

XIENCE V™ Everolimus Eluting Coronary Stent System FDA Review of P070015

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Device Description

- Combination Product
- Stent Platform: MULTILINK VISION and MINI VISION balloon-expandable cobalt chromium stent
 - 2.5 to 4.0mm in diameter and 8 to 28mm in length
 - Approved July 16, 2003 (VISION) and September 10, 2004 (MINI VISION)
- Polymer Primer Layer
- Drug Matrix Layer:
 - copolymer of vinylidene fluoride and hexafluoropropylene (PVDF-HFP)
 - Anti-proliferative drug everolimus (Certican®, Novartis Pharmaceuticals Corporation)
- Catheter delivery systems
 - Over-The-Wire (OTW)
 - Rapid Exchange (RX)

Proposed Indications for Use

- The XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS) is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to *de novo* native coronary artery lesions (length \leq 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.

FDA Review Team

- Center for Drug Evaluation & Research (CDER)
 - Office of Clinical Pharmacology (OCP)
 - Office of New Drug Evaluation I (ODEI)
 - Office of New Drug Quality Assessment (ONDQA)
- Center for Devices & Radiological Health (CDRH)
 - Office of Device Evaluation (ODE)
 - Office of Surveillance & Biometrics (OSB)
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- LeRoy Schroeder, PhD
- Belay Tesfamariam, PhD
- Xu (Sherry) Yan, PhD

Review of Drug Substance Safety Data

- Information referenced and contained within Certican® NDA (Novartis)
 - Safety Pharmacology
 - Toxicology
 - Absorption, Distribution, Metabolism, and Excretion (ADME) Studies (Certican NDA)
 - Human IV Dosing

Pre-Clinical Review of the Finished Product

- Stent Functional Testing
- Stent Coating Testing
- Stent Delivery System Testing
- Animal Studies
- Chemistry, Manufacturing, and Controls (CMC)
- Sterilization
- Biocompatibility
- Manufacturing (QS/GMP)

Clinical Studies

Clinical Trial	US	Enrollment	Primary Endpoints	Anti-Platelet Therapy:	Available Follow-up
SPIRIT FIRST		XIENCE V: 28 VISION: 32	180d In-stent Late Loss	ASA 1 year + Clopidogrel 3m	3yr
SPIRIT II		XIENCE V: 223 TAXUS: 77	180d In-stent Late Loss	ASA 1 year + Clopidogrel 6m	1yr
SPIRIT III RCT	X	XIENCE V: 669 TAXUS: 333	240d In-segment Late Loss 270d Ischemia driven TVF	ASA 1 year + Clopidogrel 6m	1yr
SPIRIT III 4.0 mm arm	X	XIENCE V: 69	240d In-segment Late Loss	ASA 1 year + Clopidogrel 6m	1yr

FDA Presentation

- Clinical Review – Robert Fiorentino, MD, MPH
- Statistical Review – Xu (Sherry) Yan, PhD
- Epidemiology Review – Hesha Duggirala, PhD

FDA Clinical Review

XIENCE V™

Everolimus Eluting Coronary Stent System

Robert P. Fiorentino, MD, MPH

FDA, Center for Devices and Radiological Health

Division of Cardiovascular Devices

November 29, 2007

Outline

- Relevant Study Definitions
- Key Study Eligibility Criteria
- Randomized Clinical Trials
- Non-Randomized Studies
- 1 year Combined RCT analysis
- 2 year Completer Analysis
- Summary

Key SPIRIT Definitions

■ CLINICAL OUTCOMES

- Target Lesion Revascularization (**TLR**):
Ischemia-driven repeat intervention of the target lesion of the target vessel
- Target Vessel Revascularization (**TVR**):
Ischemia driven repeat intervention (PCI or CABG) of the target vessel
- Target Vessel Failure (**TVF**): Composite of TVR, cardiac death, or MI
- Major Adverse Cardiac Events (**MACE**):
Composite of cardiac death, MI, TLR by CABG or PCI

Key SPIRIT Definitions (cont'd)

■ ANGIOGRAPHIC OUTCOMES

■ Late Lumen Loss (LL)

- Difference between the post-procedure MLD and MLD at follow-up angiography
- In-segment vs. In-stent

■ Angiographic Binary Restenosis (**ABR**)

- Angiographic follow-up % diameter stenosis of $\geq 50\%$

■ Percent Diameter Stenosis (**%DS**)

- Calculated as $100 * (1 - \text{MLD}/\text{RVD})$ using the mean values from two orthogonal views (when possible) by QCA

Analysis Lesion

- Analysis lesion is defined as the target lesion for subjects with **single** *de novo* lesion and a randomly selected lesion for subjects with **two** *de novo* lesions. If the randomized analysis lesion could not be treated for any reason, the other target lesion, by default, became the analysis lesion.

Stent Thrombosis

Per Protocol Definition

Stent thrombosis was categorized as acute (≤ 1 day), subacute (>1 day ≤ 30 days) and late (>30 days) and was defined as any of the following:

SPIRIT III

- Clinical presentation of acute coronary syndrome with angiographic evidence of stent thrombosis (angiographic appearance of thrombus within or adjacent to a previously treated target lesion)
- In the absence of angiography, any unexplained death, or acute MI (ST segment elevation or new Q-wave) in the distribution of the target lesion within 30 days.

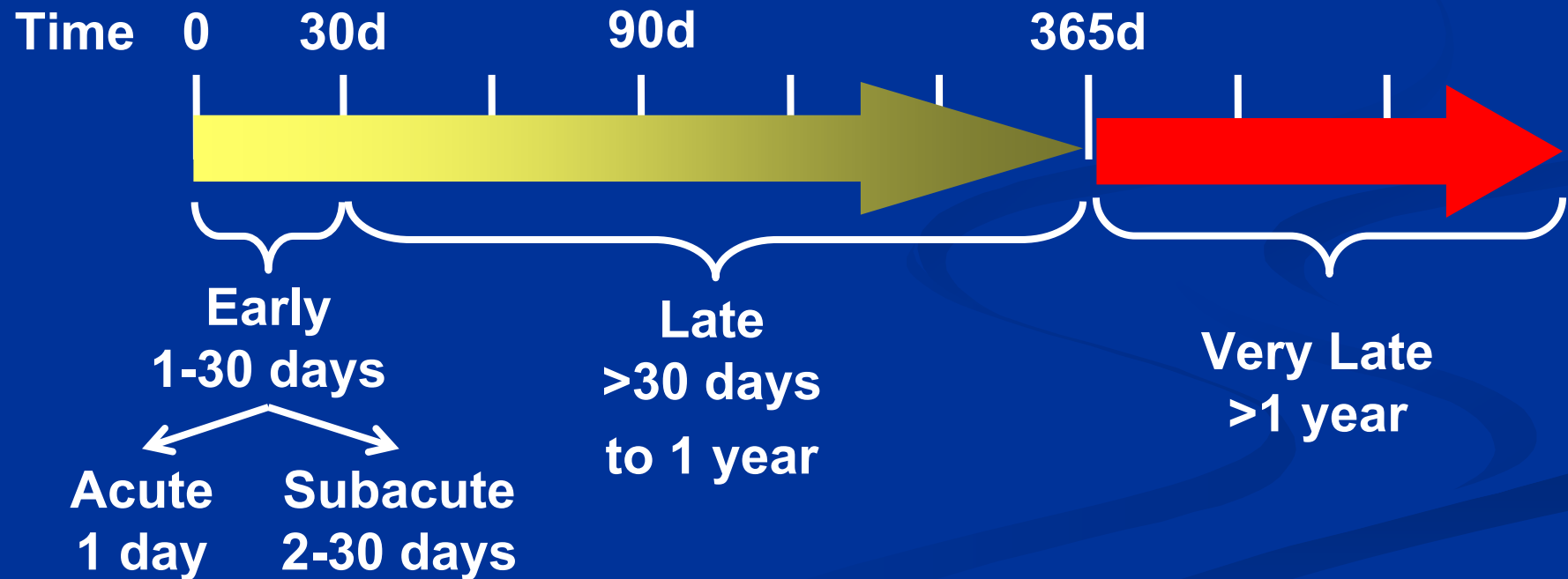
SPIRIT II (key differences):

- requirement of a complete occlusion and/or a flow limiting thrombus
- in the absence of angiography, any cardiac death and AMI not attributable to a non-target vessel

ARC Stent Thrombosis

Timing of Event

A common definition of stent thrombosis based on the timing of the thrombotic event as well as the level of clinical evidence available for each case



ARC Stent Thrombosis

Levels of Evidence

■ Definite/Confirmed

- Acute coronary syndrome *AND*
 - Angiographic confirmation of thrombus or occlusion
 - OR*
 - Pathologic confirmation of acute thrombosis

■ Probable

- Unexplained death within 30 days
- Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion

■ Possible

- Unexplained death after 30 days

SPIRIT Program

Key Inclusion/Exclusion Criteria

■ Key Inclusion Criteria:

- Evidence of myocardial ischemia (e.g., angina, silent ischemia, positive functional study or a reversible changes in the ECG consistent with ischemia)
- The target lesion(s) must be in a major artery or branch with a visually estimated stenosis of $\geq 50\%$ and $< 100\%$ with a TIMI flow of ≥ 1
- Target lesion length:
 - ≤ 28 mm in length by visual estimation (SPIRIT II & III)
 - ≤ 12 mm (SPIRIT FIRST)
- Target vessel reference diameter:
 - ≥ 2.5 mm and ≤ 3.75 mm (SPIRIT III)
 - > 3.75 mm and ≤ 4.25 mm (SPIRIT III 4.0 mm arm)
 - ≥ 2.5 mm and ≤ 4.25 mm (SPIRIT II)
 - 3.0mm only (SPIRIT FIRST)

XIENCE V Clinical Program

- SPIRIT FIRST
- SPIRIT II
- SPIRIT III
 - RCT
 - 4.0mm arm
- Pharmacokinetic (PK) Substudies
 - SPIRIT II and III

SPIRIT FIRST

- 1:1 randomized, single-blind superiority trial versus BMS control
- **Objective:** A First in Man Study to assess the feasibility and performance of XIENCE V (aka, MULTI-LINK VISION-E) in the treatment of subjects with a single *de novo* target lesion in a native coronary artery with reference vessel diameter (RVD) of 3.0 mm and lesion length \leq 12mm assessed by QCA
- **Primary endpoint**
 - In-stent late loss at 180 days
- **Important secondary endpoints**
 - In-stent percent volume obstruction (%VO) at 180 days that was measured by 3D IVUS analysis

SPIRIT FIRST

- **OUS: Conducted at 9 European sites**
- **60 subjects enrolled from Dec. 2003 to Apr. 2004**
- **Following the index procedure subjects were clinically evaluated at 30, 180 and 270 days and at 1 year**
 - **Telephone/office visits occur yearly thereafter out to 5 years**

SPIRIT FIRST: BASELINE DEMOGRAPHICS

	XIENCE V (n=27)	VISION (n=29)
Age (yrs)	64.21 ± 9.56 (27)	61.36 ± 9.31 (29)
Male	70.4% (19/27)	75.9% (22/29)
Current Cigarette Use	28.0% (7/25)	31.0% (9/29)
Any Diabetes	11.1% (3/27)	10.3% (3/29)
Diabetes Req. Medication	3.7% (1/27)	3.4% (1/29)
Hypertension Req. Medication	70.4% (19/27)	41.4% (12/29)
Hyperlipidemia Req. Medication	70.4% (19/27)	75.9% (22/29)
Prior Myocardial Infarction	24.0% (6/25)	13.8% (4/29)
Prior Cardiac Intervention	19% (5/27)	7% (2/29)
Stable Angina	37.0% (10/27)	51.7% (15/29)
Unstable Angina	0.0% (0/27)	3.4% (1/29)

SPIRIT FIRST

Lesion and Vessel Characteristics

	XIENCE V (n=27)	Vision (n=29)
Reference vessel diameter, mm*	2.61 ± 0.40 (26)	2.71 ± 0.28 (29)
Lesion length, mm*	10.08 ± 2.56 (26)	10.88 ± 3.31 (29)
Pre-procedure % Stenosis*	64.25 ± 9.32 (26)	61.17 ± 10.38 (29)
Vessel Location		
LAD	48.1% (13/27)	44.8% (13/29)
LCX	22.2% (6/27)	20.7% (6/29)
RCA	29.6% (8/27)	34.5% (10/29)
Post-procedure % Stenosis*		
In-Stent	12.34± 4.02 (27)	15.37 ± 5.63 (29)
In-Segment	20.82± 7.65 (27)	23.66 ± 8.04 (29)

*Mean ± SD

SPIRIT FIRST Results

PRIMARY ENDPOINT	XIENCE V (n=27)	VISION (n=29)	Difference [95% CI]	p-Value
180-day In-stent Late Loss, mm	0.10 ± 0.23 (23)	0.85 ± 0.36 (27)	-0.76 [-0.93, -0.59]	< 0.0001

XIENCE stent had significantly lower observed in-stent late loss compared to the VISION bare metal control

SPIRIT FIRST

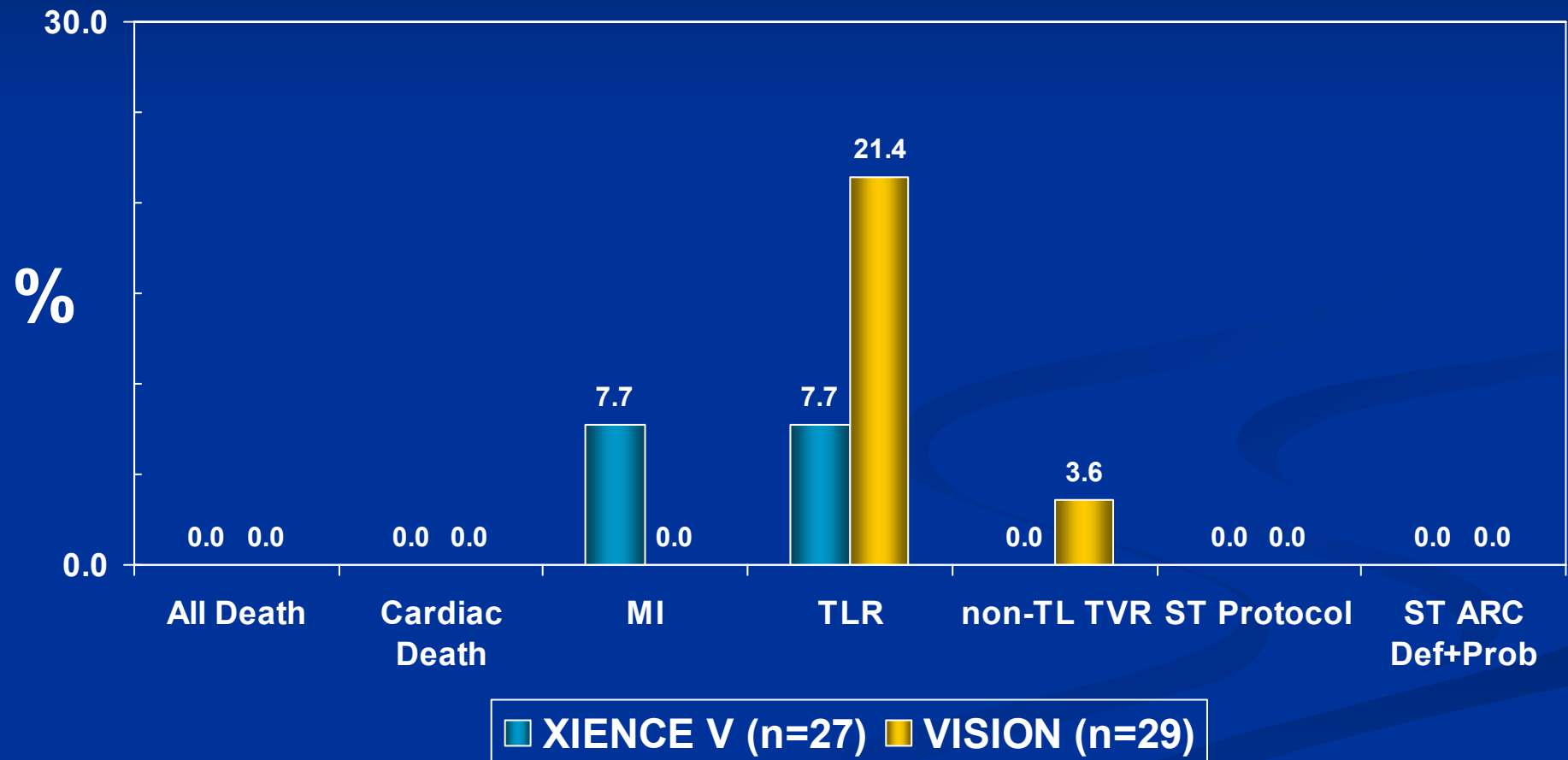
Angiographic Results at 180 Days

	XIENCE (n=27)	VISION (n=29)	Difference [95% CI]
180-day in-stent %Volume Obstruction	7.95 ± 10.44 (21)	28.11 ± 13.98 (24)	-20.16 [-27.53, -12.79]
In-stent % diameter stenosis	15.57 ± 7.64 (23)	38.61 ± 14.25 (27)	-23.05 [-29.45, -16.64]
Binary in-stent restenosis	0.0% (0/23)	25.9% (7/27)	-25.93% [**]

** Assumption of normal approximation is not met due to small sample size or frequency of events

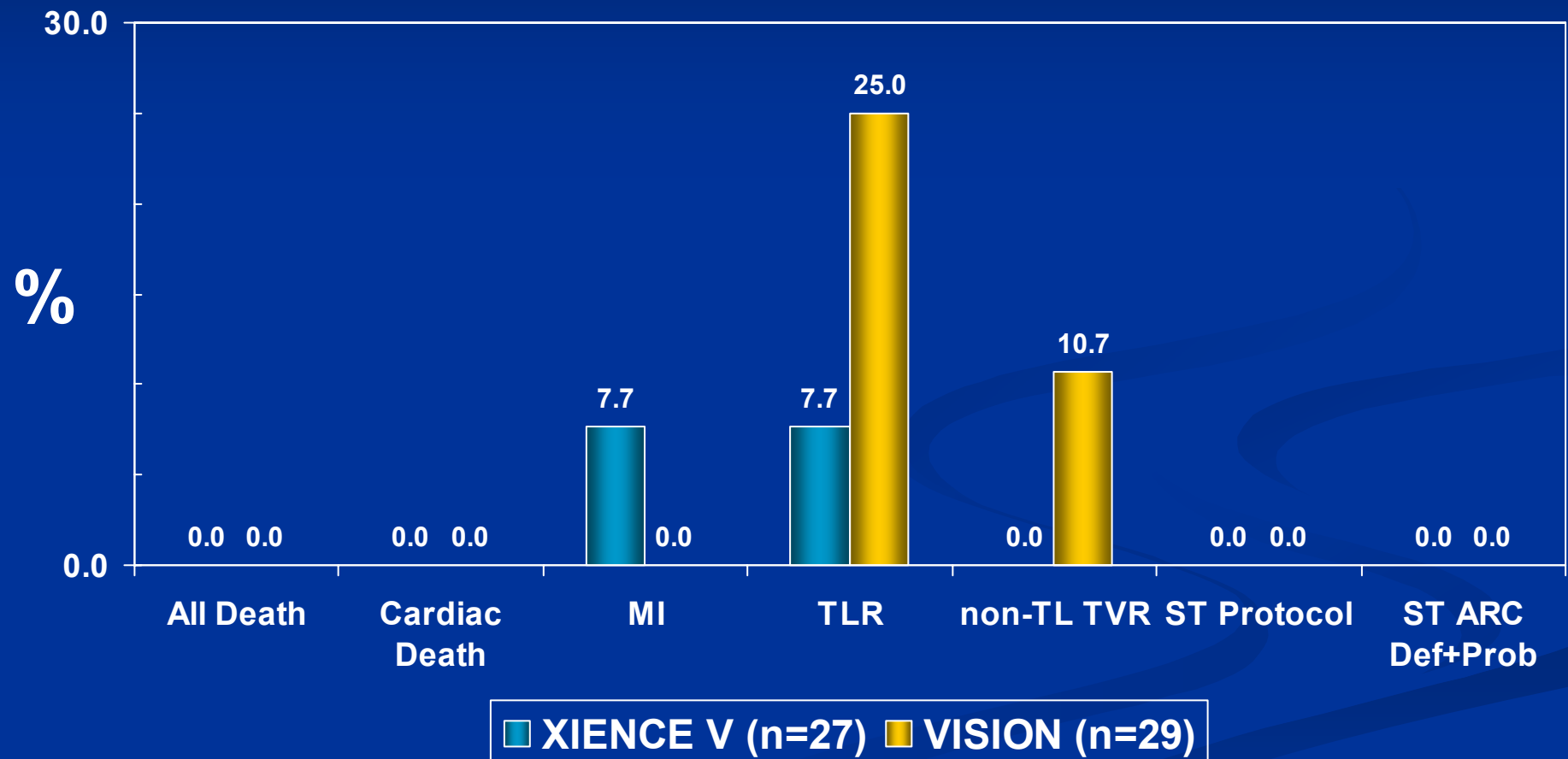
SPIRIT FIRST

Major Clinical Endpoints at 1 year



SPIRIT FIRST

Major Clinical Endpoints at 3 years



SUMMARY: SPIRIT FIRST

- The SPIRIT FIRST study met its primary endpoint with lower 180-day in-stent late loss for the XIENCE stent compared to the bare metal control
- Angiographic data demonstrated consistently lower rates of angiographic measures of restenosis versus the bare metal stent control.
- No stent thrombosis events were observed from 0 to 3 years in this study
- **Key Limitations:**
 - *Small sample size*
 - *Study was not powered to adequately assess clinical endpoints or safety outcomes*

SPIRIT II

- Randomized, controlled, **non-inferiority (plus superiority)**, OUS trial in **300** subjects
 - Randomized 3:1 (XIENCE V : TAXUS Express²)
- **Objective:** To demonstrate non-inferiority of XIENCE V to the TAXUS Express² drug eluting stent in subjects with a **maximum of two** *de novo* native coronary artery lesions, each in a different epicardial vessel with RVD of ≥ 2.5 mm and ≤ 4.25 mm and lesion length ≤ 28 mm
- **Primary endpoint:** Angiographic in-stent late loss (LL) at 180 days
 - Non-inferiority margin (δ) = 0.16 mm, 1-sided alpha = 0.05
 - Null hypothesis: In-stent LL XIENCE V - In-stent LL TAXUS $> \delta$
 - Four interim analyses were planned, only two performed (80 & 120 days)

SPIRIT II

Baseline Characteristics

	XIENCE V N=223, M=260	TAXUS N=77, M=91
Age (yrs)	61.95 ± 10.29 (223)	61.92 ± 9.44 (77)
Male	70.9% (158/223)	79.2% (61/77)
Current Cigarette Use	31.6% (66/209)	29.9% (20/67)
Any Diabetes	22.9% (51/223)	23.7% (18/76)
Diabetes Req. Insulin	4.9% (11/223)	6.6% (5/76)
Hypertension Req. Medication	67.3% (150/223)	64.9% (50/77)
Hyperlipidemia Req. Medication	68.7% (149/217)	75.0% (57/76)
Prior Myocardial Infarction	34.8% (77/221)	24.7% (19/77)
Prior PCI	22.0% (49/223)	22.1% (17/77)
Prior CABG	3.1% (7/223)	1.3% (1/77)
Stable Angina	61.9% (138/223)	62.3% (48/77)
Unstable Angina	26.9% (60/223)	32.5% (25/77)

Note: N is the total number of subjects; M is the total number of lesions

SPIRIT II

Baseline Lesion and Vessel Characteristics

	XIENCE V N=223, M=260	TAXUS N=77, M=91
Reference vessel diameter, mm*	2.70 ± 0.52 (246)	2.82 ± 0.58 (87)
Lesion length, mm*	12.98 ± 5.72 (246)	13.20 ± 6.41 (87)
Pre-procedure % Stenosis*	60.88 ± 11.97 (256)	59.25 ± 9.83 (89)
Vessel Location		
LAD	40.8% (106/260)	47.3% (43/91)
LCX	28.5% (74/260)	18.7% (17/91)
RCA	30.0% (78/260)	34.1% (31/91)
LMCA		
Post-procedure % Stenosis*		
In-Stent	13.01 ± 6.02 (260)	12.66 ± 5.53 (91)
In-Segment	22.51 ± 8.98 (260)	23.36 ± 11.20 (91)

*Mean±SD

SPIRIT II

Procedural Success and 30 Day MACE

- Clinical device success (per lesion)
 - XIENCE V 98.8% vs. TAXUS 98.9%
- Clinical procedure success (per subject)
 - XIENCE V 99.1% vs. TAXUS 97.4%
- 0 to 30 Day MACE

	XIENCE V (n=223)	TAXUS (n=77)
MACE	0.9%	3.9%
Q-wave MI	0.0%	0.0%
Non Q-wave MI	0.9%	3.9%

SPIRIT II

Primary Endpoint Results

Primary Endpoint	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI]
180-day In-stent Late Loss, mm	0.11 ± 0.27 (201)	0.36 ± 0.39 (73)	-0.24 [-0.34, -0.15]

Non-inferiority: $p < 0.0001$

Superiority: $p < 0.0001$

PRIMARY ENDPOINT MET

SPIRIT II

Other Angiographic Results at 180 Days

All Target Lesions Analysis	XIENCE V N=223 M=260	TAXUS N=77 M=91	Difference [95% CI]
In segment Late Loss, mm	0.07 ± 0.33 (237)	0.15 ± 0.38 (86)	-0.08 [-0.17, 0.01]
In-stent %DS	15.70 ± 9.88 (237)	20.89 ± 11.59 (86)	-5.18 [-7.96, -2.41]
In-segment %DS	23.61 ± 11.65 (237)	27.05 ± 12.68 (86)	-3.44 [-6.53, -0.35]
In-stent ABR	1.3% (3/237)	3.5% (3/86)	-2.22% [**]
In-segment ABR	3.4% (8/237)	5.8% (5/86)	-2.44% [-7.89%, 3.02%]

N is the total number of subjects; M is the total number of lesions

** Assumption of normal approximation is not met due to small sample size or frequency of events



SPIRIT II

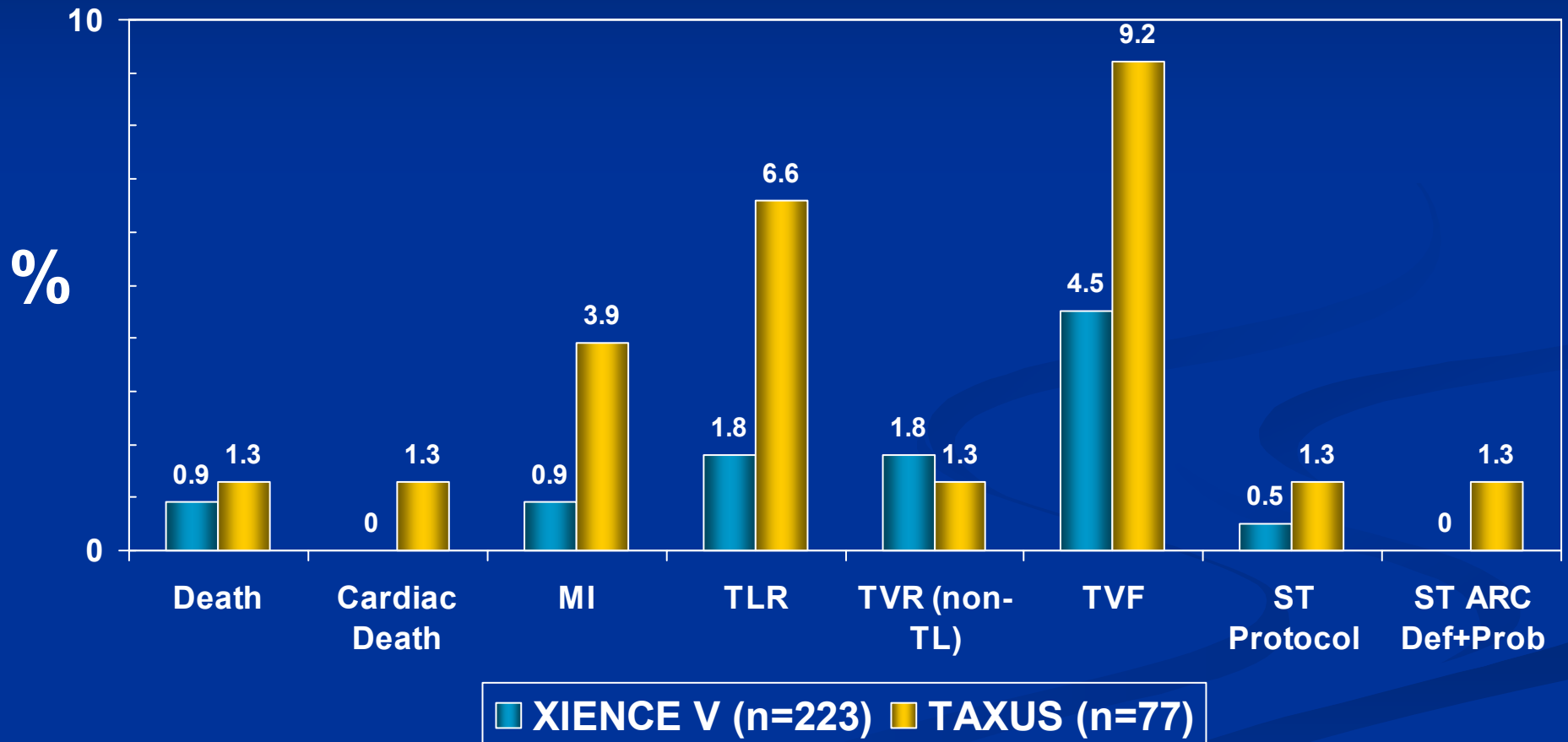
Other IVUS Results at 180 Days

IVUS Data: 180-day Follow-up	XIENCE V N=113 M=132	TAXUS N=39 M=45	Difference [95%CI]
NIH volume, mm ³	3.83 ± 6.55 (99)	14.42 ± 16.03 (40)	-10.60 [-15.87, -5.32]
In-stent %VO	2.51 ± 4.68 (99)	7.36 ± 7.05 (40)	-4.85 [-7.27, -2.42]
Post-procedure Inc. Apposition	6.5% (7/108)	5.6% (2/36)	0.93% [**]
Incomplete Apposition	2.9% (3/103)	0.0% (0/39)	2.91% [**]
Persisting Incomplete Apposition	2.5% (3/120)	0.0% (0/42)	2.50% [**]
Late acquired Incomplete Apposition	0.0% (0/104)	0.0% (0/39)	0.00% [**]

** Assumption of normal approximation is not met due to small sample size or frequency of events

SPIRIT II

Major Clinical Outcomes at 1 year



Summary: SPIRIT II

- Data from the SPIRIT II trial indicates that the XIENCE V stent was superior to TAXUS with respect to in-stent LL at 180 days.
- Additionally, there was a consistent trend of lower rates of angiographic restenosis across multiple angiographic and IVUS-based secondary endpoints.

Summary: SPIRIT II

- Study was not adequately powered to allow robust comparisons between the treatment and control arms with respect to clinical endpoints
- Study was not adequately powered to detect low frequency events
- It cannot be ruled out that the interim analyses potentially biased the study conclusions

SPIRIT III

Trials in the SPIRIT III program:

- SPIRIT III RCT

- two *de novo* lesions ≤ 28 mm in length in native coronary arteries with **RVD ≥ 2.5 mm to ≤ 3.75 mm**

- SPIRIT III 4.0mm registry

- to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with **RVD > 3.75 mm to ≤ 4.25 mm**

- PK Studies

- Subjects in the SPIRIT III RCT who volunteered to be in a PK sub-study

SPIRIT III RCT

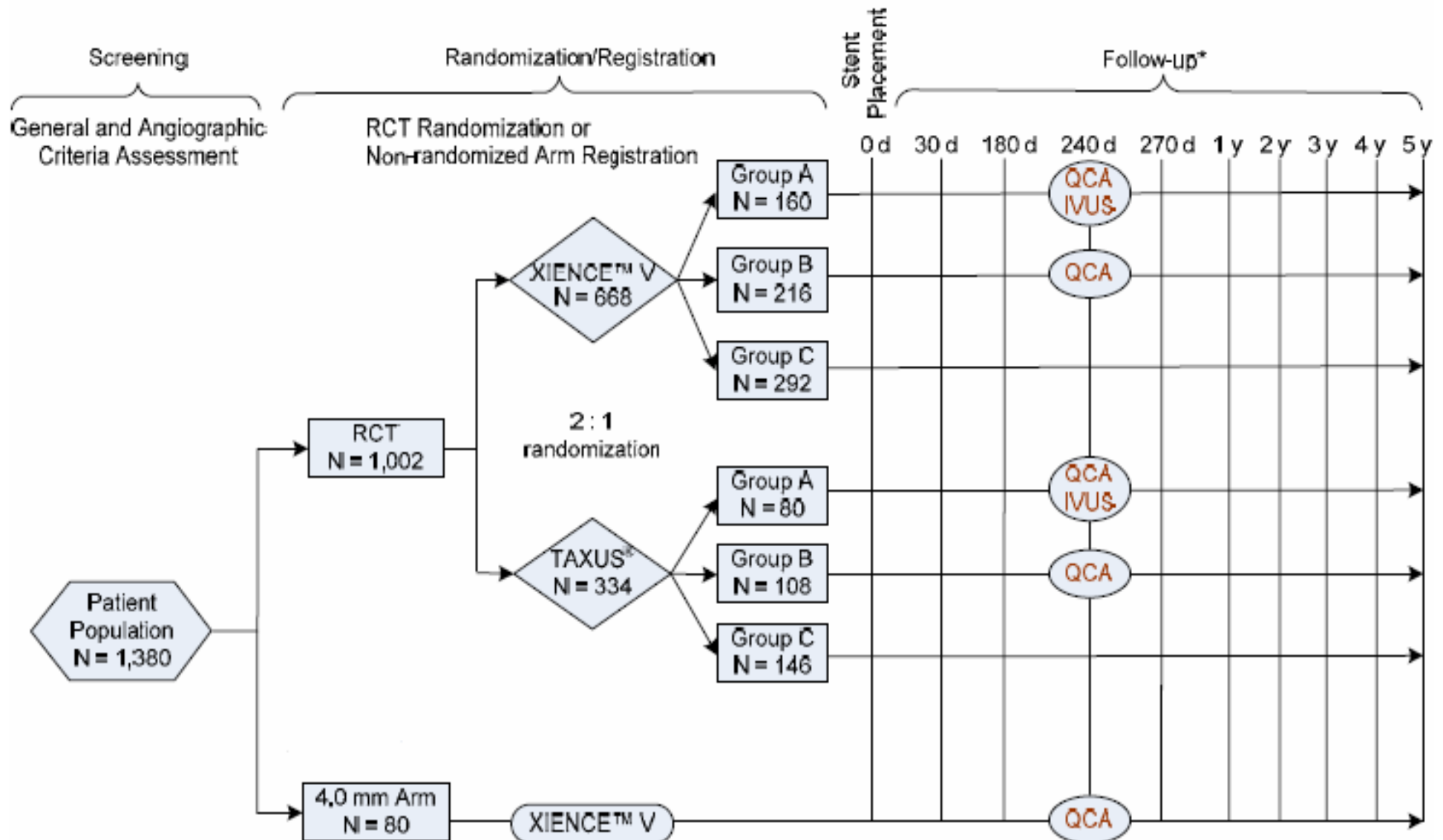
- **Pivotal US trial**
- **Randomized (2:1), single-blind, non-inferiority trial in 1002 subjects**
- **Objective:** Evaluation of the XIENCE V compared to TAXUS in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD ≥ 2.5 mm to ≤ 3.75 mm
- **Two co-Primary endpoints**
 - **In-segment late loss (LL) at 240 days**
 - one-sided alpha of 0.025 and a difference of in-segment late loss between the XIENCE V and TAXUS arms of no more than 0.195 mm
 - **Ischemia driven Target Vessel Failure (TVF) at 270 days**
 - one-sided alpha of 0.05 and a difference in TVF rate of no more than 5.5%

SPIRIT III RCT

Important secondary endpoints

- TVF, TLR, and MACE at 30, 180, 270 days, and 1, 2, 3, 4, and 5 years
- Persisting incomplete stent apposition, late-acquired incomplete stent apposition, and thrombosis at 240 days
- Acute success (clinical device and clinical procedure)
- Proximal, distal and in-stent LL at 240 days
- In-stent and in-segment percent diameter stenosis (%DS) and percent angiographic binary restenosis (% ABR) rate at 240 days
- In-stent percent volume obstruction (%VO) at 240 days

SPIRIT III Study Design



SPIRIT III RCT

Baseline Demographic and Clinical Characteristics

	XIENCE V N=669	TAXUS N=333
Age (yrs)	63.23 ± 10.53 (669)	62.80 ± 10.24 (332)
Male	70.1% (469/669)	65.7% (218/332)
Current Cigarette Use	23.4% (154/659)	22.5% (73/324)
Any Diabetes	29.6% (198/669)	27.9% (92/330)
Diabetes Req. Insulin	7.8% (52/669)	5.5% (18/330)
Hypertension Req. Medication	76.2% (510/669)	74.0% (245/331)
Hyperlipidemia Req. Medication	74.2% (489/659)	71.5% (233/326)
Prior Myocardial Infarction	19.9% (130/652)	18.0% (59/327)
Prior PCI	26.3%(175/666)	27.7%(92/332)
Prior CABG*	8.56%(57/666)	3.61%(12/332)
Stable Angina	53.3% (350/657)	47.7% (156/327)
Unstable Angina*	18.7% (123/657)	25.1% (82/327)

SPIRIT III RCT

Baseline Lesion and Vessel Characteristics

	XIENCE V N=669	TAXUS N=333
Number of lesions/vessels treated		
One	84.6% (566/669)	84.6% (281/332)
Two	15.4% (103/669)	15.4% (51/332)
TARGET LESION(S)		
RVD, mm	2.77 ± 0.45 (767)	2.76 ± 0.46 (382)
Lesion length, mm	14.70 ± 5.59 (767)	14.73 ± 5.70 (379)
Pre-procedure % Diameter Stenosis	69.96 ± 13.34 (767)	69.44 ± 13.62 (382)
Vessel Location		
LAD	41.3% (317/768)	42.9% (164/382)
LCX	25.5% (196/768)	26.2% (100/382)
RCA	31.0% (238/768)	28.5% (109/382)
Post-procedure % Diameter Stenosis		
In-Stent	0.33 ± 8.93 (762)	-0.22 ± 9.94 (379)
In-Segment	13.54 ± 7.58 (765)	14.40 ± 7.10 (379)

SPIRIT III RCT

Procedural Success and 30-Day MACE

- Clinical device success (per lesion)
 - XIENCE 98.3% vs. TAXUS 98.7%
- Clinical procedure success (per subject)
 - XIENCE 98.5% vs. TAXUS 97.3%
- 30 Day MACE

	XIENCE V (n=669)	TAXUS (n=333)
MACE	1.2%	2.4%
Q-wave MI	0.0%	0.0%
Non Q-wave MI	0.9%	2.1%

SPIRIT III RCT

Primary Endpoint Results

	XIENCE V (n=376)	TAXUS (n=188)	Difference [95% CI]	Non-inferior p-value ¹
240-Day In segment Late Loss (mm)	0.14 ± 0.41 (301)	0.28 ± 0.48 (134)	-0.14 [-0.23, -0.05]	<0.0001

¹ One-sided non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195mm, compared at a 0.025 significance level.

SPIRIT III RCT

Primary Endpoint Results

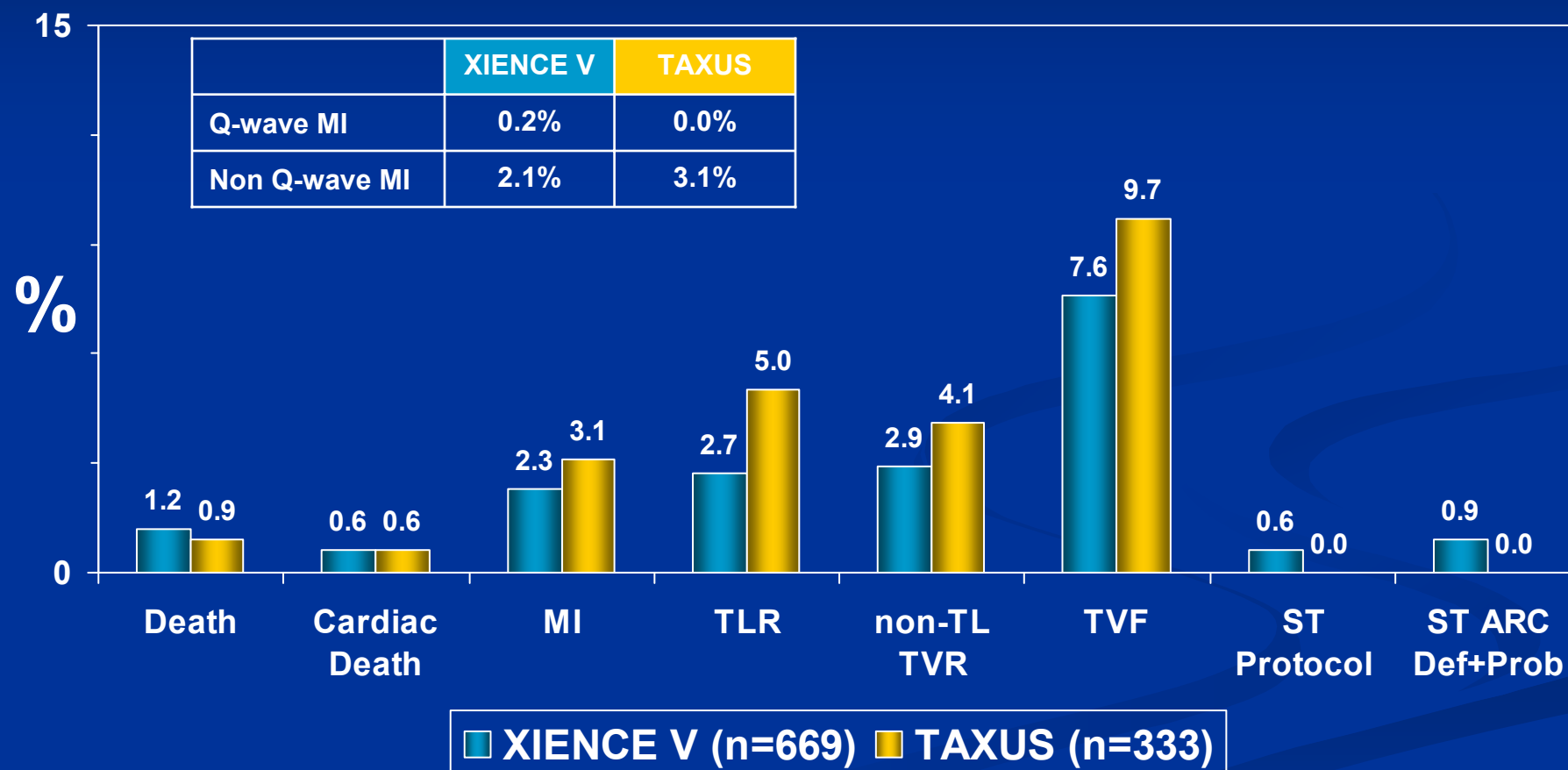
	XIENCE V (n=669)	TAXUS (n=333)	Difference [95% CI]	Non-inferior p-value ²
9 month TVF	7.6% (50/657)	9.7% (31/320)	-2.08% [-5.90%, 1.75%]	<0.0001

² One-sided non-inferiority test using asymptotic test statistic with non-inferiority margin of 5.5%, to be compared at a 0.05 significance level.

BOTH CO-PRIMARY ENDPOINTS MET

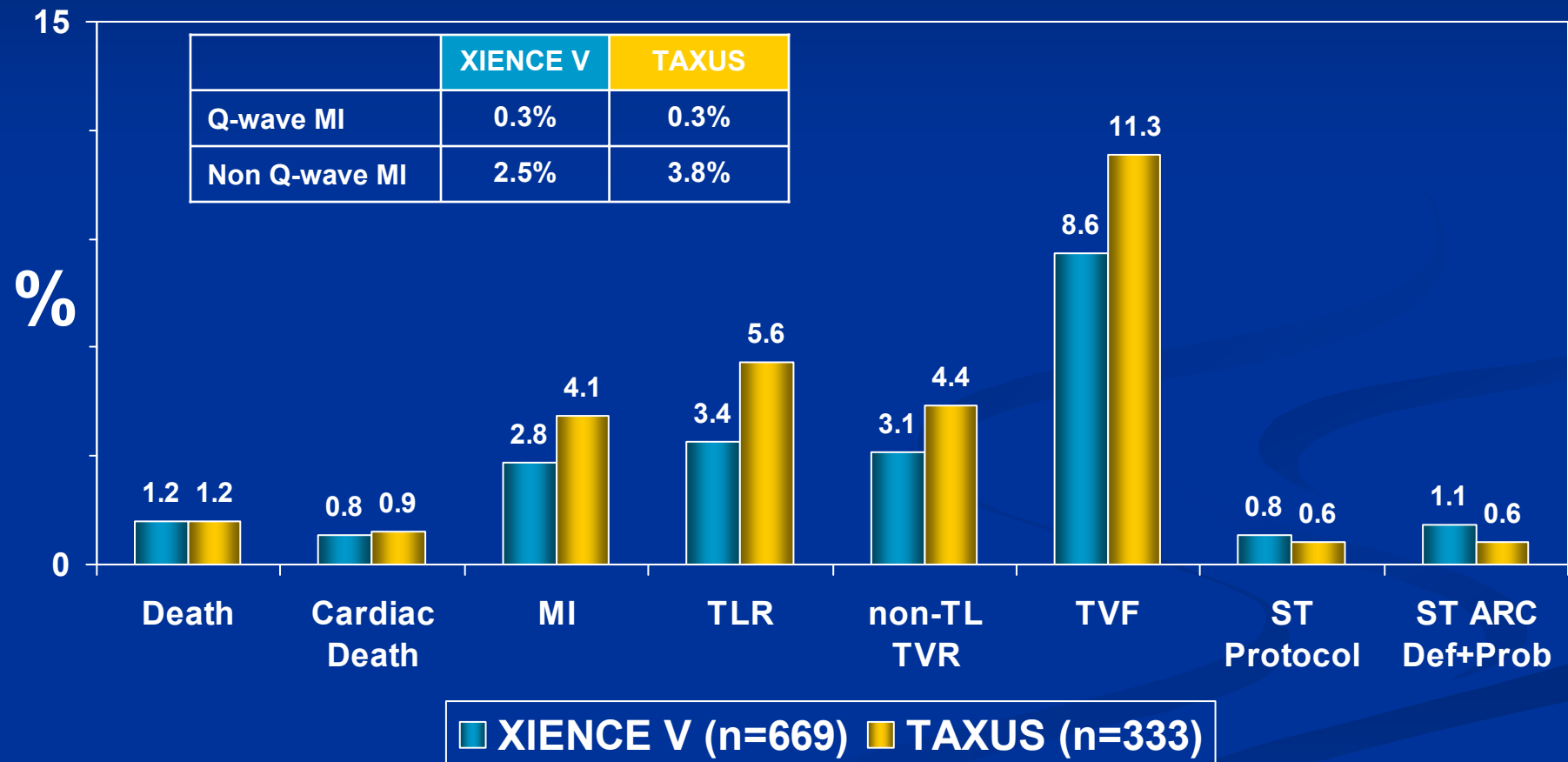
SPIRIT III RCT

Clinical Outcomes at 9 months



SPIRIT III RCT

Clinical Outcomes at 12 Months



SPIRIT III RCT

12 Month Stent Thrombosis

	XIENCE V N=669	TAXUS N=333
Stent Thrombosis (Per Protocol)		
Acute (1 day)	0.1% (1/669)	0.0% (0/330)
Subacute (1 to 30 days)	0.3% (2/667)	0.0% (0/330)
Late (31 to 393 days)	0.3% (2/646)	0.6% (2/317)
Total:	0.8% (5/647)	0.6% (2/317)
Stent Thrombosis (Per ARC definite + probable; TLR <i>not</i> censored)		
Acute (1 day)	0.1% (1/669)	0.0% (0/330)
Subacute (1 to 30 days)	0.4% (3/667)	0.0% (0/330)
Late (30 to 393 days)	0.5% (3/651)	0.6% (2/319)
Total: [95% Confidence interval]	1.1% (7/648) [0.44%, 2.21%]	0.6% (2/317) [0.08%, 2.26%]

SPIRIT III RCT

Other Angiographic results at 8 months

	XIENCE V N=669 M = 772	TAXUS N=333 M= 383	Difference [95% CI]
In stent late loss, mm	0.16 ± 0.41 (342)	0.30 ± 0.53 (158)	-0.15 [-0.24, -0.05]
In-stent %DS	5.92 ± 16.40 (343)	10.30 ± 21.43 (158)	-4.38 [-8.16, -0.60]
In-segment %DS	18.77 ± 14.43 (344)	22.82 ± 16.35 (158)	-4.05 [-7.03, -1.06]
In-stent ABR	2.3% (8/343)	5.7% (9/158)	-3.36% [-7.32%, 0.59%]
In-segment ABR	4.7% (16/344)	8.9% (14/158)	-4.21% [-9.17%, 0.75%]

N is the total number of subjects; M is the total number of lesions

SPIRIT III RCT

Other IVUS results at 8 months

	XIENCE V (N=669, M=772)	TAXUS (N=333, M=383)
NIH volume, mm³	10.13 ± 11.46 (101)	20.87 ± 31.51 (41)
%VO	6.91 ± 6.35 (98)	11.21 ± 9.86 (39)
Incomplete Apposition:		
Post-procedure	34.4% (31/90)	25.6% (11/43)
At 240 Days	25.6% (23/90)	16.3% (7/43)
Persisting	24.4% (22/90)	14.0% (6/43)
Late acquired	1.1% (1/90)	2.3% (1/43)

N is the total number of subjects; M is the total number of lesions

Summary of SPIRIT III RCT

- The SPIRIT III RCT successfully met both of its co-primary endpoints by demonstrating non-inferiority of XIENCE V to TAXUS with respect to 240-day in-segment late loss and 270 day Target Vessel Failure (TVF)
- Angiographic and IVUS results suggest a consistent trend toward lower restenosis in XIENCE V compared to TAXUS
- The Xience V stent had comparable safety outcomes out to 12 months compared to TAXUS

Summary of SPIRIT III RCT (cont'd)

■ Key Limitations

- As in many experimental studies, SPIRIT III was not designed to establish safety and efficacy in specific patient subgroups or secondary clinical endpoints
- Post-hoc data analyses and apparent trends toward significance need to be interpreted cautiously when assessing performance in specific patient subgroups or across multiple secondary endpoints
- 199 subjects at 37 sites overall (140 XIENCE V and 59 TAXUS subjects) were evaluated by unblinded study personnel at 9-month follow-up visit, representing nearly 20% (199/1002) of the total SPIRIT III RCT cohort. However, excluding the subjects that were evaluated by unblinded study personnel did not alter the study outcome
- Evaluable angiographic data was available for 77% of subjects randomized to receive 8-month angiography for analysis of the co-primary endpoint of in-segment late loss

SPIRIT III 4.0mm arm

- The SPIRIT III 4.0 mm arm was a single-arm, non-randomized, prospective, multicenter study
- **Objective**
 - To evaluate XIENCE V compared to TAXUS in the treatment of up to two *de novo* lesions ≤ 28 mm in length in native coronary arteries with RVD > 3.75 mm to ≤ 4.25 mm
- **Primary endpoint**
 - **In-segment LL at 240 days** in the 4.0 mm XIENCE V arm was compared with that of the TAXUS arm from the RCT with a non-inferiority margin (delta) of 0.195 mm
 - The interim analysis was conducted on the first 69 subjects enrolled (after unblinding of the RCT) with an adjusted p-value (decision boundary) applied to the analysis of in-segment LL

SPIRIT III 4.0

Baseline Demographic and Clinical Characteristics

	XIENCE V 4.0mm (N=69)
Age (yrs)	61.93 ± 11.20 (69)
Male	72.5% (50/69)
Current Cigarette Use	27.9% (19/68)
Any Diabetes	30.4% (21/69)
Diabetes Req. Insulin	8.7% (6/69)
Hypertension Req. Medication	65.2% (45/69)
Hyperlipidemia Req. Medication	77.9% (53/68)
Prior Myocardial Infarction	17.4% (12/69)
Prior PCI	18.8%(13/69)
Prior CABG	5.8%(4/69)
Stable Angina	47.8% (32/67)
Unstable Angina	19.4% (13/67)

SPIRIT III 4.0

Baseline Lesion and Vessel Characteristics

	XIENCE V 4.0 mm Arm (N=69)(M=69)	TAXUS RCT Angiographic Group (N=188) (M=220)	XIENCE V RCT Angiographic Group (N=376) (M=427)
Target Vessel			
LAD	26.1% (18/69)	43.6% (96/220)	40.5% (173/427)
Circumflex or Ramus	17.4% (12/69)	28.6% (63/220)	27.9% (119/427)
RCA	56.5% (39/69)	27.7% (61/220)	31.6% (135/427)
LMCA	0.0% (0/69)	0.0% (0/220)	0.0% (0/427)
Pre-Procedure RVD (mm) Mean ± SD (m)	3.53± 0.36 (69)	2.77 ± 0.46 (220)	2.75 ± 0.44 (427)
Pre-Procedure %DS Mean ± SD (m)	71.37± 13.38 (69)	70.33 ± 13.48 (220)	70.41 ± 13.32 (427)
Lesion Length (mm) Mean ± SD (m)	15.43 ± 6.21 (69)	14.99 ± 5.88 (218)	14.92 ± 5.73 (427)
Note: N is the total number of subjects; M is the total number of lesions			

SPIRIT III 4.0

Procedural Success and 30-Day MACE

- Clinical device success (per lesion)
 - XIENCE 4.0mm 98.5% vs. TAXUS 98.7% vs. XIENCE RCT 98.3%
- Clinical procedure success (per subject)
 - XIENCE 4.0mm 94.2% vs. TAXUS 97.3% vs. XIENCE RCT 98.5%
- 30 Day MACE

	XIENCE V 4.0mm (n=69)	TAXUS RCT (n=333)
MACE	4.3%	2.4%
Q-wave MI	0.0%	0.0%
Non Q-wave MI	4.3%	2.1%

SPIRIT III 4.0mm

Primary Endpoint Results

	XIENCE V 4.0mm Arm (N=69)	TAXUS RCT (N=188)	“Non- Inferiority” p-Value ¹
240 Day In-Segment LL Mean \pm SD (n)	0.17 \pm 0.38 (49)	0.28 \pm 0.48 (134)	<0.0001
¹ One-sided by non-inferiority test using asymptotic test statistic with non-inferiority margin of 0.195mm, compared at a 0.0377 significance level			

PRIMARY ENDPOINT MET

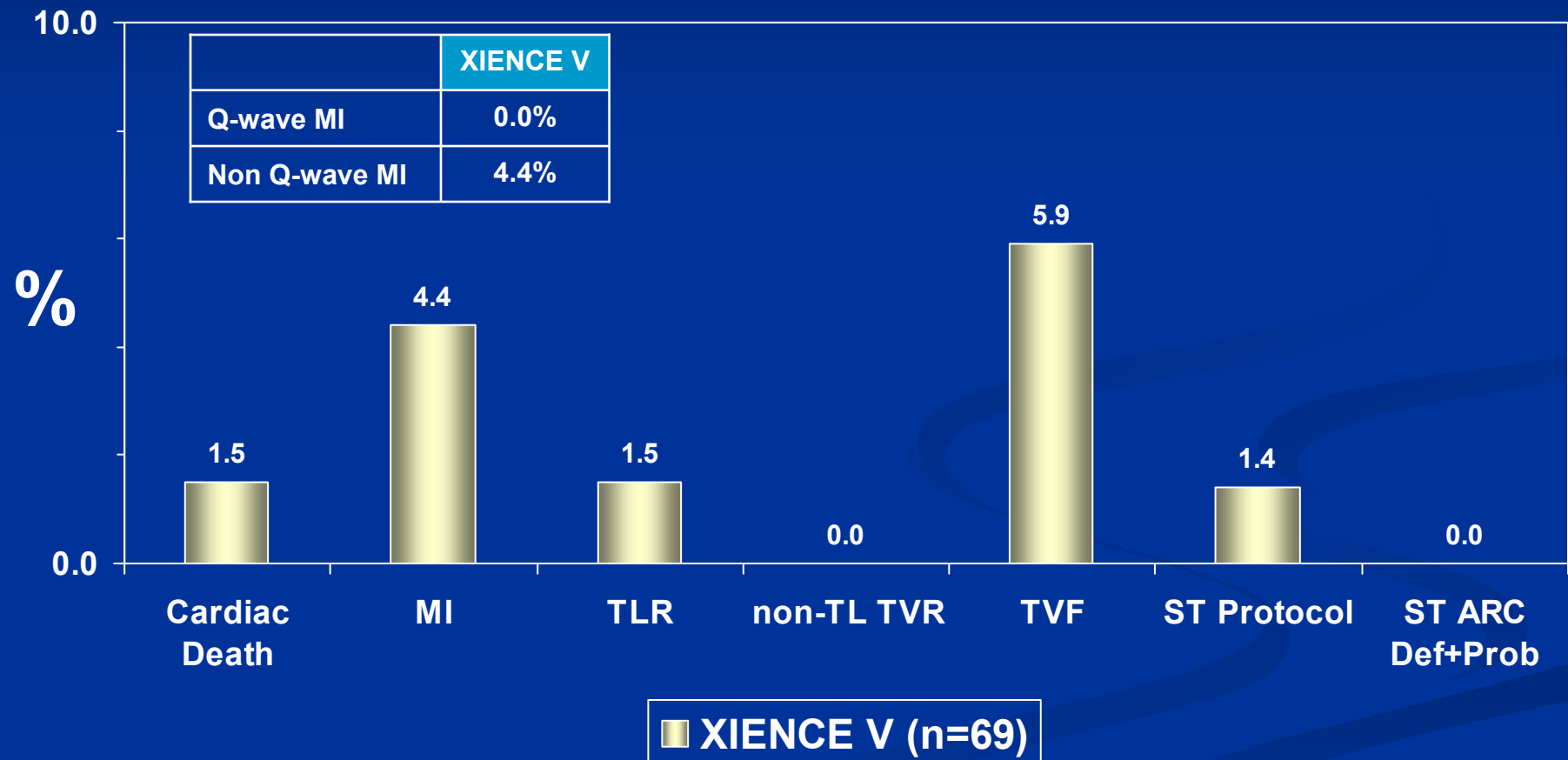
SPIRIT III 4.0mm

Angiography results at 8 months

	XIENCE V 4.0 mm Arm (N=69) (M=69)	TAXUS RCT (N=188) (M=220)	XIENCE V RCT (N=376) (M=427)
Pre-Procedure RVD (mm) Mean \pm SD (m)	3.53\pm 0.36 (69)	2.77 \pm 0.46 (220)	2.75 \pm 0.44 (427)
Pre-Procedure Percent Diameter Stenosis (%DS) Mean \pm SD (m)	71.37\pm 13.38 (69)	70.33 \pm 13.48 (220)	70.41 \pm 13.32 (427)
240 day In-Segment %DS Mean \pm SD (m)	17.92 \pm 10.83 (49)	22.82 \pm 16.35 (158)	18.77 \pm 14.43 (344)
In-Stent Late Loss (mm) Mean \pm SD (m)	0.12 \pm 0.34 (49)	0.30 \pm 0.53 (158)	0.16 \pm 0.41 (342)
240 day In-Segment Angiographic Binary Restenosis (ABR)	2.0 % (1/49)	8.9% (14/158)	4.7% (16/344)
Note: N is the total number of subjects; M is the total number of lesions			

SPIRIT III 4.0mm

Clinical Outcomes at 9 and 12 Months



Summary of SPIRIT III 4.0mm

- The SPIRIT III 4.0 mm Arm successfully met its primary endpoint of 240-day in-segment late loss
- Secondary angiographic endpoints demonstrated lower observed rates of restenosis compared to the TAXUS control and were also similar to XIENCE V data from the SPIRIT III RCT
- The SPIRIT III 4.0mm arm was not designed to adequately evaluate clinical outcomes, but for the subjects available for clinical analysis, the results of the XIENCE V 4.0 mm were comparable to those seen in the SPIRIT III RCT

Summary of SPIRIT III 4.0mm

■ Key Limitations

- SPIRIT III 4.0mm was non-randomized
- Only 71% (49/69) of enrolled subjects had qualifying follow-up angiograms
- Study was not designed to evaluate clinical endpoints, but to establish the effectiveness of the 4.0mm platform by demonstrating comparability of in-segment late loss to TAXUS in the SPIRIT III RCT

SPIRIT PK STUDIES

- Abbott conducted three PK substudies
 - SPIRIT II PK Substudy
 - SPIRIT III PK US RCT Substudy
 - SPIRIT III Japan Registry Substudy
- Global PK data includes a total of 73 subjects
- Objective for each substudy: To determine the pharmacokinetics of everolimus delivered by XIENCE V
- The 73 subjects who volunteered to participate in the pharmacokinetic sub-study had blood drawn prior to the first stent implant, and at 14 sampling points out to 30 days
- The total dose of everolimus received by the subjects within the three substudies varied from 53 to 588 μg (# stents varied from 1 to 4)

SPIRIT PK Substudies

Pharmacokinetic Parameters of Everolimus							
	SPIRIT III RCT PK Substudy		SPIRIT III Japan Registry PK Substudy		SPIRIT II PK Substudy		
	88 mg	181 mg	88 mg	113 mg	88 µg	113 µg	181 µg
n	3 ^b	6 ^c	6	4	13 ^d	4 ^e	4
t _{max} , hours median (range)	0.50 (0.50 - 1.88)	0.50 (0.07 - 1.00)	1.00 (0.50 - 1.02)	0.51 (0.50 - 0.53)	0.50 (0.13 - 2.17)	0.50 (0.50 - 0.50)	0.46 (0.17 - 1.00)
C _{max} , ng/mL mean ± SD	0.3867 ± 0.09866	1.175 ± 0.6817	0.5017 ± 0.1398	0.6500 ± 0.08756	0.4369 ± 0.1507	0.5850 ± 0.2630	0.7925 ± 0.1406
AUC _{0-24h} , ng.h/ml mean ± SD	3.458 ± 0.1981	9.601 ± 4.015	4.476 ± 1.087	6.154 ± 0.7523	5.156 ± 1.976	6.820 ± 4.373	10.27 ± 1.035
AUC _{0-t} , ng.h/mL mean ± SD	5.319 ± 4.114	23.73 ± 13.63	5.049 ± 2.138	11.02 ± 4.002	8.255 ± 5.863	42.54 ± 58.83	28.07 ± 13.18
AUC _{0-∞} , ng.h/mL ^a mean ± SD	-	44.00 ± 28.67	12.98 ± 7.078	19.97 ± 7.890	19.60 ± 15.30	22.79 ± 31.47	52.71 ± 27.40

^aAccurate determination not possible; ^bn = 2 for AUC_{0-24h}; ^cn = 5 for AUC_{0-24h} and n = 4 for AUC_{0-inf}, t_{1/2term} and CL;

^dn = 1 2 for AUC_{0-24h}; ^en = 3 for AUC_{0-inf}, t_{1/2term} and CL



SPIRIT II and III: Combined Analysis

- FDA requested post-hoc analyses of **1 year** outcomes for patients in the SPIRIT II RCT and SPIRIT III RCT
- The primary goal for this analysis was to provide improved estimates of the true rates of death, MI and stent thrombosis in the XIENCE and TAXUS DES platforms, primarily by increasing the evaluable sample size in a post-hoc manner.
- Important Subgroups
 - Single Vessel vs. Dual Vessel Treated subjects
 - Diabetics
- Follow-up through 1 year

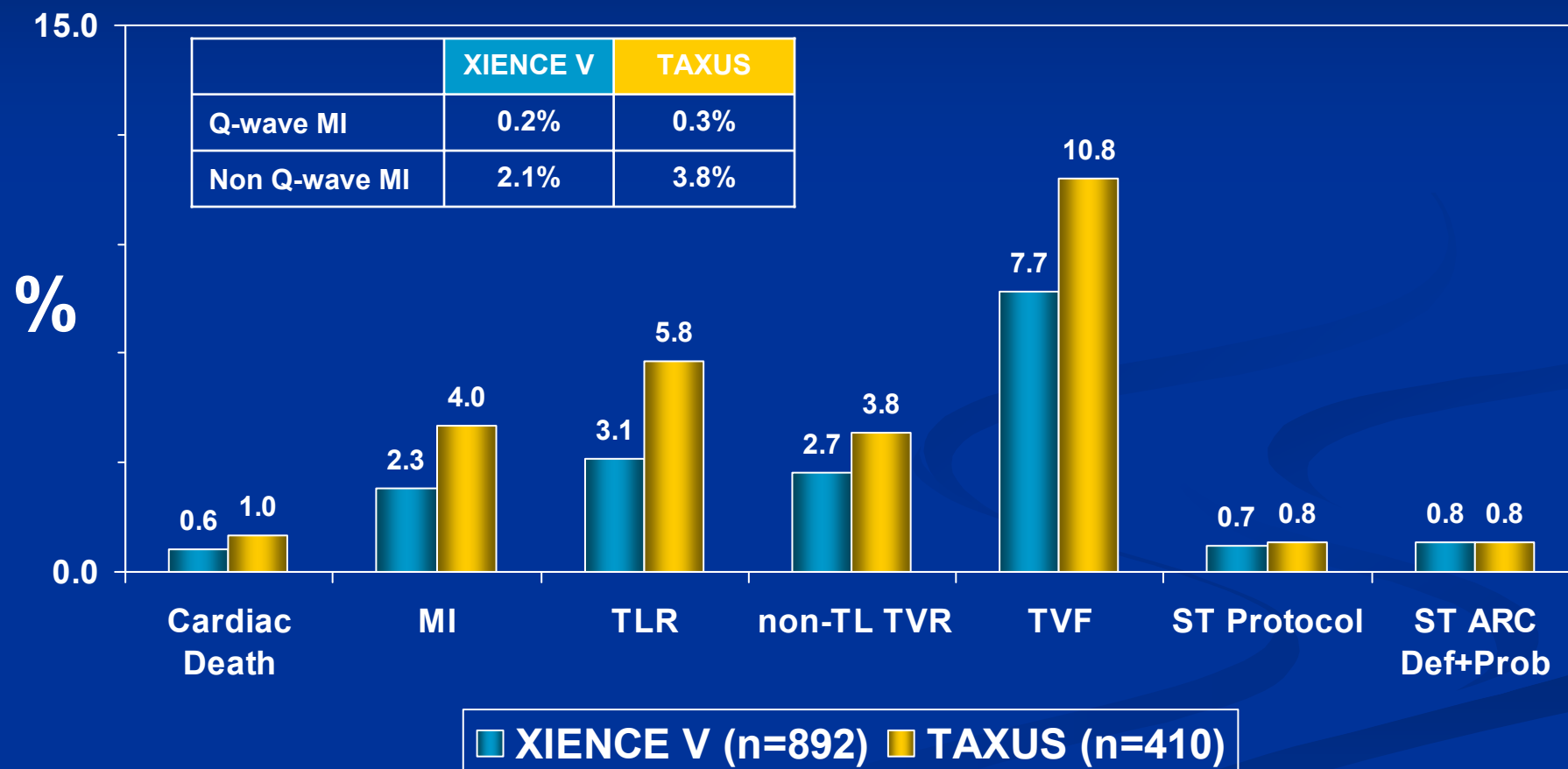
Combined Analysis: All Patients

- The pooled population from SPIRIT II and SPIRIT III RCT consisted of 1302 subjects. Of the 1302 subjects 892 were randomized to XIENCE V and 410 were randomized to TAXUS

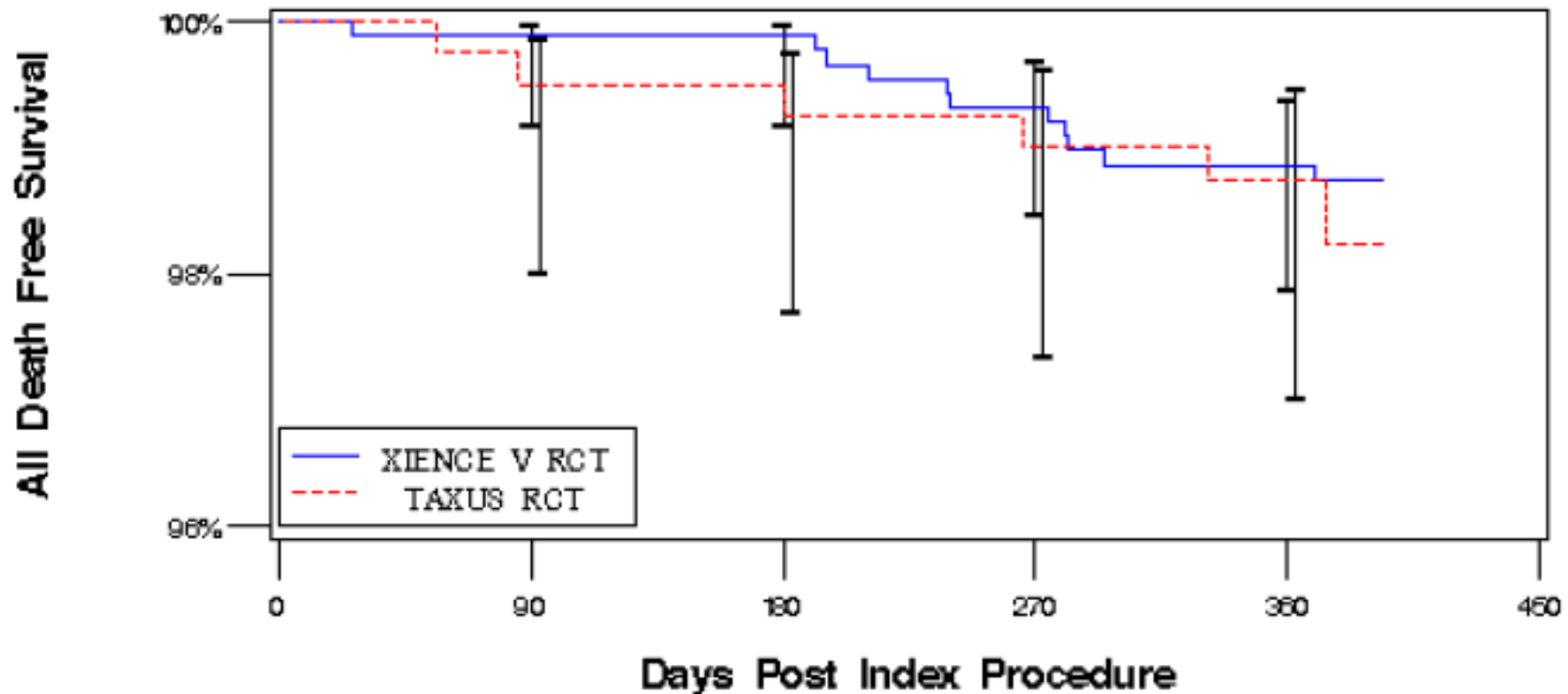
	SPIRIT II RCT	SPIRIT III RCT
Number, sites	300 patients 31 sites	1002 patients 65 sites
XIENCE V:TAXUS	3:1 (223:77)	2:1 (669:333)
Geography	Europe, Asia	USA
Vessel Diameter (mm)	2.5 - 4.0	2.5 - 3.75
Lesion Length (mm)	≤ 28	≤ 28
N lesions, vessels	1-2 lesions 1 per vessel	1-2 lesions 1 per vessel
Clinical visits (First year)	1, 6, 9, 12 m	1, 6, 8, 9, 12 m

SPIRIT II and III Combined Analysis

Clinical Outcomes to 1 Year

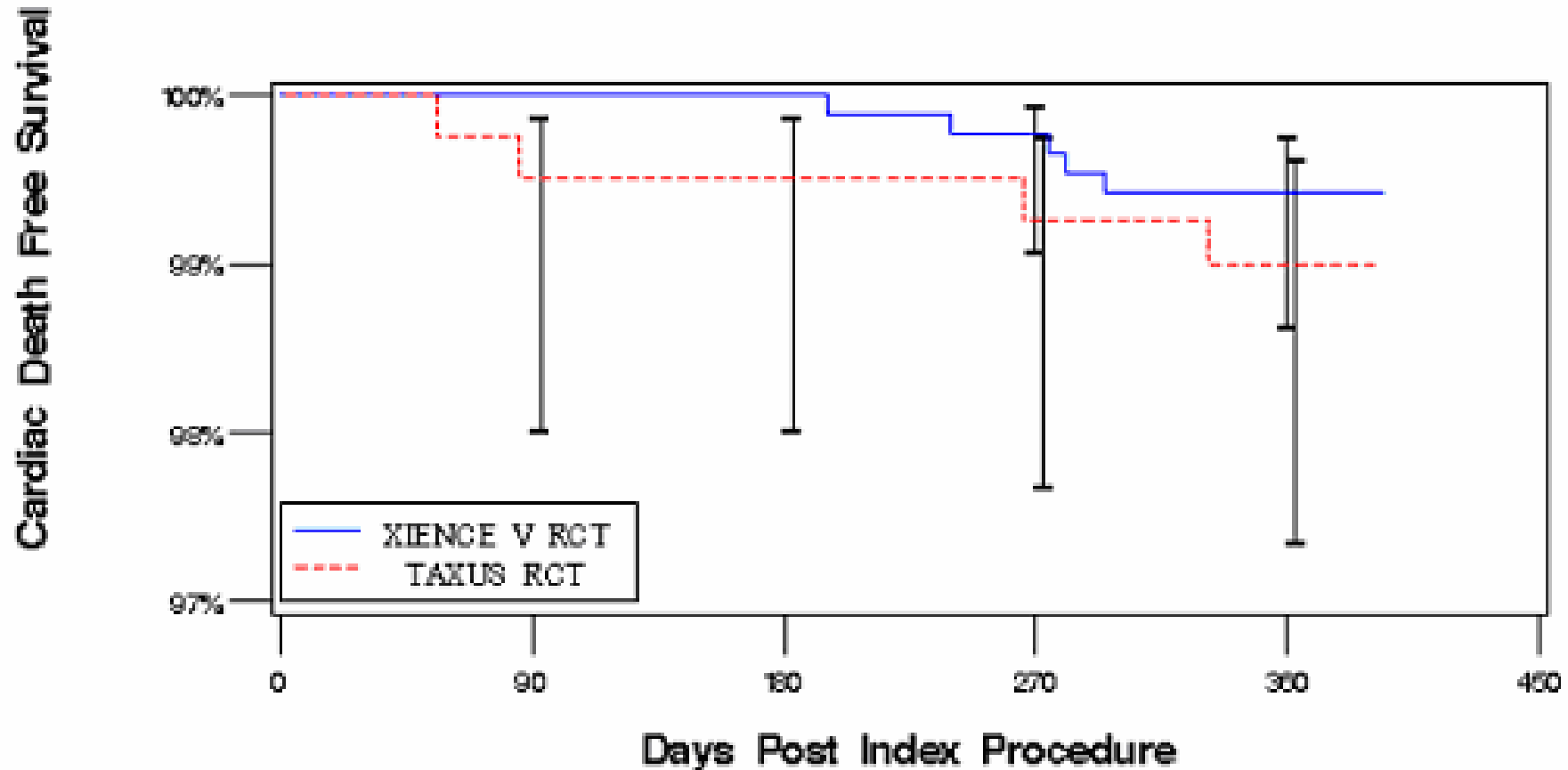


SPIRIT II and III Combined Analysis Freedom From All Death



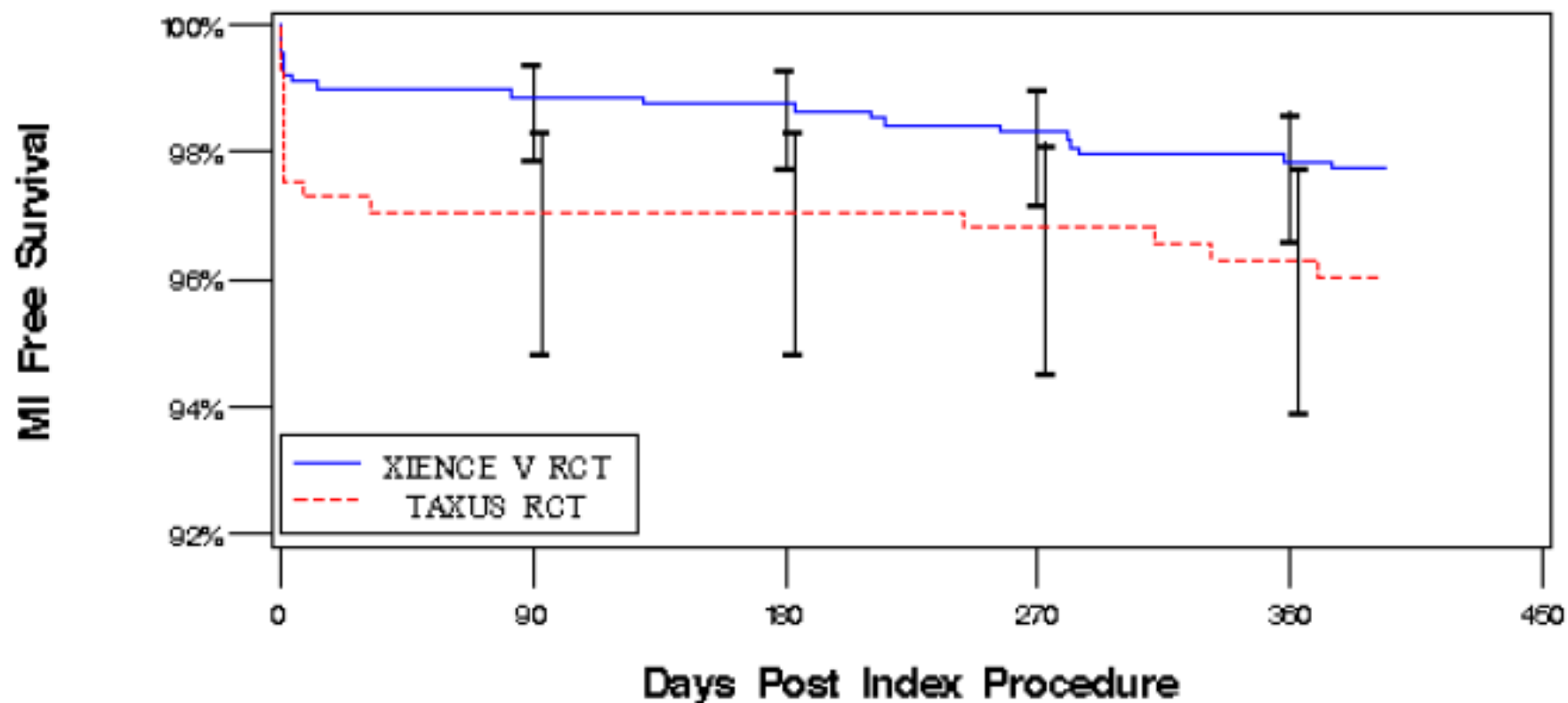
393 Day Number at Risk: XIENCE V 865, TAXUS 389
Log-rank p-value = 0.4811

SPIRIT II and III Combined Analysis Freedom From Cardiac Death



393 Day Number at Risk: XIENCE V 865, TAXUS 389
Log-rank p-value = 0.3913

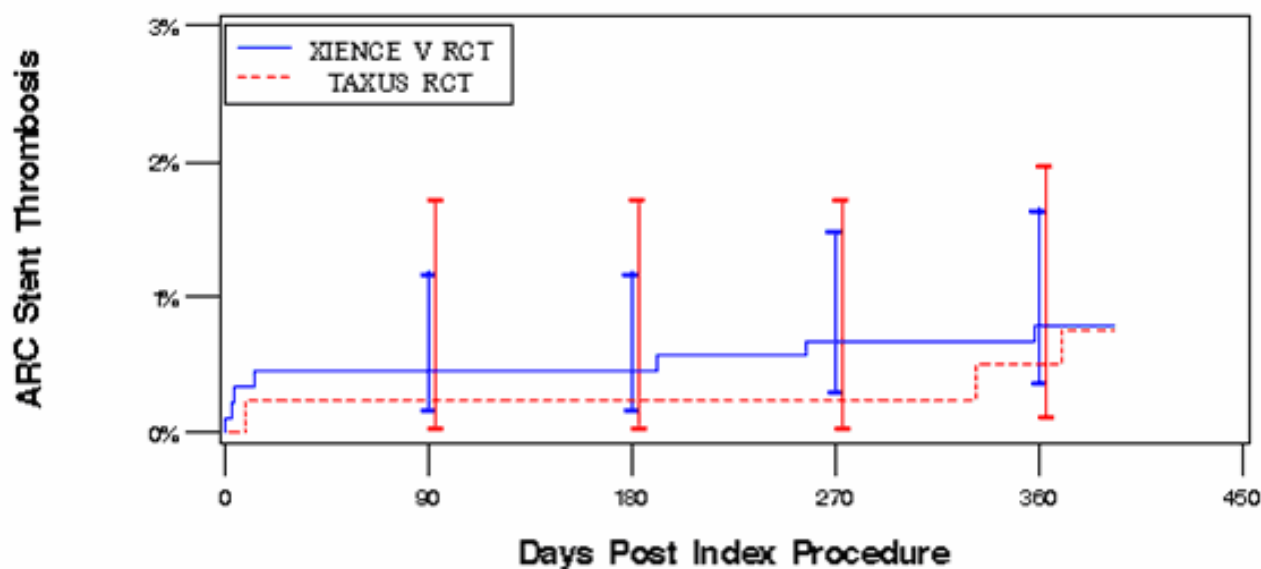
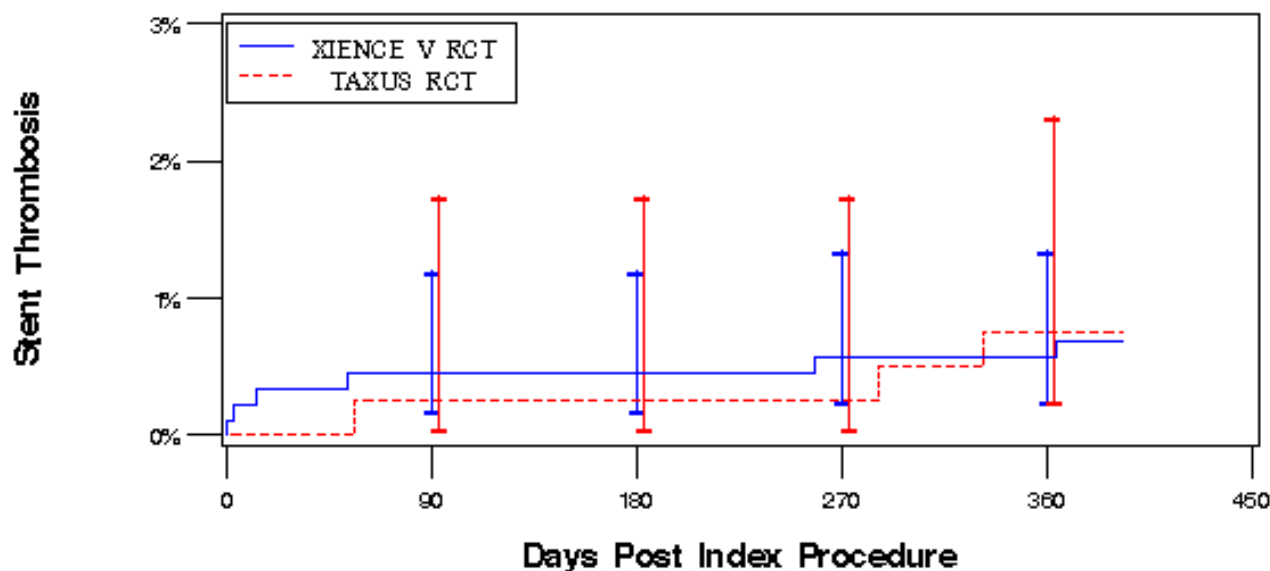
SPIRIT II and III Combined Analysis Freedom From MI 393 Days



393 Day Number at Risk: XIENCE V 847, TAXUS 376
Log-rank p-value = 0.0836

SPIRIT II and III Combined Analysis

Cumulative Stent Thrombosis



PROTOCOL DEFINED
393 Day Number at Risk:
XIENCE V 860
TAXUS 388

Log-rank p-value = 0.8970

A.R.C. DEF + PROB
393 Day Number at Risk:
XIENCE V 860
TAXUS 388

Log-rank p-value = 0.9280

Combined Analysis: Stent Thrombosis 0 to 12 Months

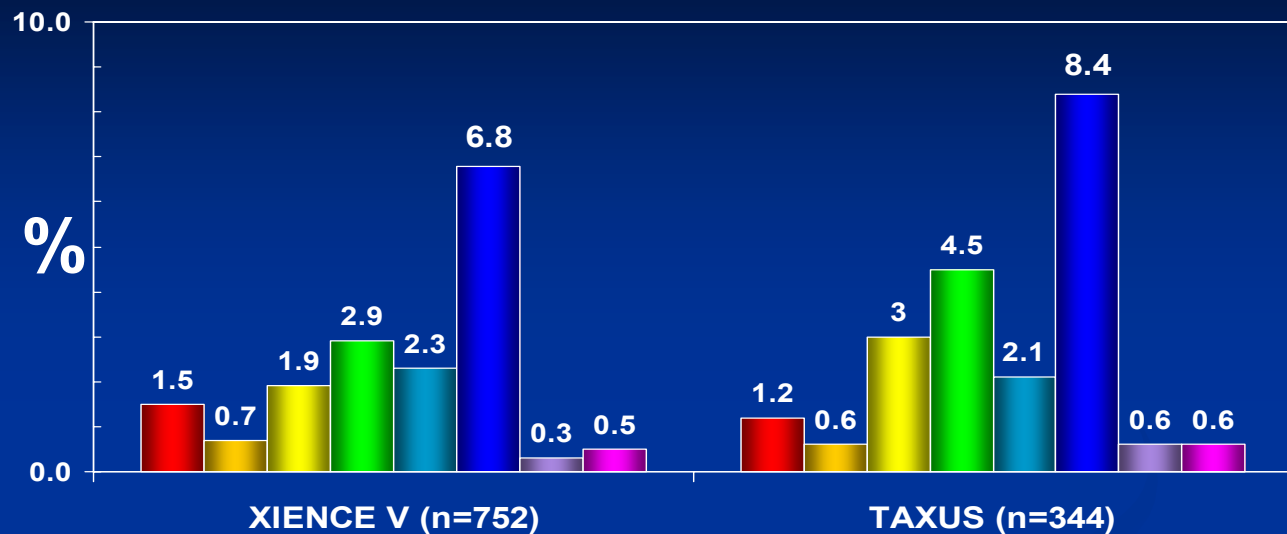
Stent Thrombosis	XIENCE V (N=892)	TAXUS (N=410)
Protocol Defined	0.7% (6/867) [0.25%, 1.50%]	0.8% (3/394) [0.16%, 2.21%]
ARC definite + probable (TLR-uncensored)	0.8% (7/868) [0.32%, 1.65%]	0.8% (3/394) [0.16%, 2.21%]

Single vs. Dual Vessel

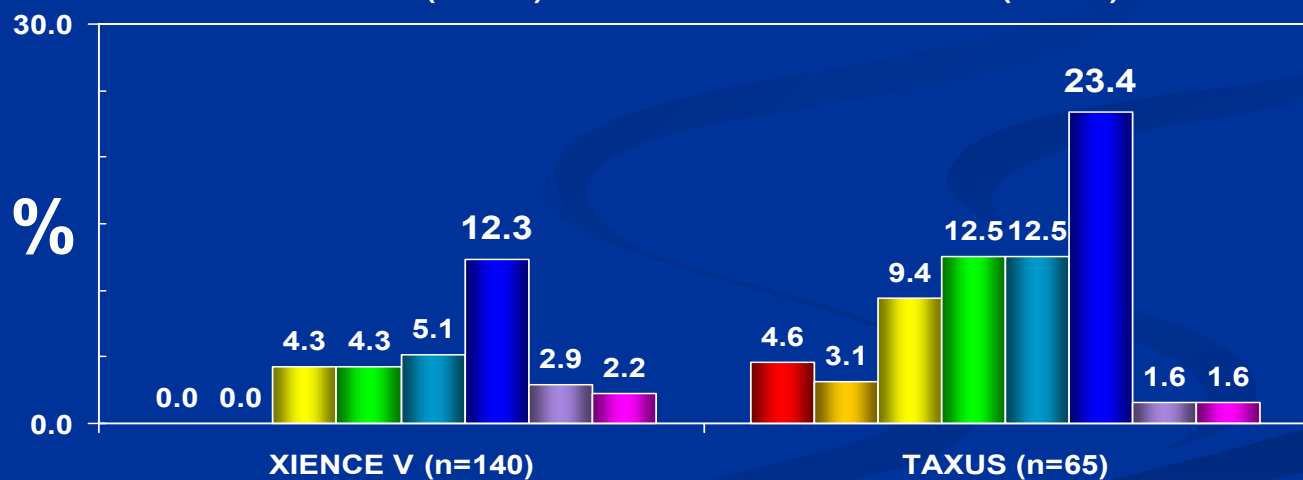
Events through 393 days (Single and Dual Vessel Treated Subgroup)				
	XIENCE V Dual Vessel Treated (N=140)	TAXUS Dual Vessel Treated (N=65)	XIENCE V Single Vessel Treated (N=752)	TAXUS Single Vessel Treated (N=344)
TVF	12.3% (17/138)	23.4% (15/64)	6.8% (50/735)	8.4% (28/333)
All Death	0.0% (0/138)	4.6% (3/65)	1.5% (11/739)	1.2% (4/333)
Cardiac Death	0.0% (0/138)	3.1% (2/64)	0.7% (5/735)	0.6% (2/333)
MI	4.3% (6/138)	9.4% (6/64)	1.9% (14/735)	3.0% (10/333)
TLR	4.3% (6/138)	12.5% (8/64)	2.9% (21/735)	4.5% (15/333)
TVR (CABG/PCI), non Target lesion	5.1% (7/138)	12.5% (8/64)	2.3% (17/735)	2.1% (7/333)
Stent Thrombosis				
Protocol defined	2.9% (4/138)	1.6% (1/62)	0.3% (2/729)	0.6% (2/332)
ARC definite + probable (TLR <i>not</i> censored)	2.2% (3/138)	1.6% (1/62)	0.5% (4/730)	0.6% (2/332)

Single vs. Dual Vessel Treated

SINGLE VESSEL



DUAL VESSEL



Diabetics

- Diabetics comprise an important patient population at increased risk for cardiovascular morbidity and mortality
- Like previous DES applications diabetic patients were not excluded in the SPIRIT clinical trials
- Although there were no pre-specified hypotheses or trial design features to warrant a specific labeled indication for the use of the XIENCE V stent in diabetics, FDA believes that clinical outcomes in diabetics should be considered in the review of the XIENCE V stent program.

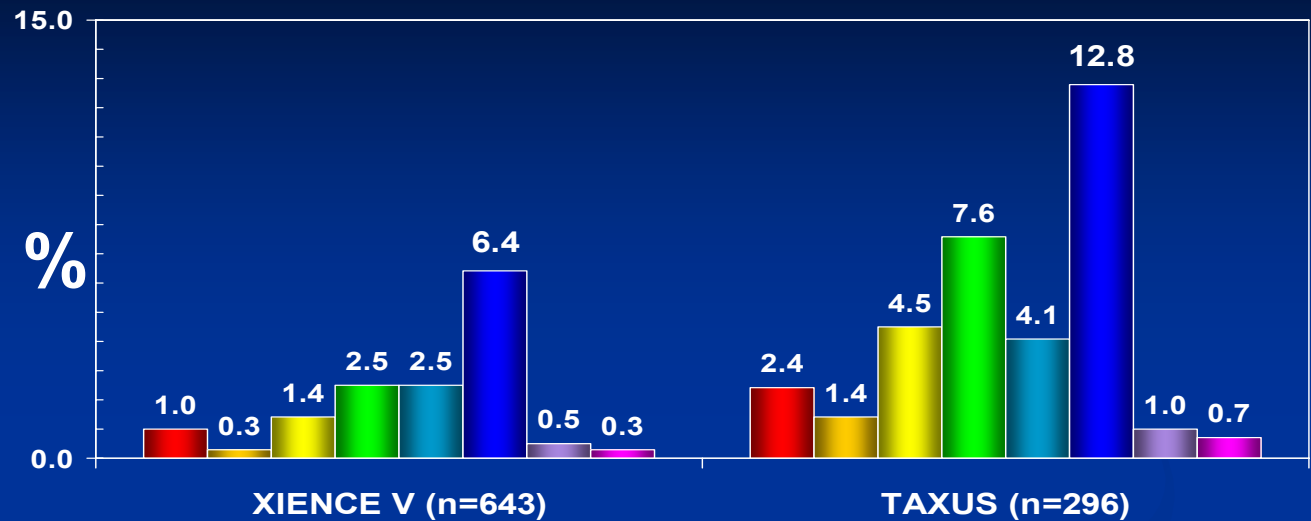
Clinical Events in Diabetics through 1 year

	Non-Diabetics		All Diabetics	
	XIENCE V (N=643)	TAXUS (N=296)	XIENCE V (N=249)	TAXUS (N=110)
TVF	6.4% (40/629)	12.8% (37/290)	11.1% (27/244)	5.8% (6/104)
All Death	1.0% (6/631)	2.4% (7/291)	2.0% (5/246)	0.0% (0/104)
Cardiac Death	0.3% (2/629)	1.4% (4/290)	1.2% (3/244)	0.0% (0/104)
MI	1.4% (9/629)	4.5% (13/290)	4.5% (11/244)	2.9% (3/104)
TLR	2.5% (16/629)	7.6% (22/290)	4.5% (11/244)	1.0% (1/104)
TVR (CABG/PCI), non TL	2.5% (16/629)	4.1% (12/290)	3.3% (8/244)	2.9% (3/104)
Stent Thrombosis				
Protocol defined	0.5% (3/627)	1.0% (3/287)	1.3% (3/240)	0.0% (0/104)
ARC definite + probable (TLR <i>not</i> censored)	0.3% (2/627)	0.7% (2/287)	2.1% (5/241)	1.0% (1/104)

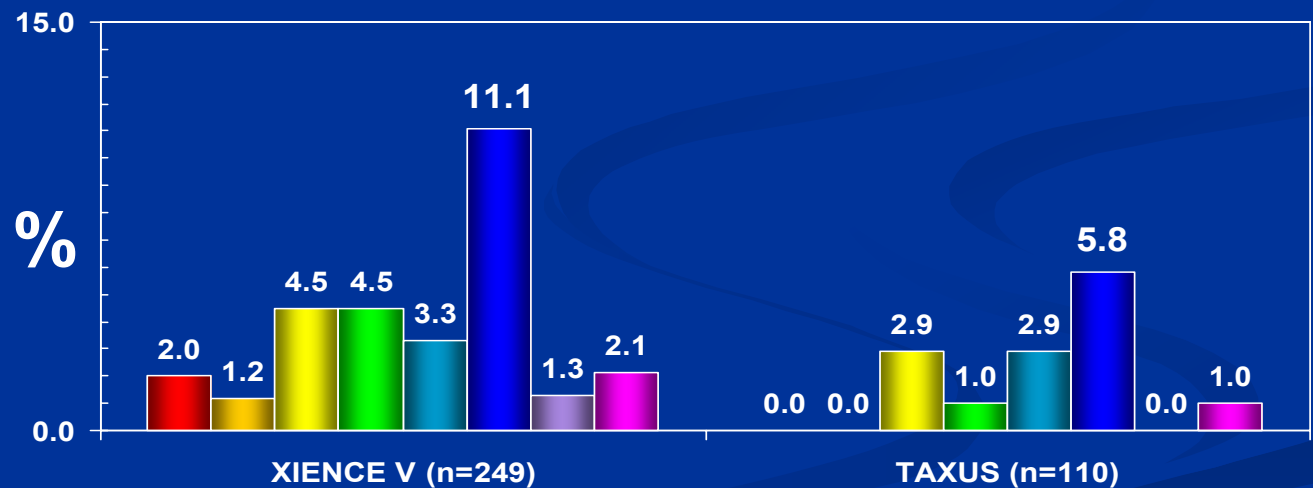


Diabetics vs. Non-Diabetics

NON-DIABETICS



DIABETICS



Death
TLR
ST Protocol

Cardiac Death
TVR, non TL
ST ARC Def + Prob

MI
TVF

Combined SPIRIT II and III 2 Year Ad hoc Analysis

- In the original Panel Pack materials mailed out on November 6, 2007, the clinical dataset provided by Abbott Vascular and reviewed by FDA consisted of:
 - Spirit FIRST – follow-up through 36 months
 - Spirit II – follow-up through 12 months
 - Spirit III – follow-up through 12 months
- Follow-up has been ongoing

Combined SPIRIT II and III 2 Year Ad hoc Analysis

- Abbott Vascular has performed an *ad hoc* analysis on a subset of combined SPIRIT II and III subjects who have completed 2 year follow-up assessments as of October 30, 2007
- FDA has agreed to receive and review such an analysis to give the applicant an opportunity to present the most up-to-date safety data available on XIENCE V™, despite the limitations of such an analysis

Combined SPIRIT II and III 2 Year Ad hoc Analysis

- As of October 30, 2007, 603 subjects who were enrolled in the SPIRIT II and SPIRIT III RCTs had completed their two year follow-up (n=529) or were terminated early (n=74)
- Data on these subjects was subsequently monitored and clinical events sent for adjudication and to apply ARC definitions of stent thrombosis
- Of the 603 subjects who were completers or early terminators, 422 subjects received XIENCE V and 181 subjects received TAXUS
 - **SPIRIT II: 251 subjects**
 - XIENCE V: 186, TAXUS: 65
 - **SPIRIT III: 352 subjects**
 - XIENCE V: 236, TAXUS: 116

Combined SPIRIT II and III

2 Year Ad hoc Analysis

- Clinical events from 0 to 758 days in the 2 year cohort were numerically higher than the one year data
- Rates of cardiac death and MI from 1 to 2 years were low in the 2 year completer cohort

394 to 758 days	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Cardiac Death	0.5% (2/379)	0.0% (0/153)
QMI	0.0% (0/379)	0.0% (0/153)
NQMI	1.1% (4/379)	0.7% (1/153)

Combined SPIRIT II and III 2 Year Ad hoc Analysis

- In the 2-year completer cohort, there were two additional *Protocol Defined* stent thromboses observed in the XIENCE V arm and none in the TAXUS arm between 1 and 2 years.

Protocol Defined	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Very Late Stent Thrombosis (394 - 758 days) [95% Confidence Interval] ¹	0.5% (2/378) [0.06%, 1.90%]	0.0% (0/153) [0.00%, 2.38%]

¹ By Clopper-Pearson exact confidence interval

Combined SPIRIT II and III 2 Year Ad hoc Analysis

- In contrast there was one *ARC Definite + Probable* stent thrombosis in the XIENCE V arm between 1 and 2 years of follow-up.

ARC Defined	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Very Late Stent Thrombosis (394 - 758 days) Definite/Probable [95% Confidence Interval] ¹	0.3% (1/377) [0.01%, 1.47%]	0.0% (0/153) [0.00%, 2.38%]

¹ By Clopper-Pearson exact confidence interval

Combined SPIRIT II and III 2 Year Ad hoc Analysis

Total Stent Thrombosis (0 - 758 days)	XIENCE V 2-Y FU Subset (N=422)	TAXUS 2-Y FU Subset (N=181)
Protocol defined [95% Confidence Interval] ¹	1.6% (6/379) [0.58%, 3.41%]	1.9% (3/155) [0.40%, 5.55%]
ARC Definite/Probable [95% Confidence Interval] ¹	1.3% (5/379) [0.43%, 3.05%]	1.3% (2/155) [0.16%, 4.58%]

Combined SPIRIT II and III 2 Year Ad hoc Analysis

Summary

- For the 2 year analysis cohort, rates of additional cardiac death, myocardial infarctions and stent thrombosis events occurring between one and two years of follow-up were low.

Combined SPIRIT II and III 2 Year Ad hoc Analysis

Key Limitations

- This is an ad hoc analysis; it should not be interpreted as an interim analysis
- Data is derived from a subset of the total SPIRIT II and III study cohorts and contains only data that was available to the applicant
- Events that occurred in subjects who had not yet reached the 2 year follow-up window may not be included in this analysis
- Absent from the data are subjects who were eligible for 2 year follow-up, but have not yet been assessed
- Subjects may have had their 2 year follow-up, but did not have their data reported to the applicant by the October 30, 2007 cutoff
- Inclusion of data from sites that submitted 2 year data was non-random
- Adjudication of clinical events and determination of ARC-defined stent thromboses were not performed by the same committee for each subject

Final Summary

- Clinical endpoints
 - XIENCE V stent met the prespecified co-primary endpoint versus TAXUS of 9-month TVF in the pivotal SPIRIT III RCT
- Angiographic endpoints
 - XIENCE V stent met its late loss endpoints versus TAXUS in SPIRIT II, SPIRIT III RCT and SPIRIT III 4.0mm
 - XIENCE V demonstrated consistently lower angiographic and IVUS measures of restenosis compared to TAXUS

Safety

- The SPIRIT clinical studies include a total of 986 subjects received XIENCE V stents, with 959 patients followed out to 12 months and limited data on 422 subjects out to 24 months
- Increased rates of death, cardiac death, and MI for the XIENCE V stent vs. TAXUS have not been observed
- Combined analyses and available data beyond 1 year did not demonstrate unanticipated safety signals

Thank You

P070015
Abbott Vascular
XIENCE V DES
Statistical Evaluation

Xu (Sherry) Yan, PhD

Division of Biostatistics
Office of Surveillance and Biometrics
CDRH/FDA
November 29, 2007

Trial Overview

	SPIRIT First (OUS)	SPIRIT II (OUS)	SPIRIT III	
			RCT (US)	4.0 mm (US)
# of Centers	9	28	65	30
Randomization	1:1	3:1	2:1	Single-arm
Comparison Group	VISION (BMS)	TAXUS (DES)	TAXUS (DES)	TAXUS in RCT
# of Enrolled XIENCE V: Control	28 : 32	223:77	669: 333	69
Intended Treatment	Single vessel	Up to two vessels	Up to two vessels	Up to two Vessels

SPIRIT First

- Objective: To assess the feasibility and performance of XIENCE V
- Primary Endpoint: 180-day In-stent Late Loss

	XIENCE V (N=27)	VISION (N=29)	Difference in Mean [95% CI]	p-Value
180-day In-stent Late Loss Mean \pm SD (n)	0.10 \pm 0.23 (23)	0.85 \pm 0.36 (27)	-0.76 [-0.93, -0.59]	< 0.0001

n is the number of evaluable patients.

95% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in [].

SPIRIT II

- Objective: To assess the safety and performance of XIENCE V to TAXUS in subjects with a maximum of two *de novo* native coronary artery lesions, each in a different epicardial vessel with RVD of ≥ 2.5 mm and ≤ 4.25 mm and lesion length ≤ 28 mm.
- Primary Endpoint: 180-day In-stent Late Loss (LL).

SPIRIT II

- Non-inferiority Hypotheses:

H₀: Mean In-stent LL XIENCE V – Mean In-stent LL TAXUS \geq 0.16 mm

H_A: Mean In-stent LL XIENCE V – Mean In-stent LL TAXUS $<$ 0.16 mm

- Superiority Hypotheses:

H₀: Mean In-stent LL XIENCE V \geq Mean In-stent LL TAXUS

H_A: Mean In-stent LL XIENCE V $<$ Mean In-stent LL TAXUS

Nominal significance level	Nominal power	Calculated sample size	Actual sample size
1-sided 0.05 for non-inferiority	91% for non-inferiority	180: 60 for XIENCE V: TAXUS	223:77 for XIENCE V: TAXUS
2-sided 0.05 for superiority			

SPIRIT II Interim Analyses

- O'Brien-Fleming boundary for non-inferiority test specified in the protocol.

Look	Total subjects	Nominal α	Total α
1	40	<0.0001	<0.0001
2	80	0.0007	0.0007
3	120	0.0054	0.0054
4	160	0.0146	0.0164
5	240	0.0448	0.0500

- Interim analyses reportedly conducted at 80 and 120 subjects, respectively.
- Final analysis conducted at nominal α of 0.0448 based on 300 subjects.

SPIRIT II Interim Analyses

- The purpose of the interim analyses is not clear: the sponsor stated no early stopping was intended.
- Decision boundary for superiority was not clearly specified.
- The interim analyses results were un-blinded to the sponsor, but not available to FDA.
- The interim analyses may introduce potential bias to the study conclusions.

Primary Outcome of SPIRIT II

Primary Endpoint: 180-day In-stent Late Loss, mm (n)

	XIENCE V (N=223)	TAXUS (N=77)	Difference [95% CI]	Non-inferiority nominal p-value ($\delta=0.16$)	Superiority nominal p-value
Complete Case Mean \pm SD (n)	0.11 \pm 0.27 (201)	0.36 \pm 0.39 (73)	-0.24 [-0.34, -0.15]	<0.0001	<0.0001
Q3 _ Q1 Case	0.13 \pm 0.27 (223)	0.34 \pm 0.39 (77)	-0.21 [-0.30, -0.11]	<0.0001	<0.0001
Worst Case	0.26 \pm 0.51 (223)	0.31 \pm 0.43 (77)	-0.05 [-0.17, 0.06]	0.002	0.355
95% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in []					

Tipping Point Analysis

- Tipping Point: the difference of mean for the missing patients, at which the study conclusion would change.
- Algorithm:
 - $i = 0$
 - Imputed missing value for XIENCE $V = \bar{X}_{XIENCE} + i$
 - Imputed missing value for TAXUS $= \bar{X}_{TAXUS} - i$
 - Calculate std. and p-value based on the complete and imputed data
 - $i = i + 0.0005$. Stop iteration when $p > 0.05$.

\bar{X}_{XIENCE}

Tipping Point Analysis (SPIRIT II)

Imputed value for missing patients

	XIENCE V (n=22)	TAXUS (n=4)	Difference
Complete Case	.	.	.
Q3 _ Q1 Case	0.36	-0.005	0.365
Worst Case	1.595	-0.565	2.16
Tipping Point	1.056	-0.586	1.642

SPIRIT III RCT

- Objective: To determine the safety and effectiveness of XIENCE V for the treatment of subjects with a maximum of two *de novo* native coronary artery lesions.

SPIRIT III (RCT)

- Primary Endpoint: 240-day In-segment Late Loss (LL)
- Non-inferiority Hypotheses:

H_0 : In-segment $LL_{XIENCE V} - \text{In-segment } LL_{TAXUS} \geq \delta$

H_A : In-segment $LL_{XIENCE V} - \text{In-segment } LL_{TAXUS} < \delta$

where $\delta=0.195$.

A sample size of 338 in XIENCE V and 169 in TAXUS will have a power of 99% at one-sided alpha level of 0.025.

- Superiority Hypotheses:

H_0 : In-segment $LL_{XIENCE V} \geq \text{In-segment } LL_{TAXUS}$

H_A : In-segment $LL_{XIENCE V} < \text{In-segment } LL_{TAXUS}$

at two-sided alpha level of 0.05.

SPIRIT III (RCT)

- Co-Primary Endpoint: 270-day ischemia driven Target Vessel Failure (TVF)

- Non-inferiority Hypotheses:

$$H_0: \text{TVF}_{\text{XIENCE V}} - \text{TVF}_{\text{TAXUS}} \geq 5.5\%$$

$$H_A: \text{TVF}_{\text{XIENCE V}} - \text{TVF}_{\text{TAXUS}} < 5.5\%$$

A sample size of 660 in XIENCE V and 330 in TAXUS will have a power of 89% at one-sided alpha level of 0.05.

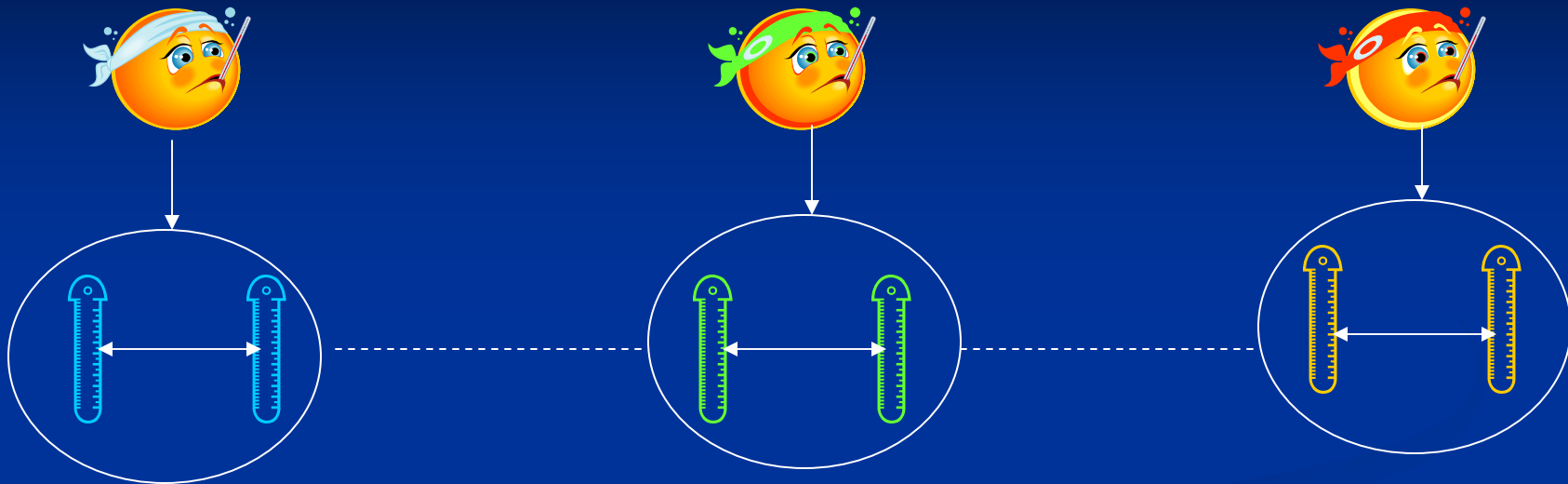
- Superiority Hypotheses:

$$H_0: \text{TVF}_{\text{XIENCE V}} \geq \text{TVF}_{\text{TAXUS}}$$

$$H_A: \text{TVF}_{\text{XIENCE V}} < \text{TVF}_{\text{TAXUS}}$$

at two-sided alpha level of 0.05

Generalized Estimating Equations



- Measurements on the same patient are usually assumed to be correlated
- Measurements on different patients are assumed to be independent
- The GEE (Generalized Estimating Equations) method can handle such correlation

Results of SPIRIT III (RCT)

Primary Endpoint: 240-day In-segment Late Loss, mm

	XIENCE V (N=376) (M=427)	TAXUS (N=188) (M=220)	Difference [95% CI]	Non- inferiority p-value ($\delta=0.195$)	Superiority p-value
Analysis Lesion Mean \pm SD (n)	0.14 \pm 0.41 (301)	0.28 \pm 0.48 (134)	-0.14 [-0.23, -0.05]	<0.0001	0.0037
GEE Least-Square Mean \pm SE (m)	0.14 \pm 0.02 (343)	0.26 \pm 0.04 (158)	-0.13 [-0.21, -0.04]		

N is the total number of subjects; M is the total number of lesions;
95% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in [].

Results of SPIRIT III (RCT)

Co-Primary Endpoint: 9-month TVF

	XIENCE V (N=669)	TAXUS (N=333)	Difference [95% CI]	Non- inferiority p-value ($\delta=5.5\%$)	Superiority p-value
Complete Case	7.61% (50/657)	9.69% (31/320)	-2.08% [-5.90%, 1.75%]	<0.0001	0.27
Worst Case	9.27% (62/669)	9.31% (31/333)	-0.04% [-3.86%, 3.78%]	0.001	0.98
95% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in [].					

Missing Angiographic Data in SPIRIT III (RCT)

	XIENCE V (N=376)	TAXUS (N=188)
Completers	80.1% (301/376)	71.7% (134/187)
One subject did not provide written informed consent and was inadvertently randomized into TAXUS RCT. Data from this subject is excluded from all data analysis.		

Sensitivity Analysis of In-segment Late Loss (SPIRIT III RCT)

	XIENCE V (N=376)	TAXUS (N=188)	Difference [95% CI]	Non- inferiority p-value ($\delta=0.195$)	Superiority p-value
Complete Case	0.14 \pm 0.41 (301)	0.28 \pm 0.48 (134)	-0.14 [-0.23, -0.05]	<0.0001	0.0037
Multiple Imputation	0.15 \pm 0.44 (371)	0.29 \pm 0.54 (185)	-0.14 [-0.23, -0.06]	<0.0001	0.0001
Q3 _ Q1 Case	0.16 \pm 0.41 (376)	0.20 \pm 0.48 (187)	-0.04 [-0.12, 0.04]	<0.0001	0.33
Worst Case	0.58 \pm 0.96 (376)	0.07 \pm 0.53 (187)	0.52 [0.37, 0.66]	1	1

Numbers are shown in (mean \pm standard deviation).

95% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in [].

Tipping Point Analysis (SPIRIT III RCT)

Imputed value for missing patients

	XIENCE V (n=75)	TAXUS (n=53)	Difference
Complete Case	.	.	.
Q3 _ Q1 Case	0.25	0	0.25
Worst Case	2.36	-0.47	2.83
Tipping Point for Superiority	0.29	0.13	0.16
Tipping Point for Non-inferiority	0.67	-0.25	0.92

9-month TVF in SPIRIT III (RCT) by Blinding Status

	XIENCE V	TAXUS	Difference [95% CI]
Blinded Evaluator	7.13% (37/519)	8.78% (23/262)	-1.65% [-5.73%, 2.43%]
Unblinded Evaluator	7.25% (10/138)	10.17% (6/59)	-2.92% [-11.77%, 5.92%]

SPIRIT III (XIENCE V 4.0 mm)

- Primary Endpoint: 240-day in-segment LL
- H_0 : In-segment LL_{XIENCE V 4.0} – In-segment LL_{TAXUS} $\geq \delta$
 H_A : In-segment LL_{XIENCE V 4.0} – In-segment LL_{TAXUS} $< \delta$
where $\delta=0.195$.

A sample size of 72 will have a power of 90% at one-sided alpha level of 0.05.

- Observational study, comparability of treatment groups may be of concern.

SPIRIT III (XIENCE V 4.0 mm)

- After 69 subjects were enrolled, the sponsor decided to submit data analysis based on these 69 subjects.
- The analysis was planned to be performed after these 69 subjects had completed their scheduled follow-up and after unblinding of the RCT.
- The primary hypothesis was tested at one-sided nominal significance level of 0.0377.

Results of SPIRIT III (4.0 mm)

Primary Endpoint: 240-day In-segment Late Loss, mm

	XIENCE V 4.0 mm (N=69)	TAXUS (N=188)	Difference [96.23% CI]
Analysis Lesion Mean \pm SD (n)	0.17 \pm 0.38 (49)	0.28 \pm 0.48 (134)	-0.11 [-0.27, 0.05]
Analysis was performed in the ITT population. 96.23% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in [].			

- The above analysis was based on the completed case, which excluded 20 subjects in 4.0 mm arm and 53 subjects in angiographic subset of TAXUS RCT arm.

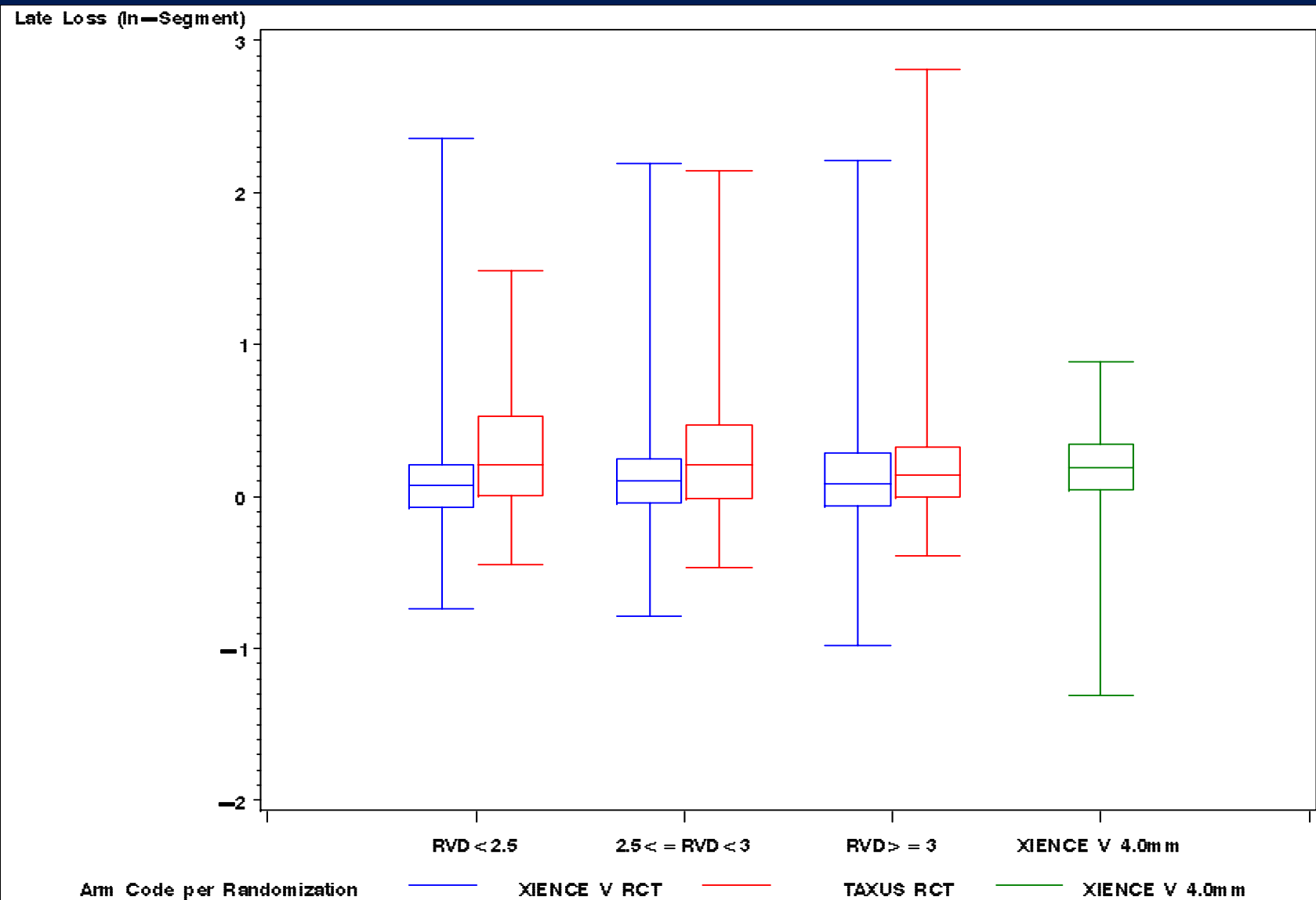
Results of SPIRIT III (4.0 mm)

- An interpretation of the above result needs to take into account the following:
 - The primary analysis was not adjusted for covariates in this non-randomized study;
 - TAXUS does not have approved 4.0mm drug eluting stent;
 - TAXUS is not indicated for the treatment of RVD > 3.75 mm, while XIENCE V 4.0 mm is intended for the treatment of RVD between 3.75 mm and 4.25 mm.

Impact of RVD on 240-day in-segment late loss

SPIRIT III RCT			
	RVD < 2.5 mm	2.5 mm ≤ RVD < 3 mm	RVD ≥ 3 mm
XIENCE V Mean ± SD (n)	0.16 ± 0.43 (99)	0.12 ± 0.39 (117)	0.15 ± 0.40 (85)
TAXUS Mean ± SD (n)	0.30 ± 0.40 (45)	0.27 ± 0.50 (61)	0.26 ± 0.56 (28)
SPIRIT III XIENCE V 4.0 mm			
XIENCE V 4.0mm Mean ± SD (n)	0.17 ± 0.38 (49)		

Impact of RVD on 240-day in-segment late loss



Sensitivity Analysis (by FDA) for In-segment Late Loss (SPIRIT III XIENCE V 4.0 mm)

	XIENCE V 4.0 mm (N=69)	TAXUS (N=188)	Difference [96.23% CI]
Complete Case	0.17 ± 0.38 (49)	0.28 ± 0.48 (134)	-0.11 [-0.27, 0.05]
Q3 _ Q1 Case	0.22 ± 0.38 (69)	0.20 ± 0.48 (187)	0.02 [-0.10, 0.14]
Worst Case	0.38 ± 0.46 (69)	0.07 ± 0.53 (187)	0.31 [0.16, 0.46]
<p>Numbers are shown in (mean ± standard deviation).</p> <p>96.23% Confidence Interval of difference in mean XIENCE V – TAXUS is displayed in [].</p>			

Tipping Point Analysis (SPIRIT III 4.0mm)

Imputed value for missing patients

	XIENCE V 4.0mm (n=20)	TAXUS (n=53)	Difference
Complete Case	.	.	.
Q3 _ Q1 Case	0.34	0	0.34
Worst Case	0.89	-0.47	1.36
Tipping Point	0.53	-0.08	0.61

Summary of Statistical Inference

- In SPIRIT First, the superiority of XIENCE V to bare metal stent appeared to be established in terms of 180-day in-stent late loss;
- In SPIRIT II, the superiority of XIENCE V to TAXUS appeared to be established in terms of 180-day in-stent late loss;
- In SPIRIT III RCT, the superiority of XIENCE V to TAXUS appeared to be established in terms of 240-day in-segment late loss, and the non-inferiority of XIENCE V to TAXUS appeared to be established in terms of 9-month ischemia driven TVF;
- In SPIRIT III 4.0 mm arm, the naïve comparison of XIENCE V 4.0 mm with TAXUS should be interpreted with caution because it is an observational study.

Abbott Xience

Post-Approval Considerations

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Outline

- General Principles
- Rationale/Postmarket Questions
- Proposed Post-Approval Study (PAS) Protocol
- Assessment of PAS Protocol

Disclaimer

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Objectives for Post-Approval Studies

- Gather postmarket information
 - Longer-term performance
 - Community performance
 - Effectiveness of training programs
 - Sub-group performance
 - Rare adverse events and real world experience
- Account for Panel recommendations

General Principles for Post-Approval Studies

Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Views on Post-Approval Studies for Drug Eluting Stents (DES)

- Study if ST rate plateaus or continues to increase over time
- Study incidence rate of cardiac death and MI
- Gather information on APT use
- Study routine clinical use of DES

Issues to be Considered in Xience PAS

- Stent thrombosis
 - Confirm incidence is $<1\%$ for each 12 month period after 1 year
- 5-year patient informed consent
- Evaluate higher risk subgroups
 - Patient characteristics
 - Lesion characteristics

Overview of Abbott's Approach

Objectives:

- Evaluate clinical outcomes in a cohort of real world patients receiving the XIENCE V Everolimus Eluting Coronary Stent System (EECSS) during commercial use by various physicians with a range of coronary stenting experience
- Evaluate patient compliance with adjunctive antiplatelet therapy and major bleeding complications
- Determine clinical device and procedural success during commercial use
- Evaluate patient health status (symptoms, physical function, and quality of life) by the Seattle Angina Questionnaire

Overview of Post-Approval Study

Study Design	Non-randomized, prospective, multi-center, single-arm registry
Population	Consecutive patient who receive Xience stent and consent to participate
Sample Size	5000 patients
Follow-up	Up to 5 years
Primary Endpoint	Stent thrombosis at 1 year
Secondary Endpoints	Include: ST up to 5 years, composite death and revascularization; composite cardiac death and MI attributed to target vessel and TLR
Antiplatelet regimen	Indefinite aspirin, clopidogrel to 6 months (12 months if no bleeding risk)

Proposed Statistical Analysis Plan

- Primary analysis: Stent thrombosis rates summarized at 24 hours, 30, 180 days and 1, 2, 3, 4 and 5 years.
- Secondary Analysis:
 - Secondary endpoints summarized
 - Descriptive analyses for patient demographics, clinical device/procedural success, antiplatelet therapy compliance, bleeding complications, medical histories, and co-morbidities.
 - Health status assessed by including predetermined categories from Seattle Angina Questionnaire.
 - Correlation analyses conducted for several parameters including, adjunctive dual antiplatelet therapy use, bleeding complications, and late stent thrombosis incidence.

Assessment of PAS Protocol

- FDA suggests primary endpoint be the evaluation of stent thrombosis rates through to 5 years
- Also suggest sponsor study a co-primary endpoint of death and MI at 1 year