

1 restenosis, 5.8 percent with TAXUS, which
2 actually is quite good in these types of
3 patients out to one year, but this is reduced
4 further by 47 percent to 3.1 percent with
5 XIENCE. And that is statistically significant
6 at the p equals 0.02 level.

7 Now, other trials that have
8 compared a low late loss stent to TAXUS has
9 not shown a reduction in target lesion
10 revascularization in randomized trials. Why
11 do we see that here? Well, we see it here
12 because when one combines the angiographic
13 measures, you can see there are very, very
14 robust reductions, both in-stent late loss and
15 in-segment late loss.

16 But, perhaps even more important
17 than that, there are also significant
18 reductions in in-stent binary restenosis and
19 in-segment binary restenosis, so binary
20 restenosis, meaning a diameter stenosis of 50
21 percent or more, this is when we start to get
22 physiologic significance of a flow-limiting

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1 recurrent lesion.

2 And other trials with low weight
3 loss stents have not shown reduction in binary
4 restenosis compared to TAXUS, presumably
5 because of low-frequency adverse events. It
6 could be strut fracture. It could be polymer
7 reactions. We don't know. But, regardless,
8 this reduction in binary restenosis is what
9 drives the reduction in clinical restenosis
10 which leads to clinical benefit.

11 Thus, if one looks at major adverse
12 cardiac events at one year, again, now we see
13 and from two consecutive randomized trials the
14 first drug-eluting stent ever compared to
15 another drug-eluting stent of the two that are
16 approved in the United States, they actually
17 improve overall safety and efficacy outcomes
18 with reduced major adverse cardiovascular
19 events almost by half, 5.2 percent with XIENCE
20 V compared to 10 percent with TAXUS, a 49
21 percent relative reduction.

22 When we look at remote target

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1 vessel revascularization, again, this is the
2 noise that you wouldn't expect to be
3 different. You see that they're not different
4 between the two stents.

5 And, thus, even when we look at
6 target vessel failure, again, we're not
7 powered for this. But still you see the
8 curves now starting to spread. And we tend to
9 get a 30 percent reduction in target vessel
10 failure with XIENCE V compared to TAXUS, a
11 p-value of .062.

12 Now, finally, I think when we look
13 at a low late loss stent, we would like to see
14 that the results are consistent in lesions
15 that are at low risk for restenosis and also
16 high risk for restenosis. And the three
17 variables time and time again that always
18 separate out the low versus the high-risk
19 restenosis patients are reference vessel
20 diameter with small vessels having higher
21 restenosis because of higher late loss, lesion
22 length with long lesions having higher late

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1 loss, and diabetics with diabetics having
2 higher late loss.

3 And here you can see looking at the
4 in-stent late loss that in these high
5 restenosis risk lesions, you can see that the
6 reductions are very robust with a 59 percent
7 reduction in late loss in the very long
8 lesions, greater than 20 millimeters, a 50
9 percent reduction in late loss, and in
10 diabetic patients a 40 percent reduction in
11 late loss.

12 And I show you where the continuous
13 measures of late loss because that does give
14 you more power to look at subgroups, but all
15 of these subgroups should be considered just
16 exploratory. Similarly, when we look at
17 in-segment late loss, we see the same sorts of
18 trends among the high-risk lesions.

19 And, finally, to try to put into
20 perspective for you the outcomes of the XIENCE
21 V stent compared to the TAXUS stent in the
22 SPIRIT trials. And I think this is important

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1 because numerous drug-eluting stents have
2 taken on the TAXUS stent to try to prove
3 non-inferiority or superiority.

4 And these are now four of the new
5 DES versus TAXUS randomized trials that have
6 been completed: Zomaxx I looking at the
7 zotarolimus-eluting stent, Zomaxx versus
8 TAXUS; Costar II looking at a new way to elute
9 paclitaxel from a unique stent versus TAXUS;
10 Endeavor IV, looking at a zotarolimus-eluting
11 stent from a different polymer than in Zomaxx
12 or the same polymer in Zomaxx but slightly
13 different stent compared to TAXUS; and now
14 SPIRIT III with the XIENCE V
15 Everolimus-Eluting Stent versus TAXUS.

16 And TAXUS has been a tough
17 competitor. In fact, it really blew out of
18 the water these first two stents. And here
19 you can see the general measures of the major
20 endpoints that we have power to show
21 reasonable numbers for; that is, in-segment
22 and in-stent late loss, even binary

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1 restenosis, target lesion and target vessel
2 revascularization and then MACE and target
3 vessel failure.

4 You can see that the red arrows are
5 TAXUS did better. The yellow arrows are the
6 new stent did better. And, again, Zomaxx and
7 Costar clearly didn't make it.

8 When we look at Endeavor IV, you
9 can actually see looking at measures like late
10 loss, restenosis, and target lesion
11 revascularization, TAXUS, either borderline or
12 statistically significantly, was better, but
13 when you look at TVR MACE and TVF, the rates
14 were very similar between the stent Endeavor
15 and TAXUS.

16 But when one looks at SPIRIT III,
17 you can see you really start to see robust
18 reductions in all of these measures, anywhere
19 from 22 percent reduction in target vessel
20 failure up to 50 percent reductions in
21 in-segment late loss.

22 So, to try to put all of the

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1 preclinical data together that we have from
2 these clinical studies that would follow up
3 complete through one year and with up to three
4 years at least in a small subset of patients
5 in SPIRIT FIRST, the XIENCE V
6 everolimus-eluting stent compared to the TAXUS
7 paclitaxel-eluting stent result in significant
8 reductions in angiographic in-stent and
9 in-segment late loss and binary restenosis,
10 significant reduction in intravascular
11 ultrasound measures, a percent volume
12 obstruction; and, importantly, without
13 positive remodeling or late acquired
14 incomplete apposition, significant reductions
15 in myocardial infarction, major adverse
16 cardiovascular events, and target vessel
17 failure at 30 days, so enhanced safety at 30
18 days, with non-significant numerical trends
19 towards less composite cardiac death and MI
20 and less target vessel failure at one year;
21 however, and very strikingly, for the first
22 time, significant reductions in target lesion

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1 revascularization and major adverse
2 cardiovascular events at one year with a new
3 drug-eluting stent compared to TAXUS. And
4 this was all achieved with comparable rates of
5 stent thrombosis.

6 I believe that the clinical
7 angiographic benefits of the
8 everolimus-eluting XIENCE V stent compared to
9 the widely utilized paclitaxel-eluting TAXUS
10 stent should be considered particularly robust
11 because we have now seen essentially the same
12 findings in two consecutive randomized trials
13 in two different geographies. And it's always
14 very reassuring when you see two separate
15 randomized trials basically showing you the
16 same thing.

17 And, finally, in the ultimate
18 conclusion, every pre-specified primary and
19 major secondary endpoint from the SPIRIT FIRST
20 randomized trial, the SPIRIT II randomized
21 trial, and the SPIRIT III randomized trial
22 were successfully met.

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1 I am now going to ask Mitch Krucoff
2 to come up, who is going to give you
3 additional safety perspectives about the
4 XIENCE V stent.

5 DR. KRUCOFF: Thank you, Gregg.

6 Good morning, everyone. My name is
7 Mitch Krucoff. I am an interventional
8 cardiologist at the Duke University Medical
9 Center and Director of the Cardiovascular
10 Devices Unit at the Duke Clinical Research
11 Institute.

12 This is a listing of my conflicts
13 of interest. I through my work with the
14 institute do moderate-level consulting and
15 work with research grants from almost all
16 manufacturers of drug-eluting stents.

17 I have no equity holdings or other
18 significant conflicts to acknowledge. I will
19 acknowledge that Abbott Vascular has paid my
20 transportation costs and hotel costs for this
21 presentation.

22 In this section of the

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1 presentation, I am going to touch on three
2 areas. Firstly is just to put into a safety
3 context the prospective study analyses that
4 you just heard from Dr. Stone; secondly, to
5 examine data from a two-year safety subset
6 that I will describe in further detail; and,
7 finally, to indicate how the integrated,
8 dedicated Abbott Vascular continued access and
9 post-approval program is structured to allow
10 us to understand the safety of and performance
11 of this device in human subjects over time.

12 So, to begin with, just as a safety
13 context, I think to bring back the one-year
14 data that Gregg just showed for the SPIRIT II,
15 SPIRIT III, and the patient-level pooled
16 analyses, there is, in fact, all of us have to
17 recognize in the permanent implantation of a
18 device in human coronary artery not a clear
19 separation between effectiveness measures and
20 safety measures. In fact, they are related.

21 So some of them are easier to
22 measure. Some of them are easier to measure

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1 in smaller populations. Some of them are
2 rarer. And they're in varying degrees of
3 clinical consequences from causing recurrent
4 chest pain or need for a second procedure out
5 to causing large myocardial infarctions and
6 death.

7 So across this spectrum, however, I
8 think we do have to keep in mind that
9 effectiveness measures and safety measures in
10 coronary implants are actually fundamentally
11 related.

12 And I think we can take an overview
13 of what you have heard in the complete cohort
14 follow-ups out to one year from each and both
15 of these studies that the measures appear to
16 be quite consistent across this entire
17 spectrum of prospectively defined safety and
18 effectiveness analyses from these completed
19 trials.

20 Chronologically, on the other hand,
21 we stand here today in a little different
22 universe than the universe that in the 2003-4

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1 time frame was the universe in which these
2 whole studies and their designs and their
3 analysis plans were completed.

4 So the SPIRIT program, as Gregg
5 mentioned, was completed before the first
6 reports that I think began to gather all of
7 our attention in the Fall of 2006, the
8 European Society of Cardiology, that, in fact,
9 drug-eluting stents may have another very
10 important feature that was not previously
11 appreciated well because it involves very rare
12 events. Event rates are, arguably, somewhere
13 between 0.3 and 0.6 percent per year.

14 In addition, as the late stent
15 thrombosis events have become more and more
16 detailed and examined, it appears quite clear
17 that this is a complex interaction between
18 aspects of the substrate, individual patient
19 characteristics, morphologic anatomic
20 characteristics, procedural and technical
21 characteristics, which stent platform, and the
22 characteristics of each stent platform, and

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1 the use and duration of dual anti-platelet
2 therapy or its interruption in compliance, but
3 all of these issues are probably intermixed in
4 some ways with regard to understanding late
5 stent thrombosis.

6 So ultimately with complex subgroup
7 considerations and this kind of event rate,
8 it's also very clear that statistical
9 certainty about the behavior of such an
10 endpoint will require large patient cohorts
11 and long-term follow-up.

12 So this is our contemporary focus.

13 This is a focus that for us in the devices
14 universe I think was a relatively new one but
15 a very important one for a device that isn't
16 put into 100 or 200 patients a year but
17 literally is put into hundreds of thousands of
18 patients a year and as a permanent implants
19 then aggregates us at a public health level
20 with millions of patients who have these
21 devices. So this is a contemporary focus that
22 is a very important one.

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1 A great deal of data with regard to
2 this has been summarized. In fact, there are
3 currently more than 15 peer-reviewed published
4 meta-analyses, predominantly examining the
5 initial side of this question, which was
6 relative to bare metal stents that had been
7 used previously to the approval of
8 drug-eluting stents. Were drug-eluting stents
9 better, worse, or the same with regard to this
10 particular rare endpoint behavior?

11 And out of all of that complexity,
12 I think perhaps for today the one most
13 important point, which has been summarized and
14 was looked at in great detail in a two-day
15 dedicated special panel, of which many of you
16 participated in last December, was that the
17 regulatory approval process worked and that in
18 approximately four years prior to this special
19 panel in 2006 with the approval of the TAXUS
20 stent, that in the on-label use of this
21 device, we still have the very clear
22 conclusion that the TAXUS stent is safe and

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1 effective in on-label use relative to bare
2 metal stents.

3 This is a very important point
4 because I don't have a lot of data to show you
5 about the XIENCE V stent versus bare metal
6 stents because the program was not designed to
7 do that.

8 In fact, on the other hand, the
9 comparator, as Gregg has mentioned, in all of
10 the pivotal data that is going to be the basis
11 of the approval decision today, is the XIENCE
12 V has been compared to the TAXUS stent.

13 So I think it is fair to say we
14 know a lot about the TAXUS stent. And the
15 TAXUS stent on label is safe and effective.
16 What we have done is to try, however, with all
17 of the data available to address a
18 contemporary focus in a program that was
19 designed to do what I think many of us at the
20 interventional level are very interested in
21 seeing, which is to go past the first
22 generation of drug-eluting stents into

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1 hopefully better products as a second
2 generation.

3 So the SPIRIT II and SPIRIT III
4 programs literally were designed to test a new
5 second generation investigational drug-eluting
6 stent platform in head-to-head randomized
7 comparison to a current approved and very
8 widely used drug-eluting stent, the TAXUS
9 stent.

10 In order to try and extend the
11 observations beyond the completed one-year
12 cohorts available from SPIRIT II and SPIRIT
13 III, we compiled a two-year safety data
14 analysis. But, again, it is important to
15 recognize this was not a prospective analysis
16 plan incorporated in the fundamental designs
17 because of the chronological timing of
18 awareness of these issues for either SPIRIT II
19 and SPIRIT III. In fact, both of these
20 programs were completed in their enrollment
21 before ESC meeting of 2006.

22 The statistical analysis plan that

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1 I am going to share with you today was
2 developed on the basis of ongoing discussions
3 with FDA. And the two-year safety subjects
4 included from the SPIRIT II and III total
5 cohorts had the following inclusion criteria,
6 which were specified in order to conduct this
7 particular two-year safety statistical
8 analysis plan.

9 Specifically, all subjects were
10 required to have completed two-year follow-up
11 or have terminated from the trial prior to
12 October 30th, 2007. So this represents all
13 data available basically up to the end of last
14 month.

15 All data needed to be completely
16 monitored and where all events were
17 independently adjudicated by blinded clinical
18 event committees. So essentially these are
19 all available data that we can consider
20 reliable data at this level.

21 The actual numbers are shown in
22 this flow chart of the 1,302 patients whom you

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1 have just head described out to one year from
2 SPIRIT II and SPIRIT III randomizing
3 head-to-head TAXUS versus XIENCE V.

4 Six hundred and three questions met
5 the criteria for this particular two-year
6 safety subset as having completed two-year
7 follow-up or terminated with completed data
8 while 699 have not. And these are patients
9 who, by and large, have not reached the
10 two-year follow-up point or a few in whom data
11 collection is still ongoing.

12 Of the 603 patients I can describe
13 to you this morning, 422 received an implant
14 of XIENCE V stent and 181 the TAXUS. Out of
15 this 603, there are 74 early terminator
16 patients. The 74 completely monitored early
17 terminators include 43 who were terminated
18 before one year after randomization in the
19 trial, 31 who were terminated between years
20 one and two.

21 So as I show you the data from
22 these 603 patients, the denominator for each

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1 of the safety endpoints that we will analyze
2 is going to change. And it's going to vary
3 because if a patient terminated for an event
4 like a death prior to two years, we will
5 include the patient. And the numerator and
6 denominator will both, of course, reflect that
7 outcome.

8 If a patient terminated before the
9 two-year endpoint and had not had a clinical
10 event, they will not appear in the
11 denominator. So depending on whether or not
12 the patient had an event prior to or at the
13 time of termination, as I show each of these
14 endpoints, you will see that the denominators
15 will range from between 534 to 563 of the 603
16 available patients for this analysis.

17 As this patient fundamentally is a
18 chronological selection process, needless to
19 say, the patients who are enrolled earliest in
20 trial will be the first patients to reach two
21 years of follow-up. So there is a
22 chronological selection involved in this

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1 process.

2 There are a number of ways that
3 confounding bias could creep into this
4 analysis. In particular, the two-year subset
5 could be fundamentally different from the
6 completed cohort. You have seen the data from
7 one year.

8 It is also conceivable that the
9 XIENCE V group or the TAXUS group would
10 themselves be different or would vary between
11 the two groups at two years relative to their
12 relative concordance at one year.

13 So I am going to show you some of
14 the general baseline characteristics,
15 angiographic characteristics, and
16 thienopyridine use characteristics of these
17 populations for the one-year completed cohort
18 in the column on the left for XIENCE V and for
19 TAXUS.

20 This is the 1,302 patients versus
21 the 2-year safety subset whose outcomes data I
22 will be sharing with you subsequently for the

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1 XIENCE V group and the TAXUS group in this
2 asymmetric randomization.

3 As we look at key baseline
4 characteristics, it is reasonable to say, " It
5 think that the relative distribution of these
6 characteristic in the two-year subset compared
7 to complete," and then XIENCE V versus TAXUS
8 across the complete subset as well as compared
9 to one another within the subset is reasonably
10 representative.

11 Similarly with the angiographic
12 characteristics relative to the complete
13 cohort versus the two-year subset and in
14 between or in comparing the XIENCE V and the
15 TAXUS subgroups within the two-year subset,
16 the representation of angiographic
17 characteristics, lesion location, reference
18 vessel diameter, et cetera, but looks
19 reasonably representative.

20 As we looked at prolonged
21 thienopyridine use and thienopyridine
22 compliance, we see something that I think is

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1 potentially notable. And that is that in the
2 patients who completed the two-year follow-up,
3 their use of extended beyond six months Plavix
4 is a little bit lower at nine months or at one
5 year than in the completed one-year cohort.

6 Depending on how much you think
7 extended duration Plavix between six months
8 and a year actually matters in terms of
9 outcomes, I note this simply to note that of
10 the 603 patients who have accessed to for this
11 analysis, they may be at a little higher risk
12 for some of these low-frequency events, just
13 because chronologically at that time there is
14 probably less physician emphasis to their
15 patients to take Plavix longer; whereas, in
16 more recently enrolled patients, at least
17 culturally, some of us are encouraging our
18 patients to do that more frequently.

19 So I am now going to share with you
20 the sequence of what we consider the less
21 frequent endpoints. You have seen these data
22 already out to one year. And I am now going

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1 to show you the data available for the
2 two-year safety subset.

3 This is all death represented in
4 red on the right for TAXUS at 6.7 percent and
5 approximately 30 percent lower numerically,
6 4.8 percent, for XIENCE V; for cardiac death,
7 2.5 percent with TAXUS, 1.8 percent with
8 XIENCE V, low numbers, relatively similar; for
9 myocardial infarction, 5.1 percent with TAXUS,
10 3.1 percent, about 40 percent lower
11 numerically, with XIENCE V at 2 years;
12 combining cardiac death and myocardial
13 infarction, 6.3 percent with TAXUS, 4.7
14 percent with XIENCE V, numerically about 30
15 percent lower.

16 As Gregg mentioned, in addition to
17 the protocol stent thrombosis designed at the
18 time these protocols were designed, we have
19 acquired an independent retrospective
20 readjudication of stent thrombosis endpoints
21 per the ARC definitions.

22 So in this slide, I am showing you

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1 both of those. On the left is the stent
2 thrombosis rates per protocol, 1.9 percent for
3 TAXUS, 1.6 for XIENCE V, essentially identical
4 and the stent thrombosis per ARC-definite and
5 probable categories literally identical at 1.3
6 percent for both.

7 Characterized by timing. And this
8 slide shows 31 days out to 2 years for
9 per-protocol on the left stent thrombosis, per
10 ARC-definite and probable on the right, event
11 rates again fairly low, 1.1 percent with
12 XIENCE versus 1.9 percent with TAXUS, 0.8
13 percent with XIENCE versus 1.3 percent with
14 TAXUS.

15 MACE, the combination endpoints
16 Gregg described, cardiac death, myocardial
17 infarction, target lesion revascularization at
18 two years in the safety subset, 13.9 percent
19 with TAXUS versus 7.2 percent with XIENCE V,
20 about a 50 percent numerical difference;
21 target vessel failure, 15.8 percent with
22 TAXUS, 11.4 percent with XIENCE V, about a 30

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1 percent numerical difference.

2 So as we look at the observations
3 of a two-year pooled analysis from all
4 available patients in SPIRIT II and SPIRIT
5 III, we can say that the chronologically
6 selected subset based on all available data
7 was relatively similar in its baseline and
8 angiographic characteristics may represent a
9 slightly lower use of long-term, nine-month or
10 one-year duration, clopidogrel, but
11 fundamentally the directionality of the
12 endpoints at two-year in the safety subset are
13 very consistent with the more statistically
14 robust equivalence and even superior outcomes
15 seen with the XIENCE V stent versus the TAXUS
16 stent in the one-year completed cohort
17 analysis.

18 They're certainly consistent with
19 those directions and leave us at the end with
20 no indication of any unusual safety signal at
21 two years based on all available monitored
22 data at this time.

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1 So as we consider reasonable
2 assurance, I think we all know that it
3 fundamentally has to be based on data, but it
4 does involve some clinical thoughtfulness and
5 some perspective about the relative risk and
6 benefit were this device to be used in medical
7 practice. And their consistency and
8 characteristics of data from several different
9 sources or different trials all ultimately
10 weigh into what we might characterize as
11 reasonable assurance of safety.

12 So you have heard today that the
13 design objectives in this second generation
14 tool met or exceeded the development of a more
15 flexible thinner strut platform using more
16 advanced polymer with a very
17 well-characterized and low dose of a known
18 drug entity in preclinical multiple animal
19 models out to two years.

20 In the human trials, we can
21 recognize that at the end of one year in the
22 completed prospective analyses, all safety and

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1 effectiveness endpoints were made at
2 non-inferior or superior level in head-to-head
3 comparisons between XIENCE V and the widely
4 used, currently approved drug-eluting stent
5 TAXUS.

6 At two years, I think the most that
7 we can say is that the safety subset analysis
8 has a directionality that is consistent with
9 its one-year more robust analyses and that
10 this at least provides some assurance that
11 this is unlikely throw us a time bomb or some
12 unusual, unexpected event out further.

13 And ultimately then I think it's
14 fair to say that we have no evidence for
15 safety concerns that are apparent relative to
16 TAXUS based on all available monitored data at
17 two-year follow-up.

18 Now, a lot of that I hope I have
19 been pretty clear has very little in the way
20 of statistical certainty. That doesn't mean
21 it isn't assuring, but for statistical
22 certainty in this type of endpoint, this is

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1 just a power chart of what if we look for an
2 event rate between .3 and .5 percent with what
3 we might clinically consider a reasonable
4 delta or relative risk around it, that to have
5 80 percent, much less 90 percent, power to be
6 statistically certain about this level of
7 endpoint, we're talking about 7 to 16
8 thousand-patient cohorts.

9 So in that perspective, I think
10 and, as you heard from Dr. Marinac-Dabic
11 today, we very much agree with the FDA that we
12 are very much in need of a credible,
13 effective, high-quality post-market
14 environment where real world use and continued
15 evaluation of devices once they have been
16 released into the market can provide reliable
17 and ongoing information and evaluation. And
18 that is what I will finish with, is a
19 description of the very dedicated and
20 integrated XIENCE V continued access program.

21 So you have seen this slide now,
22 number three. You will see it one more time

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1 before we finish. But I am going to
2 concentrate now on the bottom half of this
3 slide, which is the ongoing and planned
4 clinical data from continued access and
5 post-approval studies.

6 The SPIRIT IV study is the
7 continued access trial. This is being led by
8 Greg Stone and involves a slightly more
9 complex than SPIRIT II and III population by
10 adding a third, or three, vessel disease into
11 the mix, three lesions.

12 This is a prospective, randomized
13 trial that will examine 3,690 patients. Two
14 thousand, two hundred twenty-five of these
15 patients have already been enrolled.

16 And noteworthy perhaps, there have
17 been three Data and Safety Monitoring
18 Committee meetings over the course of this
19 trial, with no safety-related issues reported
20 to date. The primary endpoint for this trial
21 is MACE at one year. All patients will be
22 followed up out to five years.

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1 The SPIRIT V study in the European
2 community and outside the United States
3 internationally includes 3,000 patients, 300
4 in a randomized cohort, examining performed in
5 diabetics of XIENCE V versus the TAXUS
6 Liberte, 2,700 patients in a registry. This
7 is being led by Eberhard Grube.

8 And this study has just completed
9 its enrollment; again, through the course of
10 this study, three Data and Safety Monitoring
11 Board meetings, no safety-related issues
12 reported to date.

13 SPIRIT Women is a unique
14 concentration on the response in female gender
15 of drug-eluting stent outcome. This is a
16 study that has just begun that will examine
17 2,000 females, 450 in a randomized cohort
18 between the XIENCE V and CYPHER, 1,550 in an
19 ongoing registry, all patients with a primary
20 clinical outcome of death, myocardial
21 infarction, and target vessel
22 revascularization at one year, followed out to

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1 five years.

2 The cohort, who are randomized,
3 will also have angiographic evaluation by a
4 protocol at nine months. This study, with
5 Marie-Claude Morice and Stephan Windecker
6 leading it, has just begun enrollment.

7 XIENCE V India, a post-marketing
8 study being led by Ashok Seth in India, will
9 look at 1,000 all-comer real world patients
10 looking at a primary endpoint of the
11 ARC-defined stent thrombosis followed out to
12 five years; in addition, looking at the
13 performance of the device, deliverability,
14 procedural success, as well as quality of life
15 and health status assessed by the Seattle
16 Angina Questionnaire.

17 The proposed post-market study in
18 the United States is this study, the XIENCE V
19 U.S.A. study. And it's my great honor to work
20 with Jim Hermiller from Indiana as the
21 co-principal investigator for this trial.

22 This post-market proposal is a

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1 5,000-patient all-comers real world registry.

2 The primary endpoint being proposed is the
3 ARC-defined stent thrombosis through five
4 years with a secondary clinical endpoint of
5 the composite death, myocardial infarction, at
6 one year followed out through five years.

7 In addition, as with the India
8 study, procedural success, performance of the
9 device technically, as well as quality of life
10 and health status assessed by the Seattle
11 Angina Questionnaire will be acquired.

12 In addition, detailed
13 characterization of compliance and/or
14 interruption of management and bleeding
15 complications related to dual antiplatelet
16 therapy will also be characterized in the
17 course of this post-market study here in the
18 U.S.

19 I also can mention that Abbott
20 Vascular and the principal investigators have
21 discussed and are in advanced discussions on
22 shifting the composite death in MI from a

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1 secondary endpoint to a co-primary endpoint in
2 addition to the ARC stent thrombosis as well
3 as the potential to utilize this 5,000-patient
4 cohort to look much more systematically at
5 optimal dual antiplatelet therapy as part of a
6 randomized, extended duration of dual
7 antiplatelet therapy study initiative.
8 However, these two elements, I have to
9 mention, have not yet been discussed with the
10 FDA in conjunction with this post-market
11 initiative.

12 So if you look at overall the
13 committed post-market and continued access
14 program from the XIENCE V stent, what we see
15 in this slide on the left is the degree to
16 which on-label use is predicted to emerge from
17 each of these populations and will, therefore,
18 be able to continue to add approximately 7,000
19 patients who are consistent with the on-label
20 indications for this stent. And that is where
21 we will add statistical certainty about the
22 events whose rarity is such that in this

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1 pre-market evaluation we simply can't say much
2 more than reasonable assurance.

3 We cannot say very much at the
4 level of highly statistically certain
5 p-values, that this is the way that that will
6 be built through the post-market approval
7 program.

8 On the right-hand side, in addition
9 to this additional certainty about on-label
10 behavior, is the intention and direction of
11 this integrated program to advance our
12 knowledge about the behavior of this device in
13 real-world use, including multi-vessel
14 disease, real-world populations from India,
15 Europe, and the United States, gender-specific
16 behavior, and optimal dual antiplatelet
17 duration and therapy.

18 So, in conclusion, XIENCE V
19 continued access post-approval program will
20 evaluate approximately 14,690 patients
21 worldwide, about 8,600 here in the United
22 States, of whom 4,900 have already been

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1 enrolled and reviewed by data and safety
2 monitoring boards without safety concerns.

3 This is an integrated, committed
4 post-approval program that utilizes systematic
5 high-quality science that will be delivered
6 from a post-market research landscape. And
7 this is very much in concert I think with all
8 of our focus on what we need to guard the
9 public health.

10 This program will prospectively
11 provide progressively additional statistical
12 certainty about the current directions of
13 on-label XIENCE V safety as well as will
14 prospectively provide new knowledge regarding
15 off-label and real-world use of this device.

16 I will now turn the podium over to
17 Krishna Sudhir from Abbott.

18 DR. SUDHIR: Thanks. Thank you,
19 Mitch. Good morning. My name is Krishna
20 Sudhir. I'm a cardiologist and Medical
21 Director at Abbott Vascular. I will summarize
22 the data that has been presented to you and

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1 will leave you with a few concluding remarks.

2 Dr. Simhambhatla presented to you
3 the overview of the XIENCE V design. It is
4 built on the well-established VISION and MINI
5 VISION stent and stent delivery system. It is
6 a flexible stent with thin struts. And it has
7 shown proven deliverability. It has a thin
8 biocompatible drug coating. The polymer is
9 durable and has been used in other medical and
10 cardiovascular applications. The long-term
11 biocompatibility is similar to a VISION bare
12 metal stent. Everolimus, as pointed out by
13 Gary Johnson, is a well-studied drug and, as
14 such, is not a new molecular entity.

15 Dr. Coleman then presented to you
16 an overview of the preclinical program. This
17 is a comprehensive preclinical evaluation with
18 35 studies in 2 species, with study durations
19 varying from 28 days to 2 years.

20 As shown in the scanning electron
21 micrograph on the right, we presented evidence
22 of rapid re-endothelialization, a smooth

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1 muscle cell rich neointima with no persistent
2 fibrin and minimal long-term inflammation.
3 The hemocompatibility is comparable to a
4 VISION bare metal stent. Thus, the
5 preclinical safety profile is equivalent to a
6 VISION bare metal stent.

7 You have seen our integrated
8 pre-approval and post-approval clinical
9 program with over 16,000 patients a few times
10 during the last hour or so. Dr. Stone
11 presented to you details of our pre-approval
12 clinical data with the SPIRIT FIRST, SPIRIT
13 II, and SPIRIT III clinical trials. In
14 addition, Dr. Krucoff presented to you an
15 overview of all the ongoing and planned
16 clinical studies.

17 We have presented to you through
18 Dr. Stone's presentation robust evidence of
19 effectiveness. Consistent clinical and
20 angiographic benefits of the XIENCE V stent
21 have been shown compared to TAXUS in two
22 consecutive randomized trials, SPIRIT II and

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1 SPIRIT III, in multiple geographies.

2 As shown in the bar graphs on the
3 left for SPIRIT III, all pre-specified primary
4 and major secondary endpoints from the SPIRIT
5 FIRST randomized, SPIRIT II randomized, and
6 SPIRIT III randomized trials were successfully
7 met.

8 Dr. Krucoff made the case for a
9 reasonable assurance of safety through
10 demonstration of comparable one-year death,
11 MI, and stent thrombosis rates to TAXUS. And,
12 as shown in the bar graphs on the left, there
13 are no differences apparent in safety events
14 at two years between treatment groups based on
15 all available monitored data. Thus, no safety
16 concerns are apparent compared to TAXUS based
17 on all available data to date.

18 In summary, our clinical results
19 are consistent with design intent and
20 preclinical observations. The SPIRIT FIRST,
21 II, and III randomized clinical trials all met
22 their primary and major secondary endpoints.

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1 In addition, the results of SPIRIT II and
2 SPIRIT III have been confirmed in a pooled
3 analysis presented by Dr. Stone.

4 We showed superiority in the
5 angiographic endpoint of late loss and
6 non-inferiority in the clinical endpoint of
7 target vessel failure compared to TAXUS.

8 We provided reasonable assurance of
9 safety as demonstrated by similar rates of
10 death, MI, and stent thrombosis compared to
11 TAXUS up to two years.

12 And, finally, a few post-approval
13 considerations. In post-market surveillance
14 programs, sample sizes for low frequency
15 events can vary from approximately 7,000 to
16 16,000 patients. Abbott Vascular has a
17 comprehensive integrated pre-approval and
18 post-approval plan with over 16,000 patients
19 and, importantly, 5-year follow-up.

20 A robust post-approval program with
21 14,690 patients worldwide with 5-year
22 follow-up has been presented today designed to

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1 detect the true incidence of low-frequency
2 adverse events.

3 Thank you for your attention.

4 CHAIRPERSON YANCY: The panel would
5 like to thank the presenters for a very
6 thorough presentation. I was especially
7 interested in the preclinical presentations
8 that were made. I thought they were delivered
9 very nicely and really helped to add some
10 clarity and a better understanding of this
11 particular platform.

12 SPONSOR Q&A

13 CHAIRPERSON YANCY: We now have
14 approximately 30 or 35 minutes for questions
15 from the panel to the sponsor for the
16 presentations heard. Let me remind the panel
17 that this is an opportunity to seek
18 clarification. If there is a particular line
19 of questioning that would prompt the sponsor
20 to acquire more data or bring more data to
21 bear, this is the time to raise that question
22 so that they can have that available for the

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1 afternoon and can be prepared to respond later
2 to that particular line of questioning.

3 Let me begin again by
4 congratulating the sponsors and the
5 investigators on the work that was done. I
6 have one set of questions that I would like to
7 start with that hopefully will be brief. And
8 perhaps Dr. Stone will be the best person for
9 me to direct these questions towards.

10 In looking at the preclinical data,
11 I think a very nice job was done of
12 identifying potential advantages. The thin
13 struts, the lower achieved dose of drug, the
14 complete dissolution of drug from polymer, and
15 the animal data were quite impressive, the
16 early re-endothelialization, the minimal
17 evidence of inflammation. So the anticipation
18 would have been, in part, what we did see in
19 the clinical trials, certainly non-inferiority
20 in some markers of superiority.

21 But I was especially struck by the
22 target vessel failure data from SPIRIT III

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1 that were consistent with the non-inferiority
2 signal but not a superiority signal. And even
3 though there are a number of compromises in my
4 view of the analysis Dr. Krucoff shared with
5 us, the very late stent thrombosis data,
6 again, did not suggest that those presumed
7 advantages that were outlined in the
8 preclinical arena were realized in terms of
9 reduction in late stent thrombosis.

10 So I don't know if this is a
11 function of the number of observations or
12 other factors that may be involved in the
13 clinical endpoint of target vessel failure and
14 the other considerations of very late stent
15 thrombosis, but if you could just comment on
16 what I see as somewhat of a disconnect, I
17 would appreciate that.

18 DR. STONE: Thank you. I think
19 when one looks at target vessel failure, it's
20 a composite endpoint with a lot of adverse
21 events that can go into creating that
22 endpoint. There's cardiac death, some of

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1 which may be related to the stent. And some
2 of it may actually not be related to the
3 stent.

4 There's myocardial infarctions,
5 again, some of which is target lesion-related,
6 some of which is not. There's target lesion
7 revascularization, which is directly related
8 to the stent. And then there is target vessel
9 revascularization, which typically is not.
10 And that's really noise.

11 We actually looked at all of the
12 films because the target vessel
13 revascularization is remote from the lesions
14 that contributed to the slightly narrowing of
15 the TVF curve compared to the MACE curves.
16 We're about four percent in the SPIRIT III
17 trial out at nine months, which is higher than
18 we have seen in prior studies.

19 We actually looked at the films.
20 And it's just that there was a lot of disease.
21 The investigators when they were enrolling
22 patients left a lot of disease behind. And

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1 that just required equally in both arms
2 subsequent revascularization procedures.

3 I think when we look, despite that
4 fact, you actually do see that there is I
5 think a reasonably strong trend towards a 21
6 percent reduction in TVF, despite that
7 diluting effect.

8 When you look at the SPIRIT II plus
9 III meta-analysis, that p-value becomes .06.
10 And so I think it's pretty evident that what
11 we have got here is a beta error, that if we
12 had larger numbers of patients, we would see a
13 significant reduction in target vessel
14 failure.

15 The stent thrombosis is a very
16 small component of target vessel failure.
17 We're talking here at 9 months, like .8
18 percent rates of stent thrombosis. With
19 target vessel failure, we're looking more like
20 eight to ten percent rates. And if we were to
21 show you the confidence intervals around stent
22 thrombosis with 1,000 or even 1,500 or 2,000

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1 patients, the confidence intervals are 5 times
2 wider than the event rates are.

3 So, again, as was shown to you
4 before, until we get to 10 or 15 thousand
5 patients, you don't expect to see differences
6 in stent thrombosis. It's a very rare event.

7 Some of it is related to the design
8 parameters. Some of it is related to poor
9 operator technique. Some of it is related to
10 hematologic factors, such as
11 hypocoagulability, need for surgery, having
12 accidents that lead to a hypercatabolic state,
13 and other uncontrollable factors.

14 So the important thing to see there
15 is that there is just no safety signal to
16 suggest that there is an increase in stent
17 thrombosis, but, at least with these very
18 small, relatively small, numbers of patients,
19 until we get to 10,000-plus, we are not going
20 to be able to tell you more than that.

21 CHAIRPERSON YANCY: Questions from
22 other panel members? Dr. Somberg?

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1 MEMBER SOMBERG: Thank you.

2 My first question is on the
3 preclinical. Dr. Coleman, maybe you can come
4 forward and I can ask you this question.
5 There was a lot of information given on the
6 anatomic histologic differences among the
7 stents. I didn't see anything on really the
8 functional responses. Have you done any
9 preclinical work on endothelial dysfunction in
10 the target vessel over the time course because
11 while one may see greater healing, that
12 doesn't necessarily relate to physiologic
13 function? And some have corollary endothelial
14 dysfunction in the clinical realm with some of
15 these problems we see late.

16 DR. COLEMAN: Sure. We have
17 actually chosen to focus our efforts as I
18 demonstrated in terms of evaluating aspects of
19 endothelial cell function by looking at
20 expression of specific biomarkers within the
21 stent --

22 MEMBER SOMBERG: I heard your

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1 biomarker presentation.

2 DR. COLEMAN: Right.

3 MEMBER SOMBERG: But I would like
4 to see it correlated with a physiologic
5 number.

6 DR. COLEMAN: Sure. And so we have
7 done some exploratory studies to understand
8 how porcine coronary arteries respond to
9 specific vaso-reactive agents, and
10 specifically acetylcholine.

11 And we did some initial baseline
12 studies, which actually correlates, we're
13 finding, that have been reported in the
14 literature, where, in fact, porcine coronary
15 arteries tend to exhibit a paradoxical
16 response to acetylcholine. And they tend to
17 vaso-constrict.

18 And so, for that reason, we
19 actually chose not to spend a lot of time
20 actually exploring that in terms of to
21 understand what was happening within the
22 stented vessel in order to demonstrate whether

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1 or not they vaso-dilate.

2 And certainly and, in addition to
3 that, within the stented vessel, because there
4 is a rigid stent there, we really don't see
5 movement within the stented vessel. And so
6 then we're limited to looking on the
7 peri-stent region, either proximally or
8 distal, to the stent. And we felt that that
9 was less representative of what was occurring
10 within the stented vessel to look at that
11 peri-stent region.

12 And then, as I said, in addition,
13 porcine vessels tend to constrict and tend to
14 be very vaso-reactive. So we have not pursued
15 that method extensively.

16 MEMBER SOMBERG: Thank you.

17 Can I ask Dr. Stone a question as
18 well?

19 CHAIRPERSON YANCY: Sure.

20 MEMBER SOMBERG: In reference to
21 your statement of in the SPIRIT, I believe
22 III, program, you said and there was data

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1 presented that the incomplete apposition was
2 favorable to XIENCE. I was trying to
3 reconcile that with the summary table provided
4 in the material from the FDA summary, where
5 they report, really, the opposite, with
6 greater problems with apposition for the
7 XIENCE stent. Can you help me on that?

8 DR. STONE: Sure. It's --

9 CHAIRPERSON YANCY: For panel
10 members, that's table 20 in our packet. And
11 it really is pointing out the post-precision
12 persisting differences and in this late
13 acquired.

14 DR. STONE: Sure. There are
15 several different time periods that we can
16 measure in complete stent apposition. First
17 of all, we have to understand the definition
18 of incomplete stent apposition.

19 It's relatively sensitive. It
20 means, is there a time period where there is
21 even one strut that is not apposed to a vessel
22 wall? And so we look for it very, very

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1 carefully in the intravascular ultrasound core
2 laboratory.

3 And, as you can see, it's
4 relatively common in both groups in this study
5 with our increased awareness of the potential
6 importance of this. And immediately after the
7 procedure, there was not a statistically
8 significant difference in the two arms in
9 complete stent apposition, but it did trend to
10 be more in the XIENCE V arm. And then over
11 time, some of that, those small gaps, get
12 filled in and some of them don't.

13 The type that I was talking about
14 was the type that we really get concerned
15 about. And that is when you actually have
16 apposition immediately at the end of the
17 procedure but then over time the vessel grows.

18 It positively models, presumably because of
19 underlying vessel toxicity. That's what you
20 usually see pathologically. And that's the
21 type of lack of apposition --

22 MEMBER SOMBERG: I hear you, Dr.

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1 Stone, but I'm really talking about this table
2 that says 240 days where there was a
3 difference or a trend towards more incomplete
4 apposition.

5 And I think you were talking --
6 you're saying that there was one IVUS
7 evaluation at 240 days and there was another
8 one you're referring to at a different time
9 point?

10 DR. STONE: There are matched IVUS
11 investigations at post-procedure and then at
12 240 days. And then we compare the two to see
13 if what you saw initially after the procedure
14 was persistent, resolved, or if new incomplete
15 apposition developed.

16 And is this a different table?

17 CHAIRPERSON YANCY: No. It's
18 consistent. The entry that says, "Late
19 acquired" --

20 DR. STONE: Yes.

21 CHAIRPERSON YANCY: -- is identical
22 to the data that you shared with us. But we

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1 didn't see during your presentation the early
2 IVUS information, which suggests that about
3 one-third of those patients had the incomplete
4 stent apposition.

5 DR. STONE: Exactly. So that's the
6 initial post-procedure apposition, where the
7 operators placed the stent when the IVUS
8 interrogation is done. And you find that
9 there are small differences between the stent
10 strut and the vessel wall. So there are small
11 gaps.

12 Importantly, what we found was that
13 no patient that had that finding had stent
14 thrombosis. So it seems to be an innocuous
15 finding.

16 CHAIRPERSON YANCY: Dr. Lise
17 Normand?

18 MEMBER NORMAND: Hi. I think Dr.
19 Stone will help me with my question. It's
20 more of sort of somebody as a patient. I am
21 not sure why you are looking at late loss.
22 And let me go through the story here.

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1 I am assuming late loss is a
2 surrogate. Personally I don't care about late
3 loss in terms of -- tell me why I care about
4 it.

5 DR. STONE: Yes.

6 MEMBER NORMAND: And specifically
7 what I mean by that is I would like to know
8 the correspondence or correlation between late
9 loss and the need for a procedure or something
10 clinically meaningful to me, rather than a
11 measurement. So if you could help me with
12 that?

13 DR. STONE: Yes. The short answer
14 is that late loss has been shown to be a very
15 strong surrogate for clinical
16 revascularization. And we actually a paper in
17 the press in the Journal of the American
18 College of Cardiology, which actually
19 describes that. It should be out within a
20 month or two.

21 The lead author -- I am the senior
22 author of that paper. The lead author of that

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1 paper is Dr. Stuart Pocock. So perhaps I will
2 have him come up and describe the statistical
3 surrogacy.

4 MEMBER NORMAND: Well, I don't want
5 the statistical argument. I want the --

6 DR. STONE: Oh. I see.

7 MEMBER NORMAND: I want the
8 clinically meaningful translation.

9 DR. STONE: Okay. Sure.

10 MEMBER NORMAND: And I'll tell you
11 specifically what I'm looking for is that
12 you're reporting numbers.

13 DR. STONE: Yes.

14 MEMBER NORMAND: They're in a
15 particular unit. And I would like to know if
16 you see a change in those numbers or what that
17 number means relative to a change of this size
18 corresponds to having a target vessel,
19 revascular target lesion, whatever.

20 DR. STONE: Yes.

21 MEMBER NORMAND: I want some link.

22 So can you give me --

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1 DR. STONE: Yes.

2 MEMBER NORMAND: Because we're
3 looking at magnitude of things. And I have no
4 idea if --

5 DR. STONE: Sure. The magnitude of
6 the reduction in late loss and how it relates
7 to clinical target lesion revascularization,
8 first, it has been shown to be a strong
9 surrogate.

10 Second, it's a monotonic surrogate,
11 but it's also in logistic equations
12 curvilinear. So at lower levels of late loss,
13 reduction in late loss translates into less of
14 a clinical difference in TLR. At big
15 differences in late loss, it's a greater
16 difference.

17 MEMBER NORMAND: Sorry. I just
18 really am looking for a number. So I
19 understand it's monotonically related, and I
20 understand you have done a model to fit it, I
21 understand maybe a strong surrogate because of
22 p-values. I again just want to get the size

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1 of the difference.

2 DR. STONE: Sure.

3 MEMBER NORMAND: So for an X
4 percent difference or for this particular size
5 of late loss, this corresponds to a risk of
6 target --

7 DR. STONE: Sure.

8 MEMBER NORMAND: That's what I'm
9 looking for.

10 DR. STONE: At this level of late
11 loss, where we are in the curves, seeing the
12 kinds of differences in late loss we saw, we
13 would expect it to translate to about a three
14 percent absolute difference in target lesion
15 revascularization, which is approximately what
16 we saw.

17 CHAIRPERSON YANCY: Dr. Hirshfeld?

18 MEMBER HIRSHFELD: Two questions I
19 think are best addressed by Dr. Stone. Gregg,
20 I fully agree with you about the concern about
21 excessive positive remodeling that might
22 occur. And that's why I think one of the

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1 strengths of your data set is your extensive
2 intravascular ultrasound data.

3 One of the things that you
4 presented that I would have liked to have seen
5 you present with a different type of analysis
6 was your EEL changes. You presented those as
7 mean group data, rather than as comparison
8 with deltas. And it seems to me that the mode
9 of presentation that you showed is one that
10 would really minimize the ability to detect
11 any important changes in individual patients.

12 And I wondered if you also have an
13 analysis where you look at paired changes in
14 EEL at the initial ultrasound and at the
15 follow-up ultrasound and you have the
16 distribution of those so that we can then look
17 at that distribution to determine whether
18 there is a small subset of people who really
19 do have an excessive amount of positive
20 remodeling afterwards. I didn't know whether
21 you had that data available or whether if not,
22 you could access it readily.

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1 DR. STONE: The answer is we do.

2 MEMBER HIRSHFELD: I figured you
3 would.

4 DR. STONE: And, actually, we
5 pulled the slide from the presentation for
6 time. When you look at the paired differences
7 on an individual patient basis, you do tend to
8 see more large changes in the TAXUS group than
9 in the XIENCE group. And if you are
10 particularly interested, we can get you that
11 data after lunch.

12 MEMBER HIRSHFELD: Okay. Great.
13 Okay. While you are there, let me ask you the
14 second question. This has to do with pooling
15 the SPIRIT II and SPIRIT III and the stent
16 thrombosis issue.

17 SPIRIT II it appeared that you had
18 hit a home run. You hit zero stent thromboses
19 at one year in SPIRIT II in the XIENCE cohort.

20 And then in SPIRIT III, you had 1.1 percent
21 stent thromboses. When you pool these two,
22 you come up with a .8 percent.

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1 Given all the tyranny of small
2 numbers, these are rather striking
3 differences. I wonder if you have any
4 thoughts about why there was such a difference
5 between those two trials in terms of their
6 stent thrombosis rates.

7 DR. STONE: I think it is purely
8 100 percent statistical noise. It is really
9 the tyranny of small numbers. In one case in
10 100 or 300 or 400 patients, you can get zero
11 cases. In another one, you can get one or two
12 cases.

13 And none of the differences in
14 either trials even approach statistically
15 significance. So that's really just random
16 noise with these numbers of patients.

17 CHAIRPERSON YANCY: Dr. Laskey?

18 MEMBER LASKEY: So more of a
19 comment first, although for Gregg and Mitch.
20 I think I saw the word "death" repeatedly
21 here, the words "myocardial infarction." Can
22 we be clear about whether these are fatal or

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1 non-fatal as we go forward? It's really not
2 very clear in the protocol, but I think it's
3 intuitive. It would help to clear it up as we
4 move forward, make sure we're not
5 double-counting and so forth.

6 DR. STONE: All the deaths were
7 fatal.

8 (Laughter.)

9 MEMBER LASKEY: But myocardial
10 infarction is another piece.

11 DR. STONE: I know.

12 MEMBER LASKEY: Right.

13 DR. STONE: Trying to add a little
14 levity.

15 MEMBER LASKEY: Okay.

16 DR. STONE: No. The myocardial
17 infarctions were either fatal or non-fatal.
18 Those were not mutually exclusive events.

19 MEMBER LASKEY: So it's cumulative?

20 DR. STONE: Yes.

21 MEMBER LASKEY: Okay. And then
22 corollary to Sharon-Lise's comment about late

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1 loss, this is a new endpoint that we're
2 hanging our hat on. Seventy-seven percent
3 angiographic follow-up --

4 DR. STONE: Sure.

5 MEMBER LASKEY: -- or sort of
6 creaking down from the holy grail of 80. So
7 with one out of four patients not coming back,
8 how certain are we --

9 DR. STONE: Sure.

10 MEMBER LASKEY: -- that you're
11 capturing the universe, which is part of the
12 surrogate story?

13 DR. STONE: Sure. Again, the U.S.
14 is usually 175 to 80. In fact, we powered the
15 study for 75. But, regardless, we have done,
16 actually, first and second order imputed
17 analyses looking at condition means and
18 looking at propensity scales to see if
19 considering the patients who were not followed
20 up there could be any differences.

21 There was such a marked reduction
22 in late loss that, even with those analyses,

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1 the numbers change by a hundredth of a
2 millimeter, but they still remain markedly
3 statistically reduced.

4 MEMBER NORMAND: You do have
5 differential follow-up, by the way, in the two
6 arms. And so I would like to see those
7 analyses if you have them available for the
8 imputed analysis.

9 DR. STONE: We can get those for
10 you after lunch.

11 MEMBER NORMAND: That would be
12 great. That is good.

13 CHAIRPERSON YANCY: Dr.
14 Jeevanandam?

15 MEMBER JEEVANANDAM: I have two
16 questions. One is a preclinical question.
17 Looking at your slide 38, it's interesting
18 looking at inflammatory response, it does seem
19 that there is a slightly more inflammatory
20 score attributed to the XIENCE versus the bare
21 metal stent.

22 Do you think that that is reflected

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1 in what Gregg talked about, which was the
2 target vessel failure, and that perhaps this
3 inflammation doesn't really occur, only at
4 that spot of the coronary? But does it affect
5 other coronary lesions as well?

6 And my second question is,
7 everything here has been compared to the TAXUS
8 stent. How did you choose TAXUS over the
9 CYPHER stent or any other of the approved
10 stents?

11 DR. COLEMAN: So with regards to
12 the preclinical question regarding
13 inflammation, as I did mention, so we score
14 information on a score of zero to four. This
15 is in a personal coronary artery model. And
16 we consider a score of zero to one as
17 background information.

18 When we get to 180 days, one year,
19 and two years, we consider the information
20 scores that we're showing here as consistent
21 with background levels within the porcine
22 coronary artery. And the variability that you

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1 see we also consider to be normal biological
2 variability within this particular model.

3 So, generally speaking, what we
4 have seen at six months and beyond, the point
5 at which there is no longer drug detectable in
6 the tissue, we are actually seeing very little
7 to any inflammation long term.

8 CHAIRPERSON YANCY: Dr. Stone, will
9 you address the choice of other comparators?

10 DR. STONE: It's really simple. I
11 mean, at the time TAXUS was the most widely
12 used stent in the United States. It was the
13 most widely available in most cath labs. And
14 so that is why it was chosen.

15 CHAIRPERSON YANCY: Is that
16 adequate?

17 MEMBER JEEVANANDAM: Is there any
18 difference between the CYPHER and the TAXUS
19 stent in terms of data? And if you had
20 compared it to the CYPHER stent, would you
21 have anticipated a difference, as opposed to
22 comparing XIENCE to the TAXUS stent?

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1 DR. STONE: The clinical results
2 are very similar between the CYPHER stent and
3 the TAXUS stent. In fact, at the time there
4 was the large REALITY trial, which did show
5 less angiographic late loss with CYPHER
6 compared to TAXUS but no difference in
7 restenosis, no difference in clinical target
8 lesion revascularization, death MI, et cetera.
9 And most trials have shown the outcomes are
10 similar.

11 So I think that, again, if we had
12 chosen CYPHER, we probably would have had very
13 comparable late loss rates. That is what it
14 looks like when we look at the entire
15 literature, but I think we would have looked
16 quite good in terms of binary restenosis and
17 other clinical events.

18 CHAIRPERSON YANCY: Dr. Page?

19 MEMBER PAGE: Yes. My question
20 goes back to slide 22, I believe, Dr.
21 Simhambhatla. The drug dosing was studied
22 from 100 micrograms per centimeter² to 800.

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1 And 100 was chosen.

2 So are there any data in terms of
3 the animal model at lower doses? And is it
4 possible that the dose being used in these
5 studies is actually much higher than is
6 necessary with the perspective that lower dose
7 may be better, especially in these sorts of
8 long-term toxicities? What data do you have
9 to justify going with the lowest dose that was
10 studied, as opposed to exploring even further
11 doses as you design the clinical studies?

12 DR. SIMHAMBHATLA: Yes. We have
13 done exploratory research studies at lower
14 doses. The reason we didn't go below 100
15 micrograms per centimeter² for clinical
16 development is to find a balance between
17 reduced dose and manufacturability and/or
18 analytical assays, particularly for the really
19 short and small stents that don't have a lot
20 of drug on them.

21 For example, a smaller stent has
22 about 37 micrograms of drug on it. And just

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1 from a manufacturability, quality control
2 perspective, we felt it appropriate to go with
3 this dose.

4 CHAIRPERSON YANCY: Dr Morrison?

5 MEMBER MORRISON: Yes. I would
6 like to follow up and try to walk the line
7 between clinical and epidemiology. And so
8 this is for Dr. Stone. First of all, if we
9 content ourselves, as you point out, with this
10 surrogate, the surrogate of the surrogate,
11 which I think late loss is probably at least
12 three to four orders of magnitude of
13 surrogacy, would you not agree that all
14 studies are pretty concordant that the kind of
15 difference between late loss you have shown
16 here between XIENCE and TAXUS is really pretty
17 close to what has been shown between CYPHER
18 and TAXUS?

19 And, secondly, I think there are
20 some other clinical differences. I mean, part
21 of the reason, wouldn't you agree, that TAXUS
22 is more widely used is it's really a better

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1 stent platform than CYPHER? It's easier to
2 deliver and so forth.

3 And so that actually as a point of
4 comparison, then, relates to this second
5 generation model. The VISION cobalt chromium
6 thin strut stent seems to be even further
7 along the line as far as the stent qualities.

8 So that is two questions. One is a
9 surrogate late loss. I guess I should add a
10 third component. And that is, as you well
11 know, there is now at least one network
12 meta-analysis that suggests even the
13 possibility of clinical superiority of the
14 CYPHER to the TAXUS.

15 DR. STONE: There are I think three
16 questions there. But thank you. They are
17 great points.

18 First of all, it is very
19 interesting. And I was talking to Dr. Pocock
20 about this late last night. When you look at
21 many of the CYPHER versus TAXUS trials, even
22 though there is less late loss, there is

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1 similar binary restenosis.

2 So looking at worst point to worst
3 point, yes, there is more suppression of
4 tissue with CYPHER than TAXUS, but it was very
5 interesting, in fact, almost regulatory, I
6 think, in the reality trial, which enrolled
7 complex lesions in small vessels. Despite the
8 greater suppression of late loss, we saw
9 almost identical rates of binary restenosis
10 and, thus, almost identical rates of target
11 lesion revascularization.

12 Here, possibly as a result of the
13 thinner stent struts, better
14 endothelialization -- I'm speculating --
15 polymer, greater polymer integrity, perhaps
16 less strut fracture, we're not only seeing
17 less late loss, but in two consecutive trials,
18 we have seen, actually, reduced restenosis,
19 binary restenosis, and now reduction in target
20 lesion revascularization.

21 So while we have never directly
22 compared, no one has compared, XIENCE to

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1 CYPHER, I don't know for sure what the results
2 of that trial would be, but I think you can
3 speculate they might be similar.

4 Now, the network meta-analysis I
5 think, on which I was a co-author -- I've also
6 been one of the most outspoken critics of it
7 because I think that some of its conclusions
8 about mortality I think are quite valid
9 because that is a hard endpoint, but in the
10 network meta-analysis, it is a very
11 sophisticated way to try to put a lot of
12 different data into the mix. But you are
13 ending up comparing different control arms and
14 assuming that the outcomes in the different
15 control arms are the same.

16 As you yourself mentioned, we think
17 the outcomes with the CYPHER control, the Bx
18 Velocity, which has thicker struts than the
19 TAXUS stent, have always had higher restenosis
20 rates. And you're right. It is a less
21 deliverable stent in general. Most people
22 would say that. And that has led to the

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1 desirability of the TAXUS stent being used in
2 many laboratories.

3 A major difference here is the
4 thinner struts of the XIENCE stent. It's more
5 flexible, more conformable, more deliverable.

6 And along with the Endeavor stent, it is
7 clearly easier for physicians to use. And I
8 think that it is a natural progression.

9 So when you look at the design of
10 the stent, thinner polymer, thinner struts,
11 more flexible, easier to use stent, it should
12 endothelialize more rapidly. That's supported
13 with more rapid and more functional
14 endothelium by all the preclinical studies.
15 And then you see these clinical-type results
16 at one year.

17 It does make me as a clinician --
18 and I will be treating patients with this when
19 it's available, feel very comfortable that
20 this is a true next generation product that is
21 a medical advance.

22 CHAIRPERSON YANCY: Dr. Brinker,

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1 please?

2 MEMBER BRINKER: Gregg, as long as
3 you are up there, let me -- I have two
4 questions: one for you and one for Mr.
5 Johnson.

6 Pre-dilatation in the SPIRIT III
7 trial was strongly suggested and/or mandated.

8 It's not quite clear from the description.
9 But since the XIENCE stent is, arguably,
10 easier to deliver, it might be that after a
11 short experience, investigators would not
12 pre-dilate. And I feel that pre-dilatation
13 may be, in part, responsible for procedural
14 infarct.

15 So do you have any hard data on how
16 many in each group are actually pre-dilated?

17 DR. STONE: It actually was
18 mandatory to pre-dilate. So I don't have
19 those data. There might have been a few
20 patients that weren't pre-dilated, but it was
21 mandatory. And so we don't have experience
22 with XIENCE in terms of a direct stent

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1 strategy.

2 But you are right. Some
3 non-randomized comparisons have suggested that
4 direct stenting may be a way to minimize
5 injury and decrease peri-procedural MI, but I
6 can't make any statements about that.

7 MEMBER BRINKER: Okay. Second
8 question to Mr. Johnson. I don't know if you
9 are the absolute best person to answer this,
10 but it seems to me that the original intention
11 of the company was to produce a 2.25 stent to
12 go along with the other stents. Do you know
13 why that was dropped?

14 MR. JOHNSON: It just had to do
15 with the capacity of the R&D group at the
16 time. Originally it was planned to be part of
17 the portfolio. And there wasn't enough
18 capacity to do all of it. So it is going to
19 be part of our next generation.

20 MEMBER BRINKER: Arguably, that
21 would be a more important addition than a four
22 stent for the interventionist who is faced

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1 with the smaller vessels. Thank you.

2 CHAIRPERSON YANCY: Before we end
3 our discussion period, I would like to give an
4 opportunity to our consumer representative and
5 industry representative to query the sponsor.

6 MEMBER YAROSS: No questions at
7 this time. Thank you.

8 MEMBER RUE: No questions at the
9 time.

10 CHAIRPERSON YANCY: Dr. Somberg?

11 MEMBER SOMBERG: Yes. I would like
12 to ask Dr. Krucoff a question. And that is, I
13 appreciate your power analysis for stent
14 thrombosis or I guess the surrogate word is
15 low-frequency event. And you talked about
16 anywhere from 11,000 to 16,000 patients, but
17 then you present a registry in the study
18 you're doing to look at the problem of stent
19 thrombosis with 5,000 patients. Why is there
20 a discrepancy there when you were looking for
21 statistical power?

22 DR. KRUCOFF: So, John, you know

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1 the complexities here, but the bottom line is
2 that is also over five years. It is also
3 structured so that the other international
4 community registries can be pooled. And these
5 patient characteristics as well as their
6 follow-up are also structured to be integrated
7 with the pre-market evaluations, where we will
8 have ongoing follow-up.

9 So it's not just the 5,000 alone,
10 although there is, again, 5,000 over 5 years.

11 There is a numerology to that. But
12 ultimately I think we all know, and I think
13 Gregg mentioned before it may not just be the
14 stent platform. We may in this same time
15 frame see additional thienopyridine therapies.

16 You know, the world moves.

17 So the goal of the program is to be
18 able to integrate the question over time and
19 understand its behavior in the real world.

20 CHAIRPERSON YANCY: Dr. Blackstone?

21 MEMBER BLACKSTONE: I particularly
22 appreciated Dr. Stone presenting many of the

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1 patient endpoints in a time-related fashion.
2 Those were scarce and hard to find in the
3 voluminous material we had but are the most
4 meaningful.

5 If I can come back to the
6 thrombosis question for a moment? One way
7 that this will have to be studied is with more
8 patients, but, as you have just said now, the
9 other is longer follow-up. So I'm, therefore,
10 astonished that when you presented your
11 two-year data, you eliminated more than half
12 your patients.

13 Censored data analysis techniques
14 have been around for more than 300 years. And
15 there's no reason why the two-year information
16 cannot use all data with all follow-up.

17 And I wonder if either the Columbia
18 group or the Duke group has done that so that
19 we even have a glimpse over a two-year span of
20 what thrombosis time-relatedness is.

21 Thank you.

22 CHAIRPERSON YANCY: And, Gene, if

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1 you will allow me, let me piggyback onto that.

2 There were 74 early terminators. And of the
3 74, there were 30 deaths. So if we could
4 readdress why those patients were excluded
5 from the two-year analysis, that would at
6 least help me as well.

7 DR. POCOCK: Let me introduce
8 myself to answer. These are somewhat
9 statistical points. I am Stuart Pocock,
10 professor of medical statistics in London
11 School of Hygiene and Tropical Medicine.

12 I think I declared conflicts. My
13 travel and hotel were funded. And I work on a
14 variety of drug-eluting stent projects, mainly
15 data-monitoring committees, also for Boston
16 Scientific and Johnson and Johnson.

17 Now, in relation to the first
18 point, we have presented all the one-year data
19 in part of your documentation. So we're
20 simply supplementing that with the two-year
21 data for patients who have completed from
22 one-year to two-year data. So it might not be

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1 exactly in the form that you personally would
2 like to see, but it's all there.

3 And I think an alternative approach
4 I did point out myself would have been to use
5 Kaplan-Meier techniques and such. I think it
6 was partly in response to an FDA request that
7 it was done the way it was is my
8 understanding. But the situation on stent
9 thrombosis would not change, whichever way you
10 did it.

11 There are actually -- though one
12 can look at Kaplan-Meier plots, they are not
13 as meaningful sometimes as the numbers of
14 events. And, actually, in stent thrombosis
15 between one year and two years, there's just
16 two of them known to have happened in the
17 XIENCE V stent. And so you don't really need
18 a plot to tell you there were two. So that's
19 one way of thinking of that.

20 In terms of the patients who were
21 censored not in the denominators, I think that
22 was really done to make the results as clear

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1 as they could be in a simple form. I think
2 whether they were annual or not would make
3 very little difference, actually, to the
4 perception that you would get from the
5 results.

6 Thank you.

7 CHAIRPERSON YANCY: Is there
8 follow-up, Dr. Blackstone?

9 DR. KRUCOFF: Clyde, do you want me
10 to answer your question? I'm sorry. Just to
11 make clear, the deaths, --

12 CHAIRPERSON YANCY: Yes.

13 DR. KRUCOFF: -- the early
14 terminators are in all of the denominators.
15 So the only patients who are excluded from the
16 denominators were early terminators who did
17 not have an event prior to termination
18 relative to the time at which they terminated.

19 CHAIRPERSON YANCY: That actually
20 really perplexes me because in slide 115, a
21 footnote -- okay. It does suggest that those
22 patients are included --

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1 DR. KRUCOFF: Yes.

2 CHAIRPERSON YANCY: -- if I look at
3 this. It wasn't clear during the
4 presentation, but I understand now.

5 DR. KRUCOFF: I apologize if it
6 didn't come through, but all of the deaths or
7 all of the patients who had an event prior to
8 termination who were in that early terminator
9 group were included with the event analysis.

10 CHAIRPERSON YANCY: Thank you.

11 Are there other questions from the
12 panel?

13 DR. ZUCKERMAN: Yes.

14 CHAIRPERSON YANCY: Dr. Zuckerman?

15 DR. ZUCKERMAN: Okay. I would like
16 Abbott to go back to slide 69. And to follow
17 up with Dr. Normand's request for preparation
18 this afternoon, she has pointed out the
19 potential problem of differential follow-up.

20 And I want the sponsor to be clear
21 that I believe what Sharon is talking about is
22 not only showing the impact on angiographic

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1 results but showing in the angiographic versus
2 non-angiographic subset what exactly are the
3 clinical event rates because they aren't the
4 same, and we need to really flesh this out and
5 see how limitations of angiographic follow-up
6 could develop that.

7 If you could further underline
8 that, we will get the best presentation this
9 afternoon.

10 MEMBER NORMAND: Yes. I think
11 there certainly are differential ascertainment
12 issues in terms of the two groups with more
13 follow-up in the XIENCE group than the TAXUS
14 group, I believe.

15 Moreover, the way that my
16 understanding -- and someone could clarify if
17 I've got this wrong, but it sounds like the
18 way the subjects in the trial were selected
19 into the groups A, B, and C was based on time.

20 The first X got to group A. The next X got
21 to group B, I presume. And the last X got to
22 group C.

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1 And so that has some issues. I
2 have some issues with that because you might
3 use up most of your patient pool at the
4 beginning. And the types of people that come
5 in later might not be the same.

6 Now, I'm just speculating. I just
7 want some assurance of that.

8 DR. ZUCKERMAN: Yes.

9 MEMBER NORMAND: So, with that in
10 mind, that sort of makes one nervous about who
11 is actually included in the follow-up and
12 especially since you do have differential
13 rates of ascertainment for this surrogate
14 measure that you're using as your primary
15 endpoint.

16 DR. STONE: Well, to address Bram's
17 concerns, we will show you after lunch the
18 clinical outcomes in the cohorts of patients.

19 And I think that will hopefully allay some of
20 those concerns.

21 And, as I did mention in my
22 presentation but didn't show you on a slide,

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1 looking at those 564 first consecutive
2 patients in the angiographic follow-up cohort
3 compared to the 442 or whatever afterwards,
4 there were no differences in any baseline
5 characteristics. So they do look like the
6 angiographic follow-up cohort and the
7 non-angiographic follow-up cohort were
8 represented.

9 MEMBER NORMAND: Can you just tell
10 me the slide number of that because I can't --

11 DR. STONE: It is not there, but we
12 --

13 MEMBER NORMAND: It's not there?
14 Oh.

15 DR. STONE: But we can show it to
16 you after lunch. In the follow-up cohort to
17 the non-follow-up cohort, they were really
18 very similar. And I will show you that after
19 lunch.

20 CHAIRPERSON YANCY: It is 10:50.
21 And if there is a burning question that is
22 brief, we will take that. Dr. Somberg?

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1 MEMBER SOMBERG: Well, just someone
2 may try to clarify this later. I have a
3 concern. And I may have the wrong number
4 here, but there was sort of like an attempt to
5 get into real-world patients. So, therefore,
6 people can have more than one lesion that's
7 affected by the stent II lesions there.

8 Now, if someone has an effect or
9 some outcome with one lesion, an adversity or
10 they drop out or something else, how do you
11 handle statistically that you really can't
12 count them twice because they have now been
13 censored or something from the counting?

14 So how does one deal with that
15 second vessel issue? Is the denominator based
16 on the number of patients or the number of
17 vessels? I wasn't quite clear of that.

18 MS. WHITE: Hello. I'm Roseann
19 White, the Director of Global Biostatistics
20 and Clinical Data and Systems.

21 Let me repeat your question just so
22 that I am clear in the answer. What you would

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1 like to know is since some of the patients had
2 dual vessel treatment, how did we treat the
3 clinical endpoints given they had that dual
4 vessel treatment?

5 We treated every patient as a
6 patient. So if they had any one of the TVF
7 events or the MACE events, et cetera, they
8 were counted. So if they had a TLR in one
9 vessel if they were a dual vessel treatment,
10 they got included in the composite endpoint
11 and in the non-hierarchical endpoints.

12 So it was always a patient count.
13 So you would expect those patients with dual
14 vessel treatment to have higher rate of
15 events. However, we stratified the
16 randomization so that there was an equal
17 balance between the TAXUS and the XIENCE arms
18 in terms of dual vessel treatment.

19 Does that answer your question?

20 Thank you.

21 CHAIRPERSON YANCY: Thank you.

22 Once again I would like to thank the sponsor

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1 for really quite relevant and quite
2 informative presentations. Let me just
3 recapitulate the concerns and questions that
4 were raised by the panel so that they can be
5 revisited when you have a chance to address
6 this again.

7 You heard from Dr. Hirshfeld that
8 we would like to see more data on paired
9 changes in EEL. You heard from Dr. Normand
10 that we would like to see some clinical
11 relevance of the late loss analyses and some
12 additional information, time-related, et
13 cetera, regarding these late loss endpoints.

14 You heard from several of us about
15 the clinical relevance of the descriptions of
16 the data. And if there is a way that you can
17 crystallize that for us, I think we would be
18 more reassured.

19 And then you heard yet another
20 theme that I think was expressed by Dr.
21 Blackstone that we are concerned that there
22 were some compromises in the data set that

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1 identify the long-term concerns of stent
2 thrombosis and other long-term events.

3 And so if there is a way that you
4 can illuminate that more and give us some more
5 comfort about the quality of the long-term
6 data and the adequacy of the long-term data, I
7 think that would be very, very important.

8 If I have missed another thing that
9 they need to emphasize, please help me.

10 (No response.)

11 CHAIRPERSON YANCY: Okay. With
12 that having been said, then, we will take a
13 break. And we will reconvene at five minutes
14 after 11:00. Thank you very much.

15 (Whereupon, the foregoing matter
16 went off the record at 10:53 a.m. and went
17 back on the record at 11:09 a.m.)

18 CHAIRPERSON YANCY: We will now
19 have the FDA presentation. The first FDA
20 presenter is Dr. Heather Agler, the review
21 team leader for this PMA. Please proceed.

22 FDA PRESENTATION

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1 DR. AGLER: Good morning. First I
2 would like to thank the panel members for
3 their time and effort to review this device.
4 My name is Heather Agler, and this morning I
5 would like to begin by presenting the FDA
6 review of the XIENCE V Everolimus-Eluting
7 Coronary Stent System.

8 The XIENCE V Everolimus-Eluting
9 Coronary Stent System is a device-drug
10 combination product for which the lead review
11 was conducted by the Center for Devices
12 because the device component, the stent, is
13 considered the primary mechanism of action.
14 The stent platform is the FDA-approved
15 Multi-Link VISION and Mini Link VISION
16 Balloon-Expandable Cobalt Chromium Stent.

17 In sizes ranging from 2.5
18 millimeters in diameter and 8 to 28
19 millimeters in length, the stent platform is
20 first coated with a polymer primer layer and
21 is next coated with the drug matrix layer
22 consisting of a copolymer blended with the

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1 anti-proliferative drug everolimus.

2 Everolimus, also known as Certican,
3 is under review by the FDA as a new drug
4 application for the prevention of organ
5 transplant rejection and has obtained market
6 approval outside of the U.S. To date Novartis
7 has received two approvable letters from the
8 FDA for Everolimus.

9 The coated stent is then clipped
10 onto one of two delivery systems: either the
11 over-the-wire or rapid exchange. The sponsor
12 has proposed the XIENCE indicated for
13 improving coronary luminal diameter in
14 patients with symptomatic heart disease due to
15 de novo native coronary artery lesions of
16 length less than 28 millimeters, with
17 reference vessel diameters of 2.5 millimeters
18 to 4.25 millimeters.

19 FDA has conducted a comprehensive
20 review of the XIENCE V PMA. And since this
21 drug-device combination product is a
22 drug-device combination product, our review

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1 has included both the Center for Drug
2 Evaluation and Research and the Center for
3 Devices and Radiological Health.

4 As outlined here, members from
5 eight offices across the two centers have
6 worked together to complete the review. I
7 would like to acknowledge these individuals
8 for their contributions in reviewing this
9 device. The reviewers listed here reviewed
10 various forms of animal studies by
11 compatibility and pharmacokinetics data.
12 These contributors evaluated in vitro finished
13 product testing and product manufacturing.

14 These members of FDA staff provided
15 review of Abbott Vascular's investigational
16 device exemption submission, under which the
17 SPIRIT III U.S. pivotal trial of the XIENCE V
18 Everolimus-Eluting Stent System was conducted.

19 Abbott Vascular referenced the
20 Novartis NDA for drug substance safety data on
21 Everolimus, the referenced NDA, including
22 information on safety pharmacology,

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1 toxicology, absorption, distribution,
2 metabolism, and excretion studies, as well as
3 a series of human IV dosing studies. At the
4 time of the submission of the IDE, information
5 within the NDA had been reviewed. And
6 Novartis had received an approvable letter.
7 Reviews of these data did not indicate any
8 safety concerns and support initiation of the
9 human clinical studies for XIENCE V.

10 Testing of the finished product
11 consisted of stent functional testing, coating
12 testing, delivery system testing, animal
13 studies, and biocompatibility testing. The
14 sterilization and manufacturing, both a CMC
15 from a CDER perspective and QS/GMP from a
16 device perspective, were also evaluated. As
17 noted in your panel pack, minor deficiencies
18 remain regarding the data provided. The FDA
19 is working interactively with the sponsor to
20 ensure that these issues are resolved in a
21 timely fashion.

22 There were three clinical trials in

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1 the XIENCE V program provided for review in
2 the PMA. The SPIRIT III trial, which included
3 both the randomized controlled study as well
4 as the 4.0-millimeter arm, comprise the bulk
5 of the data under review. SPIRIT FIRST
6 consisted of a superiority angiographic
7 comparison to the VISION bare metal stent.

8 SPIRIT II consisted of a
9 non-inferiority angiographic comparison to
10 TAXUS. And SPIRIT III consisted of a
11 non-inferiority angiographic and clinical
12 comparison to TAXUS.

13 Please note that the SPIRIT FIRST
14 and SPIRIT II clinical trials were both
15 conducted outside of the U.S. And their
16 protocols were not reviewed by the FDA. The
17 SPIRIT III clinical trial is the U.S. pivotal
18 trial.

19 All clinical protocols recommended
20 the use of aspirin for a minimum of one year.

21 The SPIRIT FIRST protocol required
22 clopidogrel administration for a minimum of

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1 three months while the SPIRIT II and SPIRIT
2 III protocols required clopidogrel for a
3 minimum of six months. Each of these trials
4 will be discussed in more detail later in our
5 presentation.

6 At this time I would like to
7 introduce Dr. Robert Fiorentino. He will
8 present a clinical review of the XIENCE V
9 program.

10 DR. FIORENTINO: Good morning. My
11 name is Robert Fiorentino. And I will be
12 presenting the FDA clinical review of the data
13 supporting XIENCE V Everolimus-Eluting
14 Coronary Stent pre-market application.

15 This is an outline of my
16 presentation. Since I will be discussing
17 several clinical trials, I will first review
18 important study definitions and key
19 eligibility criteria across the XIENCE V
20 clinical programs. I will then review the
21 three randomized controlled trials as well as
22 the discussion of non-randomized data.

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1 A combined analysis of the SPIRIT
2 II and III RCTs will be discussed next with
3 clinical outcomes presented for important sum
4 groups, such as diabetes and dual vessel
5 treated subjects. The final topic will be
6 discussion of the analysis the applicant has
7 performed on subjects who have completed a
8 two-year follow-up assessment. I will
9 conclude my remarks with a summary of the
10 SPIRIT clinical programs.

11 Important clinical outcomes include
12 those shown here. Revascularization endpoints
13 are divided into target lesion or target
14 vessel revascularizations. The composite
15 endpoint of target vessel failure incorporates
16 TVR; whereas, a definition of MACE includes
17 TLR.

18 Standard angiographic outcomes were
19 also evaluated. In-stent and in-segment late
20 loss, angiographic binary restenosis, and
21 percent diameter stenosis are all commonly
22 accepted measures of restenosis within the

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1 coronary artery following implantation of a
2 drug-eluting stent.

3 Although the SPIRIT program allowed
4 for the treatment of up to two de novo
5 lesions, each in a different epicardial
6 vessel, a single lesion was chosen as the
7 analysis lesion. The analysis lesion was
8 defined as a target lesion for subjects who
9 had single de novo lesions treated and a
10 randomly selected lesion for subjects with two
11 de novo lesions treated. If the randomized
12 analysis lesion could not be treated for any
13 reason, the other target lesion by default
14 became the analysis lesion.

15 Per-protocol stent thrombosis was
16 categorized as acute, subacute, and late.
17 There was variability between the definitions
18 of stent thrombosis in two of the RCTs to be
19 discussed. In the pivotal U.S. study, or
20 SPIRIT III, stent thrombosis was defined as
21 either clinical presentation of acute coronary
22 syndrome with angiographic evidence of stent

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1 thrombosis or in the absence of angiography,
2 any unexplained death, or acute MI, in the
3 distribution of the target lesion within 30
4 days.

5 The preceding RCT, or SPIRIT II,
6 used a definition that included a requirement
7 for complete occlusion and/or flow-limiting
8 thrombus on angiography. Also in this study,
9 any cardiac death or AMI not attributable to
10 the target vessel satisfied the definition of
11 step thrombosis.

12 As illustrated by the previous
13 slide and those discussed at the December 2006
14 FDA panel meeting on DES thrombosis, protocol
15 definitions of stent thrombosis have
16 historically varied among DES trials.
17 Consistent definition of stent thrombosis
18 across trials is, therefore, important when
19 discussing this topic.

20 FDA participated in the Academic
21 Research Consortium, a roundtable of
22 investigators, industry, and regulators who

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1 proposed a common definition of stent
2 thrombosis based on the level of clinical
3 evidence available for each case as well as
4 the timing of the thrombotic event.

5 This slide illustrates the time
6 frame established for these definitions:
7 early being one to 30 days; late, greater than
8 30 days to one year; and very late, beyond one
9 year.

10 The levels of evidence for stent
11 thrombosis per the ARC definitions are shown
12 here. FDA believes that events that meet the
13 definite plus probable provide the most
14 reasonable choice for captioned thrombotic
15 events without unacceptably high false
16 positives.

17 FDA requested that Abbott Vascular
18 independently adjudicate their data per the
19 ARC definite plus probable criteria and in
20 addition to the protocol definitions.

21 Key inclusion criteria across the
22 SPIRIT program are shown here. And general

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1 subjects were required to have evidence of
2 myocardial ischemia, have greater than or
3 equal to 50 percent stenosis of the target
4 lesion, and have lesion lengths and vessel
5 diameters that would be amenable to the
6 treatment protocol for each study.

7 The SPIRIT FIRST study had the most
8 restrictive lesion inclusion criteria due to
9 its first in man or feasibility design.
10 However, SPIRIT II investigated lesions up to
11 28 millimeters in length and vessels 2.5 to
12 4.25 millimeters in diameter. The pivotal
13 SPIRIT III program evaluated the subjects with
14 lesions lengths of 2.8 millimeters with vessel
15 diameters from 2.5 to 3.75 millimeters in the
16 RCT and up to 4.25 millimeters in a single arm
17 registry.

18 These are the trials that represent
19 the SPIRIT program. SPIRIT FIRST was a first
20 in man study conducted in Europe. SPIRIT II
21 was an RCT also conducted outside of the U.S.
22 SPIRIT III was conducted entirely in the U.S.

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1 and consisted of two separate trials: an RCT
2 and a single arm registry evaluating the
3 largest diameter, or 4-millimeter XIENCE
4 stent.

5 The SPIRIT FIRST trial was a
6 prospective, one-to-one randomized controlled
7 superiority trial designed to enroll 60
8 subjects. The objective was to assess the
9 feasibility and performance of XIENCE V known
10 as Multi-Link VISION-E at the time and the
11 treatment of subjects with a single de novo
12 target lesion in a native coronary artery with
13 reference vessel diameters of 3 millimeters
14 and lesion length up to 12 millimeters. A
15 single 3 by 18-millimeter stent was the only
16 plant stent in both arms.

17 Primary endpoint was in-stent late
18 loss at 180 days. Additional secondary
19 endpoint of percent volume obstruction was
20 also evaluated.

21 SPIRIT FIRST was conducted at nine
22 European sites and enrolled 60 subjects

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1 between 2003 and 2004. Following the index
2 procedure, subjects were clinically evaluated
3 at intervals out to one year and by annual
4 telephone or office visits out to five years.

5 This table shows key baseline
6 demographics in both arms of SPIRIT FIRST.
7 The only variable shown above that was
8 statistically different between the two arms
9 was hypertension requiring medication.
10 However, comparison of baseline demographics
11 for each arm of SPIRIT FIRST is limited by the
12 small sample size in this first-in-man study.

13 Despite the small sample size,
14 baseline and lesion vessel characteristics
15 shown here were generally well-balanced
16 between both arms. Angiographic variables
17 that appear to be unbalanced include lesion
18 angulation greater than 45 degrees, not shown
19 here but provided to the panel, and in-stent
20 post-procedure percent diameter stenosis.

21 Of the 56 treatment evaluable
22 patients, 27 received the XIENCE V stent and

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