes in diabetics should be considered in the review of the XIENCE V stent program.

In the combined SPIRIT II and III analysis, diabetics comprised approximately 28 percent of the total population. FDA requested that the sponsor perform post hoc tabulations of clinical events according to diabetic status and treatment arm. The results are shown here.

Data from that table is graphically represented in this slide. Again, target vessel failure is shown in the blue bar, with non-hierarchical clinical components to its left.

A general trend towards lower clinical events in XIENCE versus TAXUS in non-diabetics does not appear to be seen in diabetics. However, the low sample sizes in these subgroups, potential confounders

associated with diabetics, and the post hoc nature of this analysis limits robust comparisons.

The original panel pack materials mailed out on November 6, 2007, the clinical data set provided by Abbott Vascular and reviewed by FDA consisted of three-year follow-up data for SPIRIT FIRST and 12-month data on SPIRIT II and III. However, given the time elapsed since enrollment was complete, SPIRIT II and III, a number of subjects in these trials have now become eligible for two-year follow-up. A portion of these eligible subjects is completing their two-year follow-up assessment on an ongoing basis.

Abbott Vascular has performed an ad hoc analysis on a subset of combined SPIRIT II and III subjects who have completed two-year follow-up assessments as of October 30th, 2007.

FDA has agreed to receive and review such an analysis to give the applicant

an opportunity to present the most up-to-date data available on the XIENCE V, despite the limitations of such an analysis.

As of October 30th, 2007, 603 subjects who were enrolled in the SPIRIT II and III trials had completed their two-year follow-up or were terminated early. Subjects who were terminated early included those who withdrew from the study, were lost to follow-up, or died.

Abbott was able to determine which investigational sites had subjects who completed their two-year follow-up by October 30th, 2007. Data on these subjects was subsequently monitored and clinical events sent for adjudication and to apply our definition of stent thrombosis.

Of the 603 subjects who were completers or early terminators, 422 subjects received XIENCE V, and 181 subjects received TAXUS. Of these 603 subjects, 251 were enrolled SPIRIT II and 352 were enrolled in

SPIRIT III. As shown, treatment assignment frequencies reflected the randomization ratios in these two studies.

Baseline demographics appear to be similar to that in the overall SPIRIT II and III cohorts with possible exceptions including unstable angina, prior MI, and MI within two months. Baseline lesion characteristics were generally comparable with possible exceptions of lesion eccentricity and ACC-AHA lesion classes.

Not unexpectedly, clinical events from zero to 758 days in a two-year cohort were numerically higher than the one-year follow-up data. As shown in the table here, rates of cardiac death and MIs from one to two years were low in the two-year completer cohort.

In the two-year completer cohort, there were two additional protocol-defined stent thrombosis observed in the XIENCE V arm and none in the TAXUS arm between one and two

years.

By contrast, there was one ARC-definite plus probable stent thrombosis in the XIENCE V arm and none in the TAXUS arm between one and two years of follow-up.

As tabulated here, total stent thrombosis rates at two years for the completer cohort were numerically similar between the XIENCE V and TAXUS stents.

In summary, for the two-year analysis cohort, rates of additional cardiac death, myocardial infarctions, the stent thrombosis events occurring between one and two years of follow-up were low.

Now, the following limitations of this analysis are outlined here. This was an ad hoc analysis presented for the purpose of providing additional two-year data available to Abbott by the arbitrarily chosen cutoff date of October 30th, 2007. It should not be interpreted as a formal interim analysis of the two-year data.

Also, data is derived from a subset of the total SPIRIT II and III study cohorts and contains only data that was available to the applicant. It is possible that the data available for this analysis or subjects from which the data were derived have characteristics that are different from the remaining subjects not included. Furthermore, it cannot be excluded that bias may have been introduced by the manner in which data was reported or monitored.

Events that occurred in subjects who had not yet reached the two-year follow-up window may not be included in this analysis. Absent from the data are subjects who are eligible for two-year follow-up but have not been assessed.

It is possible that there are subjects who have had their two-year follow-up but did not have their data reported to the applicant by the cutoff date.

Inclusion of data from sites that

submitted two-year data was non-random. Lastly, adjudication of clinical events and determination of ARC-defined stent thrombosis were not performed by the same committee for each patient.

And the final summary, XIENCE V met the pre-specified co-primary endpoint, non-inferiority, versus TAXUS, of nine-month target vessel failure in the pivotal SPIRIT III RCT.

XIENCE also met its late loss endpoints versus TAXUS in SPIRIT II and SPIRIT III and also demonstrate consistently lower angiographic and IVUS measures of restenosis compared to TAXUS.

In the SPIRIT clinical studies, a total of 986 subjects received XIENCE V stents, 959 patients followed out to 12 months, and more limited data on 422 XIENCE subjects up to 24 months. Numerically increased rates of death, cardiac death, and MI for the XIENCE V stent versus TAXUS have

not been observed. Combined analyses across the XIENCE trials and available data beyond one year did not show unanticipated safety signals.

Thank you.

DR. YAN: Good morning. My name is Sherry Yan, and I will be presenting the FDA's statistical review of the Abbott Vascular XIENCE V Coronary stent submitted.

There were three clinical studies prospectively conducted to evaluate the performance of XIENCE V for safety and effectiveness. This slide provides a general overview of these three studies.

The object of SPIRIT FIRST was to assess the feasibility and performance of XIENCE V. The study primary endpoint was 180-day in-stent late loss. A superiority test was specified to compare XIENCE V with VISION in terms of 180-day in-stent late loss. The p-value is less than .0001. Hence, the superiority of XIENCE V to VISION appears to

be established in terms of 180-day in-stent late loss.

The objective of SPIRIT II was to assess the safety and performance of XIENCE V to TAXUS in subjects with a maximum of two de novo native coronary artery lesions, each in a different epicardial vessel with RVD of 2.5 millimeters to 4.25 millimeters and a lesion length of 28 millimeters or less. The study primary endpoint was 180-day in-stent late loss.

The plan was to perform a non-inferiority test at one-sided alpha level of .05 with the non-inferiority margin of .16 millimeters. The sample size of 240 was calculated to provide 91 percent power for this non-inferiority test. To account for 20 percent attrition rate, a total of 300 subjects were enrolled.

In the protocol, the sponsor pre-specified that if non-inferiority was shown, then a superiority test would be

performed at a nominal alpha level of .05.

There were four interim analyses prospectively planned at 40, 80, 120, and 160 patients followed by the final analysis. An O'Brien-Fleming boundary was specified in the protocol. It was reported that the interim analyses were conducted at 80 and 120 patients, respectively. And the final analysis was performed at the nominal alpha level of .0448.

The sponsor stated in the protocol that those interim analyses were not for early termination of enrollment, but it is not clear what the purposes of those interim analyses were meant to be. No decision boundary for superiority seems to be specified in the protocol.

FDA did not reveal the protocol before the commencement of the study. The interim analyses results were unblinded to the sponsor but not available to FDA. Therefore, those interim analyses may introduce potential

bias to the study conclusions.

This table presents the 180-day in-stent late loss for XIENCE V and TAXUS. The complete case analysis consists of subjects with completed six-month follow-up. This analysis indicates superiority of XIENCE V to TAXUS in terms of 180-day in-stent late loss.

Since 22 subjects in XIENCE V and 4 subjects in TAXUS did not complete the 6-month follow-up, sensitivity analyses were performed by FDA. For the Q3_Q1 sensitivity analysis, the missing data in XIENCE V was imputed by the third quintal of the overall data while the missing data in TAXUS was imputed by the first quintal. This analysis still preserved the superiority.

For the worst case analysis, the missing data in XIENCE V was imputed by the maximum value of the overall data while the missing data in TAXUS was imputed by the minimum value. Superiority is no longer

supported by this analysis. Yet, non-inferiority is still preserved.

A tipping point analysis was conducted by FDA. A tipping point is the imputed means for the missing patients in TAXUS and XIENCE V arms at which the study conclusion would change.

The algorithm used to determine the tipping point is summarized as follows. The algorithm is an iterative one. The missing value in XIENCE V arm is imputed by adding an amount to its completer's mean, which start at zero and increases by .0005 at each iteration while the missing value in TAXUS arm is imputed by subjecting the same amount from its completer's mean.

The TAXUS statistic and p-value are calculated based on the iterative data site, including complete and imputed data. The iteration stops when the p-value is higher than the pre-specified significance level.

This slide presents the tipping

point in comparison to the Q3_Q1 and worst case analysis, as we can see. According to the algorithm presented in the previous slide, the superiority conclusion in terms of 180-day in-stent late loss would change when in the missing patients the mean of XIENCE V is about 1.642 millimeters higher than the mean of TAXUS, a difference that may be deemed implausibly unfavorable.

The objective of SPIRIT III was to determine the safety and effectiveness of XIENCE V for the treatment of subjects with a maximum of two de novo native coronary artery lesions.

The primary endpoint of SPIRIT III RCT was 240-day in-segment late loss. The plan was to perform a non-inferiority test at one-sided alpha level of .025, with the non-inferiority margin of .195 millimeters for in-segment late loss.

The angiographic sample size was calculated to provide 99 percent power for the

non-inferiority plane. The sponsor pre-specified that if non-inferiority was shown for in-segment late loss, superiority test would be conducted at a two-sided alpha level of .05.

The co-primary endpoint of SPIRIT III was a 270-day ischemia-driven target vessel failure. The plan was to perform a non-inferiority test at one-sided alpha level of .05, with the non-inferiority margin of 5.5 percent for TVF.

The total sample size was calculated to provide 89 percent power for the non-inferiority claim. The sponsor pre-specified that if non-inferiority was shown for TVF, superiority test would be conducted at two-sided alpha level of .05.

Before presenting the primary outcomes, I would like to briefly introduce the generalized estimating equations method, also called GEE method. Multiple measurements on the same subject are usually considered to

be correlated. The GEE method can take this into account when estimating the parameters of interest and their standard errors.

For SPIRIT III, since some subjects were treated with two diseased vessels, analysis using all lesions with the GEE method can be considered as appropriate approach.

This table presents the analysis result for 240-day in-segment late loss. XIENCE V appears to be superior to TAXUS in terms of 240-day in-segment late loss based on the analysis lesion.

And, as is the case with all lesions analyzed with the GEE method since the upper limit of 95 percent confidence interval was below zero, the superiority appears to be established. The analyses were based on the complete case, which included 129 subjects with the other 240-day in-segment late loss information, indicating 23 percent missing data.

This table presents analysis

results for 284-day ischemia-driven target vessel failure. In the complete case analysis, only subjects with available data were included in the analysis. In the worst case analysis, missing values in XIENCE V were included as failures while missing values in TAXUS were included as successes.

Non-inferiority can be established based on both complete case and worst case analysis. However, superiority was not established under either of the cases.

Note that the follow-up rates for the angiogram group were only 80.1 percent and a 71.7 percent for XIENCE V and TAXUS, respectively. This was below the FDA's requested follow-up rate of 90 percent.

The sponsor performed sensitivity analysis by using multiple imputation. The superiority can be established in terms of in-segment late loss by a multiple imputation. FDA also performed Q3_Q1 and worst case sensitivity analysis.

For the Q3_Q1 analysis, the standard deviation was kept unchanged. The missing data in XIENCE V was imputed by the third quintal in XIENCE V where the missing data in TAXES was imputed by the first quintal in TAXUS.

In this case, the non-inferiority can be established. Yet, the superiority failed. For the worst case analysis, the missing data in XIENCE V was imputed by the maximum value in XIENCE V while the missing data in TAXUS was imputed by the minimum value in TAXUS. In this case, both the non-inferiority and the superiority failed. However, the worst case analysis may be too conservative and sometimes not realistic.

A tipping point analysis was conducted by FDA using the same algorithm as has been outlined earlier. As we can see, the superiority conclusion in terms of 240-day in-segment late loss would change when in the missing patients, the mean of XIENCE V is .15

millimeters higher than the mean of TAXUS. The non-inferiority conclusion in terms of 240-day in-segment late loss would change when in the missing patients, the mean of XIENCE V is about .92 millimeters higher than the mean of TAXUS.

One hundred and ninety-nine subjects had a 37 size overall were evaluated by unblinded study personnel at the 9-month follow-up visit, representing nearly 20 percent of the total SPIRIT III RCT cohort. The sponsor evaluated the impact of unblinded study personnel on the nine months TVF. It seems that the issue of unblinding does not undermine the status conclusion regarding the nine-month TVF.

The primary endpoint for SPIRIT III 4.0 millimeter arm was 240-day in-segment late loss. Only if the RCT meets its co-primary endpoints will the 4.0-millimeter arm be evaluated as to whether it meets the primary endpoint.

The plan was to perform a non-inferiority test at a one-sided alpha level of .05 with the non-inferiority margin of .195 millimeters for in-segment late loss. A sample size of 72 subjects would provide 90 percent power for the non-inferiority claim. Please be cautious that this is an observational study, and the comparability of treatment groups may be of concern.

After 69 subjects were enrolled, the sponsor decided to submit data analysis based on the 69 subjects. The analysis was planned to be performed after these 69 subjects had completed their scheduled follow-up and after unblinding of the RCT. The primary hypothesis was tested at a point of one-sided nominal significance level of .0377.

This table presents the primary analysis result. The upper limit of 96.23 percent confidence interval is .05, which is lower than the margin of .195. The above

analysis was based on complete case only, which included 20 subjects in 4.0-millimeter arm and 53 subjects in angiographic subset of TAXUS RCT arm. However, limitations need to be kept in mind to interpret the above result.

The primary analysis was not adjusted for baseline covariates. TAXUS does not have approved 4.0-millimeter. TAXUS is not indicated for the treatment of RVD greater than 3.75 millimeters. Rather, then, 3.0 millimeter is intended for the treatment of RVD between 3.75 millimeters and 4.25 millimeters.

The top half of this slide presents 240-day in-segment late loss across different RVD sizes for each treatment arm of RCT. It seems that the mean of 240-day in-segment late loss in TAXUS is consistently higher than the mean in XIENCE V across RVD sizes. And 240-day in-segment late loss seems not to worry that much across different RVD sizes.

FDA also conducted separate

univariate analysis for XIENCE V and TAXUS based on linear regression model. The impact of RVD size is not shown to be statistically significant. The p-values are .48 and .6 for XIENCE V and TAXUS, respectively. This is consistent with the table shown in the top half of this slide.

Corresponding to the tables in the last slide, this box plot presents 240-day in-segment late loss across different RVD sizes for each treatment arm. The blue ones are XIENCE V RCT. The red ones are TAXUS RCT. And the green one is XIENCE V 4.0-millimeter.

Since the primary analysis included 20 subjects from the 4.0-millimeter arm and 53 subjects from the Texas arm due to missing data, FDA performed Q3_Q1 and a worst case sensitivity analysis. In the Q3_Q1 analysis, the non-inferiority can be established. In the worst case analysis, the non-inferiority test failed. However, the worst case analysis may be too conservative and sometimes not

realistic.

A tipping point analysis was conducted by FDA using the same algorithm, as outlined earlier. It shows that the null hypothesis in terms of 240 in-segment late loss would no longer be rejected when in the missing patients, the mean of XIENCE V 4.0-millimeter is about .61 millimeters higher than the mean of TAXUS.

To summarize, in SPIRIT FIRST, the superiority of XIENCE V to bare metal stent appears to be established in terms of 180-day in-stent late loss. In SPIRIT II, the superiority of XIENCE V to TAXUS appears to be established in terms of 180-day in-stent late loss.

In SPIRIT III RCT, the superiority of XIENCE V to TAXUS appears to be established in terms of 240-day in-segment late loss. And the non-inferiority XIENCE V to TAXUS appears to be established in terms of nine months ischemia-driven TVF. In SPIRIT III

4.0-millimeter arm, the naive comparison of XIENCE V 4.0-millimeter with TAXUS should be interpreted with caution because it is observational study.

FDA welcomes the panel's review of our summary and their responses to our submitted questions. Thank you. The next speaker is Dr. Duggirala.

DR. DUGGIRALA: Good morning. I am Hesha Duggirala, an epidemiologist in the Division of Postmarket Surveillance. Today I will present our summary and discussion of the epidemiology review of the PMA and the applicant's proposed post-approval study.

First I will describe the general principles and rationale for the post-approval study, then comment on the post-market questions that the pre-market study was not designed to answer but that may be addressed in the post-approval study. Finally, I will provide our assessment of the sponsor's protocol.

Before we talk about post-approval studies, we need to clarify that the discussion of a post-approval study prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA's suggesting the panel find the device approvable.

The plan to conduct a post-approval study does not decrease the threshold of evidence required to find the device approvable. Finally, the pre-market data submitted to the agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

One main reason to conduct a post-approval study is to gather post-market information. As we all know, pre-market clinical data are collected from patients that are highly selective and treated by the best trained physicians.

In contrast, when a device is permitted to be on the market, patients that receive the device are less restricted. And physicians who treat these patients are not limited to the best trained physicians.

Additionally, some rare adverse events that were not observed pre-market might be present in the post-market phase as the observation period extends and the patient population broadens.

Another reason for conducting post-approval studies is to address issues and concerns that panel members may raise based on their observations. Please keep in mind that post-approval studies should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial establishment of device safety and effectiveness.

As discussed in the December 2006 DES thrombosis meeting of the advisory panel, post-approval data collected on currently

approved drug-eluting stents have signaled a potential increase in late stent thrombosis after one year compared to bare metal stents.

However, it is not known if this rate plateaus or continues to increase over time, nor is the impact of stent thrombosis on the cumulative rates of cardiac death and MI completely understood. Therefore, FDA currently recommends that post-market data be collected on a series of consecutively enrolled patients.

Drug-eluting stent post-approval studies to date have demonstrated that routine clinical use of drug-eluting stents typically includes treatment outside of the labeled indications, to include higher-risk patient and lesion subsets.

Based on this previous experience, FDA recognizes that a post-approval study of consecutively enrolled patients will likely include patients representing a broader use of the product and recommends that data from such

patients be analyzed to better understand whether significant safety issues exist in the treatment of these patients.

A sufficient number of patients should be enrolled to confirm that the upper bound of the one-sided 95 percent confidence interval around the observed rate of stent thrombosis for each 12-month period after one year is less than one percent for patients treated in accordance with the labeled indication.

Depending on how the study is designed, it may be appropriate to include an adjustment for multiple comparisons in the statistical analysis plan.

FDA suggested all patients be consented for five years of follow-up. If stent thrombosis rates are demonstrated to plateau or decrease in prior years, shorter follow-up may be sufficient. Alternately, if stent thrombosis rates continue to increase, longer-term follow-up or specific labeling

changes may be appropriate.

FDA recommends that the statistical plan include planned descriptive statistics on certain subgroups in interest, including demographics, patient characteristics, and lesion characteristics. Today I will be discussing the plan as formally submitted to the FDA and as included in your panel pack.

Abbott has proposed to address FDA's concerns outlined above by conducting a prospective, open label, multi-center, observational, single-arm registry. The objectives of the studies are to evaluate clinical outcomes in a cohort of real-world patients receiving the XIENCE V stent during commercial use by various physicians with a range of coronary stenting experience, to evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications, to determine clinical device and procedural success during commercial use, and to evaluate patient health status by the

Seattle angina questionnaire.

Here is an overview of the study. Approximately 5,000 patients will be consecutively enrolled at up to 275 sites in the U.S. And clinical follow-up will continue out to five years.

The sponsor has proposed a primary endpoint to the FDA of stent thrombosis at one years, as defined by ARC. Secondary endpoints include stent thrombosis out to five years, a composite rate of death, MI, and revascularization, and a composite rate of cardiac death, TLR, and MI attributed to the target vessel.

The 5,000-patient sample size for this study was derived using the anticipated stent thrombosis rate and the precision of this estimate based on the following: a one-year cumulative ARC-defined stent thrombosis rate of 1.7 percent derived from past XIENCE V trials and a 2 percent dropout rate for the overall population at one-year

follow-up.

The estimated stent thrombosis rate and standard error correspond to an approximate 95 percent confidence interval from 1.35 to 2.05 percent. The primary analysis will look at stent thrombosis rates at various intervals out to five years.

Descriptive analysis will be provided for patient demographics, clinical device, procedural success, antiplatelet therapy compliance, bleeding complications, medical histories, and comorbidities.

After reviewing the sponsor's protocol submitted to the FDA and in your panel pack, FDA suggests that the current endpoint of stent thrombosis at one year be modified. There is not enough data from the pivotal trials or the literature to determine whether the stent thrombosis rate increases, decreases, or plateaus after one year.

We suggest the primary endpoint be the evaluation of stent thrombosis rates

through to five years. We also suggest the sponsor study a co-primary endpoint of death and MI at one year followed three to five years since this is a critical clinical outcome of interest. You will have an opportunity to discuss these issues in the afternoon when FDA presents our panel questions.

Thank you.

CHAIRPERSON YANCY: I would like to thank the FDA for paralleling this morning's presentation by similarly presenting very thorough and comprehensive assessments of the information submitted.

We have approximately 30 minutes for the Q&A. We will go until 12:45 so that we can address any major questions. We can stop sooner than that if we get all of our questions addressed.

The afternoon session obviously will have to accommodate response from the sponsor. The members of our own panel that

have reviewed this application will need to present their findings and additional panel deliberations. So this is a critical time for us to specifically query the FDA.

Let me begin by asking Dr. Fiorentino one question about the available data for longer-term assessment. Looking at what you presented to us and corresponding with what Dr. Krucoff shared with us, it looks like the aggregate, the totality of the data available out at two years is approximately 600 patients, of whom approximately 400-422 are treated with the XIENCE V application. Is that correct?

DR. FIORENTINO: Yes, that's correct.

CHAIRPERSON YANCY: The likelihood of getting more data over what period of time would be what? The total denominator is about 1,300. This is obviously a time-dependent issue. So how long do you think we would have to wait to see the other observations?

DR. FIORENTINO: Well, that would be a question for the sponsor. I think they have a better idea of the frequency that patients are receiving follow-up on an ongoing basis. But it would be some months away to get the complete cohort.

I think also it's important to -- you know, when you're thinking about the complete cohort is analyzing it properly. I'm sure Abbott can speak to this. Usually there's a period where the patients go through their assessment follow-up plan and the sponsor will collect the assessments, the case report forms, and they will have a time period where they can do that. And then the date is formally locked. And then they open the database and formally perform the analysis.

Now, that time period to get all of that done I can only speculate on how long that would be, but that would be a more formal analysis. That would be the two-year analysis of the data. And that would be sometime away,

at least past the summer, I suspect.

CHAIRPERSON YANCY: Other questions? Dr. Normand?

MEMBER NORMAND: I have I think two questions of clarification. I would like to ask the FDA something similar to what I asked earlier. And that is I am still struggling with trying to interpret something about late loss when apparently there is a study that is unpublished coming up, but we have not seen it.

And so I am trying to figure out -- I guess there was a non-inferiority margin of .195 decided upon. Just as a patient, this is sort of very distant to me. So could you please describe how that was arrived at and what it actually means for a patient in terms of risk? Again, I just don't understand.

DR. FIORENTINO: Well, I will say that in this pivotal study, DES pivotal study, the FDA has never accepted late loss as a sole primary endpoint on which a study can be

based. That is specifically why we asked for nine-month target vessel failure, which is essentially a clinical endpoint.

MEMBER NORMAND: But why make them collect late loss, then? Again, I just want to interpret it.

DR. FIORENTINO: Well, many times, it is the sponsor's prerogative, but I do think that the late loss does give information about comparative information between drug-eluting stents about that stent's ability to perform as a drug-eluting stent in effectively suppressing neointimal hyperplasia volume. And when we see rates down below about .4 millimeters, .3-.4 millimeters, of late loss, that does give us some information that it's behaving like a drug-eluting stent, rather than the bare metal stent, for the --

MEMBER NORMAND: But, again, these are two drug-eluting stents that you are comparing.

DR. FIORENTINO: Right.

MEMBER NORMAND: So, again, the difference -- I'm just trying to think of -- so you made a statement about drug-eluting stent versus bare metal stent, but now you are talking about a differential between two drug-eluting stents, and I still don't understand how to value the .195.

DR. FIORENTINO: Oh, the margin?

MEMBER NORMAND: Yes.

DR. FIORENTINO: Well, at the time, that margin -- when we look at the margin, we kind of take it with the bigger picture, but specific with the bigger picture of the alpha we want to control in the sample size.

But specifically that margin, it was felt at the time that a .195-millimeter margin would capture comparable effectiveness with respect to late loss between 2 drug-eluting stents and also preserve the treatment effect relate to bare metal stents.

MEMBER NORMAND: I guess maybe there's no data to answer the question I am

asking, and maybe I am the only one who cares about it. I am just trying to figure out if this is meaningful from a patient sort of feeling better in terms of having clinical events that are concerning.

And just because it's unpublished, I have no sense of how to value. I'm sure technically it means something, but I'm just talking from a patient's perspective. Do I really care? I'm sure --

DR. FIORENTINO: It's a valid point.

MEMBER NORMAND: But is there any information that you can share with us that is available that you can tell us about any relationship between that and clinical outcomes?

DR. FIORENTINO: I don't have specific data. There is published data on that, but that .195 margin I think, if I understand that, marginal, to translate that late loss into clinical benefit of

revascularization benefit --

MEMBER NORMAND: Yes, yes.

DR. FIORENTINO: -- is maybe what you're asking to explain. And I'm not sure exactly how to explain that to a patient, but down around the ranges of drug-eluting stents, say, .195 reduction would be difficult to say that would give the patient a similar revascularization benefit.

MEMBER NORMAND: Okay. I think I just heard you say -- and I may be wrong -- that that size of difference maybe a patient -- we're starting at a base rate. So, you know, we are talking about differences now.

Of course, the difference between going .195 between .4 and down below matters, but we're already at a rate that's really low anyhow, you're saying?

DR. FIORENTINO: That's right.

MEMBER NORMAND: Okay. So I just have one more question to ask, clarification. And it was just to do with the missing data,

Dr. Yan. You did a wonderful presentation. So I have two questions.

One, I don't remember seeing this tipping point. Were we given that? And I'm embarrassed to say I didn't see it in the package. It's not a complaint. It's just one that because you presented it now -- and I don't recall see it. It would be helpful because there were a lot of summaries you made.

I would like to get some sense of what your final conclusions were. I know you had a summary slide, but let me tell you where my confusion is.

And one is I think you showed us a number of different analyses using single-based imputation, doing worst case Q3 minus Q1, and then I think sometimes you found superiority would be declined. You wouldn't agree with superiority. And I don't think that was ever the case for inferiority. I may be wrong about that.

But you did find that superiority would not be found on some situations, but in your concluding remarks slide, you said it was fine, superiority was met. So unless I misunderstood it, it's because it's the first time I think I saw it.

Can you help me understand why sometimes you said it was found? Is it because you're saying, "The worst cause is implausible. So I'm not even going to talk about it"? So that's my question. There's a lot there.

DR. YAN: Let me make sure I understand your question clearly. So what you are asking is that why I did some sensitivity analysis and for the worst case analysis.

MEMBER NORMAND: I'm sorry. I wasn't very clear, and it's my problem. You did sensitivity analysis, and I am glad an I am happy. And that makes sense.

But the question I do have is that I believe in seeing the presentation that

sometimes with your sensitivity analysis, you conclude that it would fail the superiority test.

Yet, in your concluding remarks, your final concluding remarks, you say superiority was met. She didn't?

DR. YAN: No.

MEMBER NORMAND: Oh, you didn't? Good. Just help me because I am getting confused about things.

DR. YAN: Yes. Because in my summary, I said, "appear to be established."

MEMBER NORMAND: Appeared?

DR. YAN: I didn't make any confirmatory conclusion.

MEMBER NORMAND: Okay. And that was based on? I just want --

DR. YAN: Based on the --

MEMBER NORMAND: Worst case?

DR. YAN: The conclusion part in the final slide is based on the complete case analysis.

MEMBER NORMAND: On the complete case?

DR. YAN: Yes.

MEMBER NORMAND: But if you were to do your sensitivity analysis based on your findings -- I just want to get the -- you did the sensitivity analysis?

DR. YAN: Yes. So this is the reason. I just want to show the panel the information as much as I can and meet the panel's expertise to make the judgment.

MEMBER NORMAND: But is it fair to say that -- again, because I don't recall seeing this before. And so this is the first time I am able to look at this information. It does appear, again, a single-based imputation, which is a bit unfair, I think, to the sponsor in some regards. But it does appear in some cases that superiority would be not met. Is that a fair assessment of what you reported?

DR. YAN: Yes.

MEMBER NORMAND: Okay. Thank you.

DR. ZUCKERMAN: Dr. Normand, could we just clarify one thing for you? You have gotten the impression that the importance of late loss and the demonstration of at least partial device surrogacy is based on one paper yet to be published. That's a wrong impression.

The paper by Dr. Pocock, et al., is an important methodological paper, but when the agency planned this combined co-primary endpoint trial with the sponsor, there are other data and analyses out there that suggested that this would lead to clinically interpretable data at the end of the day.

In fact, your colleagues, Drs. Mauri and Kuntz, have published using a different methodology that basically supports the same type of relationship.

MEMBER NORMAND: So, Dr. Zuckerman, can you answer my question, then? Because I don't read their works. So, you know, I don't

typically read that. It's not a statement on their ability or anything like that. So can you tell me?

DR. ZUCKERMAN: Well, during our lunchtime, we'll look for a specific slide as well as I'm sure this sponsor will. But one thing that the slide sponsor has in their panel pack, volume I of IV, 6-110, is where they show you in this very low late loss range that .194 corresponds to only I believe a few percentage points difference in TLR, as Dr. Stone indicated. And they do have a brief discussion in their panel pack.

CHAIRPERSON YANCY: Dr. Jeevanandam?

MEMBER JEEVANANDAM: I'm looking at the FDA analysis of diabetic patients. Just I want to ask a couple of questions. I am a little concerned about that.

When you separate out diabetic patients from non-diabetic patients, -- and let me confirm that's the SPIRIT II and SPIRIT

III trials that are put together -- and if you look at diabetic patients, there's a higher incidence of target vessel failure with the XIENCE device.

And I don't see any statistics here. So I don't know. Are any of those significant or is that unable to be done because of the way the analysis was performed?

DR. FIORENTINO: I'm sorry. Could you first tell us what number slide that is?

MEMBER JEEVANANDAM: Sure. It's 80 and 81.

DR. FIORENTINO: Eighty-one.

MEMBER JEEVANANDAM: If you specifically look at slide 81, I mean, the incidence of t. vessel failure with diabetic patients for the XIENCE is pretty high. It's much higher than it is with the TAXUS. And it's the first time we've seen any evidence that the TAXUS is better than the XIENCE.

DR. FIORENTINO: Okay. So you're looking at the diabetics on the patients who

got XIENCE, and you're looking at the non-target lesion TVR. Is that correct?

MEMBER JEEVANANDAM: Right. It's 11.1 percent versus 5.8 percent. It's the first evidence that we've had that --

DR. FIORENTINO: Okay. TVF, then.

MEMBER JEEVANANDAM: Yes.

DR. FIORENTINO: I see what you are saying. So in diabetics, the composite of TVF, 11.1, is higher than the TVF in the TAXUS arm there.

Now, I do have the target rates. We have not formally done statistical analyses between these. Again, this would be -- I'm sorry. Sherry just gave me data, actually, that -- I don't know if this is a backup slide or if we presented. I think it's one of our backup slides.

So breaking down the diabetics and the non-diabetics, the rate of TVF at one year was 6.4 in XIENCE and 12.8 in TAXUS. And that difference was -- actually, maybe we can pull

up this slide. The 95 percent confidence interval for TVF for the difference was less than zero. Maybe we can pull up the slide.

In all diabetics, however, the 95 percent confidence interval for those two comparisons was -.67 and up to 11.26. So that did include zero. And so those are the comparisons that we have here.

So it would be statistical backup, number 50.

(Pause.)

DR. FIORENTINO: Okay. Sorry for the delay. We'll go ahead and put it up. So I'm not sure if this specifically answers your question, but you can see the 95 percent confidence interval, just comparing those two groups between non-diabetics and all diabetics.

And, again, this would be a post hoc analysis. I would be hesitant to draw up firm conclusions, though, based on this.

MEMBER JEEVANANDAM: I mean, I see

a statistical analysis for the non-diabetics. I don't see one for the all diabetics.

MEMBER YAROSS: Mr. Chairman, may I comment on this?

CHAIRPERSON YANCY: Please?

MEMBER YAROSS: If you look at slide 81 in the FDA package, it's interesting that the TAXUS diabetics actually performed better than the TAXUS non-diabetics. So I think that was FDA's point, that there is a paradoxical behavior of that population.

DR. FIORENTINO: That might be true, but I don't think we can really firmly say the stent performs better. Once we parse down the subgroups, you can see in that subgroup, the n is 110. So it's one of the lowest subgroups in there.

CHAIRPERSON YANCY: It could also be the tyranny of subgroup analysis.

MEMBER YAROSS: Precisely.

CHAIRPERSON YANCY: A few more minutes before we break. Dr. Page?

MEMBER PAGE: These were both very thorough discussions and presentations. One thing that is in some of the materials that was given to us but wasn't emphasized by either the FDA or the sponsor is any relationship in terms of thrombosis and Plavix treatment.

The antiplatelet issue is a major one. And all of us who sat through the meetings in December, there was a fairly long discussion about that issue. These trials were obviously designed before the December discussions.

Through the afternoon, I think it will be helpful, especially if approval were to be granted or recommended, how to come up with recommendations in terms of antiplatelet therapy. It's not a trivial thing to be on Plavix for five years. In terms of thrombosis down the line, it may be affected.

On the other hand, any of us who take care of patients, everything we do is

complicated by a patient already being on Plavix. So I think it will be valuable for us to see whatever analysis either FDA or sponsor can provide in terms of any signal at all in terms of the relationship in terms of thrombosis in the patients that have been studied already.

And then I think it will be valuable for recommendations to be given and us to consider in terms of long-term evaluation and trials what recommended dosing of antiplatelet therapy we would arrive at.

DR. FIORENTINO: I could actually provide just to help frame that question. I don't know if I will have an opportunity, but the sponsor did provide us with some data that I didn't show an adherence to do antiplatelet therapy.

And this is based on -- the sponsor can probably explain it. And they have additional data, too, but this is based on the number of subjects on aspirin these days and

also takes into consideration a discontinuation. And I think these summaries count patients at the time of their first discontinuation, only do antiplatelet therapy.

CHAIRPERSON YANCY: I think part of the question, though, is an event rate coincident with the continuation or the length of exposure.

DR. FIORENTINO: Sure, sure. In the combined analysis, these are the stent thrombosis rates for patients with that first discontinuation of clopidogrel and ticlopidine on or before 390 days. And I just have the snapshot to give us, but you can see the ARC-definite plus probable rates in those patients with their first continuation before 390 days had fairly similar stent thrombosis rates in the XIENCE and TAXUS arms.

And also the protocol-defined stent thrombosis rates are shown here.

MEMBER PAGE: If I may just follow up? It becomes an important issue because a

number of clinicians I know are providing Plavix indefinitely to their patients with the drug-eluting stents. And if, indeed, this stent is different and there are certainly some signals that it may be different, I think we need to consider strongly whether the recommendations or the clinical practice is already underway in terms of indefinite Plavix therapy is reasonable with this device.

CHAIRPERSON YANCY: Dr. Somberg?

MEMBER SOMBERG: I have three questions I would like the FDA, if they could, to clarify. My first is, why was this compound considered not a new chemical entity?

Two is my interpretation -- and I must say Dr. Normand confused me a little bit -- was that from the statistical analysis that after doing the imputation, et cetera, and the sensitivity, that it was felt that, if you will, not inferiority but the superiority in most of the comparisons was not appropriate. And is that a correct interpretation or not?

I don't want to rush you.

And the third thing is about the potential post-marketing study. I wondered if the FDA intended not to have a control group in that design.

MS. BOAM: Hi. I am Ashley Boam. I am the Branch Chief for Interventional Cardiology Devices. And if I could address your first question, Dr. Somberg, as to why FDA did not consider everolimus to be a new chemical entity or a new molecular entity?

We believe that because everolimus under the trade name Certican had been widely studied and had been thoroughly evaluated by the Center for Drug Evaluation and Research, but this drug fell under the same category as zotarolimus and paclitaxel did when they were first introduced onto a drug-eluting stent, contrasted with other agents, some of which you have seen, such as zotarolimus, others that are still in development, such as biolimus, which have not ever been studied for

any other indication other than in association with a drug-eluting stent.

So it is really the differential of whether the drug has been studied or has only been studied or is planned to be studied on a drug-eluting stent where FDA has made its assessment as to the amount of clinical data on the stent that is necessary to evaluate for potential drug toxicity-type effects.

And then in terms of the potential of the post-approval study, the conversations that FDA has had with Abbott Vascular about the post-approval study have occurred over a period of time. As they mentioned and as Dr. Duggirala mentioned, they continue at this time.

So FDA has made its recommendations in discussions with Abbott Vascular all through the development process and in the preparation of their PMA. Specifically there have not been necessarily new recommendations made to them since October if that would be

your question.

And I'll let Dr. Yan answer your statistical question. But no, our initial recommendation to the company was not necessarily that a control group was needed. If you would like further explanation of that, I would be happy to give that.

MEMBER SOMBERG: Just say that again.

MS. BOAM: That we have not recommended that post-approval studies necessarily require the use of a control group, a new prospective control group versus evaluating comparing back to data that was already available.

CHAIRPERSON YANCY: Is that acceptable, Dr. Somberg?

MEMBER SOMBERG: These were just qualifying questions. I mean, if you're asking me, no. I thought we had in previous deliberations for other situations like this felt that most post-marketing studies as my

policy -- and I don't know how other people feel here -- I would like to see some sort of comparator.

And without a comparator, I think we have single-arm observational information that becomes very hard for any group to interpret.

CHAIRPERSON YANCY: Additional questions or comments before we break? Yes, Dr. Yaross?

MEMBER YAROSS: I had a different question on the post-approval study. The sponsor has proposed a one-year endpoint for stent thrombosis, and FDA has recommended and said five-year follow-up.

Can you comment on that in the context of what has been required of other sponsors in this product class?

DR. DUGGIRALA: Well, the issue of late stent thrombosis has only applied to the more recent sponsors. And it is something that our thinking has changed on it because

the information we have has changed on it so much.

And so I don't feel like we have enough information past one year to have any idea of what the stent thrombosis rate is in the on-label population. And that is something that is critical to collect in the post-market if that answers your question.

CHAIRPERSON YANCY: We'll proceed with one final question before they break for lunch. Dr. Normand?

MEMBER NORMAND: Thank you. I just wanted to get FDA's thinking of why they assume the SPIRIT II and SPIRIT III were completely exchangeable. And what I mean by that is they are combined at the patient level.

Even though the SPIRIT II study is conducted in different sites, different locations, I do observe, at least in my mind -- you know, they are different studies, although the protocols may be dissimilar,

although there may be some obviously data collection is the same, but they are conducted in different places, I am presuming. They are conducted in different sites.

And then, moreover, there are some patient differences. I think I observed less unstable angina in one group, 20 percent versus 27 percent in the TAXUS. So there are patient differences, but just standard statistical practice would not throw the two together.

I say this. My standard statistical practice. I do a lot of work in meta-analysis. And even though they may have been in the same protocol, typically one would have to stratify by the fact they are two different studies. And so I wanted to get your thinking on why that was an acceptable strategy.

It seems my understanding is, Dr. Fiorentino, when you first talked, you said there were no patient differences. So you

combined them together. So I do have some very strong concerns about throwing them together assuming at the patient level they are completely exchangeable, which is an enormously strong assumption to make.

CHAIRPERSON YANCY: And certain protocol definitions differed as well.

DR. FIORENTINO: Yes. Those are valid concerns. You know, our primary goal was -- I understand those concerns. And looking from a clinical standpoint at some of the variables and the way the trials were designed, the fact they are randomized to the same control group, we felt that they could be combined with the purpose of increasing the evaluable sample size to just look at these very rare events.

You know, we understood there were minor differences between the trials. But overall the analysis was different by SPIRIT III, but it was hoped that with the SPIRIT II patients, we could boost the evaluable sample

size to look at those rare events given the limitations.

MEMBER NORMAND: I don't think I was arguing about combining them or not. I think I am arguing about the way you combine them. Typically if you have different studies, you need to stratify. You need to have some sort of variable in there.

Because there are differences, these are not the same trials conducted at the same sites. You know, SPIRIT II was confounded by European sites, et cetera.

So don't get me wrong. I am not saying they shouldn't be combined, but the way that they were combined would not be the way most people who do meta-analyses if you call them true meta-analyses or not, the point is when you combine them, you need to stratify in some sort of manner by study.

So, again, don't get me wrong, but I definitely would urge -- I wanted to understand your thinking on that. So you want

them to be combined, but I guess the way they're combined I would argue is not the most appropriate way.

CHAIRPERSON YANCY: It's 12:45. And it's imperative that we start at 1:30 so that everyone can have full opportunity to hear the two panel-based reviews and to allow the sponsor and FDA to respond to additional questions.

Let me encourage you to just make note of your questions. There will be a limited opportunity to reengage the FDA. And we will reconvene at 1:30. Thank you.

(Whereupon, the foregoing matter was concluded at 12:46 p.m.)

DR. YANCY: If I can get your attention, and have everyone come to their places, please. I'd like to go ahead and get started. It's just a few minutes after 1:30, and we want to be able to give all of the afternoon presentations and discussants ample time.

Let me just review how things will proceed. We have a few questions from a panel that we feel are critical for the FDA to address, several of which deal with the statistical integrity of the analyses that we've seen, and we want to have ample opportunity to discuss that.

We also have presentations that the sponsor has prepared in response to what we've requested, and we'll follow that as a second opportunity, and then we'll have Dr. Morrison and Dr. Hirshfeld round down this next hour with their reviews of the PMA.

So with that having been said, I think we need to go to Dr. Hirshfeld, who had a specific question for FDA.

DR. HIRSHFELD: This has to do with the decision to do the pooled analysis of the SPIRIT II and SPIRIT III, and present a unified pooling of those two data sets.

My question is, how much of these results of these trials or the data were known

before you made the decision to permit the pooling? And, i.e., did that permit you to anticipate what the pooled analysis was going to show before you authorized the permitting of doing it?

DR. FIORENTINO: And you're referring to even the initial pooling for the one-year data, as well. There was a one-year in there, and the two-year. Yes, when we asked for the combined two SPIRIT II and III RCT studies, we had seen I believe the nine-month SPIRIT III results, so we had seen the results of those studies.

DR. HIRSHFELD: So you could really have anticipated what the pooled results would show, because you'd seen, basically, the tabulated data.

DR. FIORENTINO: Correct. It was a post hoc analysis, and we did see the results.

DR. YANCY: Did you need to follow with any additional questions?

DR. HIRSHFELD: Well, the -- I had

asked the question earlier this morning to Greg, or Dr. Stone, and there's a very large disparity between the stent thrombosis rates in the two trials. One is zero, and the other is 1.1 percent. And by permitting the pooling, that takes the aggregate stent thrombosis rate down to eight-tenths of a percent, because that was anticipatable when you made the decision that that would be permissible.

DR. FIORENTINO: Yes, that is correct.

DR. YANCY: Dr. Stone, we'll refer to you in just a few minutes. There was another question that FDA needed to address. Dr. Somberg, could you restate that, please?

DR. SOMBERG: Well, I think it was Dr. Yan, who is going to respond to my question after Dr. Normand was confusing the issue, and that was the consideration of the sensitivity and other analyses you did looking at both non-inferiority and then superiority.

And my understanding was that you were saying that while almost invariably the non-inferiority stood. There were many instances where the superiority did not stand statistically. And although you were using maybe a harsh test, you still felt that superiority was not established. Is that correct? I don't want to put words in your mouth.

DR. YAN: Yes, it is correct.

DR. NORMAND: I'm wondering if that phrase needs to be in the Minutes about Dr. Normand confusing Dr. Somberg.

(Laughter.)

DR. SOMBERG: I'm willing to strike it from the Minutes.

DR. YANCY: Is that a badge of honor? Since we're on the same issue, perhaps so that all of us can be clear, can either member of the FDA team just give us a two or three sentence synopsis of the intent of the tipping analysis, and what we should take from

that? Does that align directly with what Dr. Somberg just summarized, or is there something else you wanted us to take from that?

DR. YAN: The reason I did tipping part analysis, I just want to give panel as much information as I can, because I did a worst case analysis, and sometimes it may not be -- it may be too conservative, and it may not be realistic. So I just want to, based on certain algorithm, to show the panel that under which imputed missing data, the difference between the treatment arms can reject -- is not able to reject the null hypothesis.

DR. YANCY: Thank you. Are there other questions from the panel for the FDA? Did the FDA want to expand upon anything that you thought you didn't get a chance to fully address?

DR. DUGGIRALA: Yes. I just wanted to expand on our answer about the control group to Dr. Somberg. The sample size that we

asked the sponsor to calculate was based on the study hypothesis, comparing the stent thrombosis rates from the pivotal trial. And so although we're not asking for current new controls to be enrolled, we are comparing the rates that we would see from the registry to another group. And that is something different from the earlier drug-eluting stent PMAs. And most of the PMAs now that we are studying at FDA, we are asking for a study hypothesis upon which the sample size is based.

DR. YANCY: Is that acceptable, Dr. Somberg? Or, Dr. Normand, did you need to comment?

DR. NORMAND: I'm sorry, I just don't understand. So you're saying there will be a comparison group?

DR. DUGGIRALA: The pivotal trial cohort is the comparison group.

DR. NORMAND: Okay. So it's going to be --

DR. DUGGIRALA: Historical control.

DR. NORMAND: Historical.

DR. DUGGIRALA: Right.

DR. YANCY: Okay. Dr. Fiorentino.

DR. FIORENTINO: Yes. I just wanted to clarify that when we combine these two analyses, we understood that these are very rare event rates, and they are susceptible to the definitions that are used, and such. Really, partly what we were looking to see is what the effect of adding extra 300 patients from SPIRIT II would do to the precision that we got around those stent thrombosis rates, because we already knew what it was in SPIRIT III, and that was 1,000 patients, and so it was our hope that we could kind of get a better estimate of what the true stent thrombosis rate would be, knowing that these point estimates are somewhat difficult to compare and interpret.

DR. YANCY: And, again, that's just one year. Correct?

DR. FIORENTINO: Yes. I'm really referring to the one year.

DR. YANCY: If you -- yes, Dr. Blackstone.

DR. BLACKSTONE: Could I follow-up on that? Among the 300 patients in SPIRIT II, have there been any thrombosis?

DR. FIORENTINO: Yes. I actually don't have the data to put up. I think Abbott can break that down for you better in their presentation.

DR. YANCY: I'd like to thank the FDA for indulging us with a few more questions, and I would now like to invite the sponsor to respond to the inquiries that we left you with this morning.

MR. JOHNSON: Thank you, Mr. Chairman. We'll take the opportunity to respond to the questions presented, as well as some clarifying questions that you asked of FDA, as well.

First, we'd like to invite Dr.

Pocock to talk a little bit about the superiority analysis that were done, and the justifications which we have for that.

DR. POCOCK: I think there's one slide that's going to appear, or am I supposed to give it to you? I thought it was already there.

MR. JOHNSON: Sorry, we got you at a wrong order. We'll go ahead and pull you up in a minute then.

Actually, sorry, my mistake. The right order we want to go to first is to really talk about the EEL analysis with Dr. Fitzgerald. Sorry about that.

DR. FITZGERALD: Thank you. My name is Peter Fitzgerald. I'm a Professor of Medicine at Stanford, and Joint Appointed in the Engineering School. I have no equity holding from Abbott Vascular. I'm a consultant, have research grants for several other stent companies by virtue of the core lab responsibility that I have at Stanford,

and I am a consultant with several other medical companies unrelated to the subject matter here.

I think that I have been involved personally with intravascular ultrasound since its origin in the late 1980s. I have virtually taught a number of interventionalists in the last two decades how to interpret early on intravascular ultrasound, and then the clinical utility of how to apply this to various percutaneous coronary interventions. I have trained over 150 research and clinical Fellows that stay a minimum of one year in my laboratory. At present, there are 12 Fellows, and those are the folks that actually perform the core lab analysis that we're going to speak about today.

As Greg eloquently described, intravascular ultrasound just provides another view, if you will, from inside the vessel. We can see if the stent struts are well manicured

up against the vessel wall. We can look at the extent of the vessel and judge that over time for integrity, and I think that's an issue that I would like to talk about.

I also would like to talk about some definitions with respect to incomplete apposition. I think Dr. Somberg brought this almost confusing nomenclature up, and I am partly responsible, I think, for some of the definitions and the changes of those over time.

What we're talking about with respect to incomplete apposition, whether it happens when you put in the stent, or whether the stents are not touching the vessel wall at baseline, they have the same definition for that particular call in the core lab, and that means that the stent struts do not touch the vessel wall. There's blood that is flowing on both sides of the stent struts. And in my laboratory, it's done by two independent blind observers in order to get that definition.

This definition has been shared not only with our core lab, which is the largest intravascular ultrasound core lab in the world, but other core labs, and has been published four times in the literature, this exact definition. So let's talk about SPIRIT III, and talk about baseline incomplete stent apposition, which is shown in this particular slide. And here you can see that the stent struts are not touching the vessel wall. This is at the time of deployment. Sometimes the angiogram looks perfect, because the dye can flow on both sides of the stent struts, and it looks like a very patent, well-deployed stent, but that's sometimes not the case when you look at it with intravascular ultrasound.

Now that can have two fates going forward at the time of follow-up. One, you can get, as Greg has talked about, the integration of tissue between where the stent struts weren't completely up against the vessel wall at baseline observed at follow-up,

or you can have persistent incomplete apposition. We see more of that with drug-eluting stents, because there's less intimal hyperplasia that occurs. So with respect to this particular trial, we see XIENCE has a 34.4 percent compared to TAXUS, baseline incomplete apposition that is no different between the two groups. And as we watch that over time, we see that some resolve, some persist, but there's no difference between either XIENCE V or TAXUS with respect to baseline incomplete stent apposition, or follow-up, whether it be resolved, or whether it be persistent.

Importantly, and this is very important to follow, there's no death, no mock heart infarction, no stent thrombosis associated with this baseline incomplete stent apposition observed in both groups.

Now let's talk about another incomplete apposition, but one that happens at follow-up. And this is what Greg voiced as

probably something we're a little bit more sensitive to, because as you can see here, the stent is well manicured up against the vessel wall baseline, and it doesn't change over time, but what has changed is abnormal remodeling of the vessel. In other words, the vessel has moved away from the stent struts over time, providing now blood to flow on both sides, the inner and the outer side of these particular stent struts.

There is some literature that possibly links this to stent thrombosis, and we have in all the core lab experiences seen a higher rate of this late incompleted stent apposition, especially with first generation stents compared to bare-metal technology.

So let's fill this slide in, if you will, and look at baseline complete stent apposition, and then the evolution of incomplete stent apposition, or late acquired stent apposition. For the XIENCE V it's 1.1 percent, for TAXUS it's 2.3 percent, no