XIENCE™ V Everolimus Eluting Coronary Stent System (EECSS)

PMA # P070015

Gary C. Johnson
Vice President, Regulatory Affairs, Clinical Research and Quality Assurance, Abbott Vascular
Agenda

• Introduction
  - Gary Johnson, Vice President, Abbott Vascular

• XIENCE V Technology
  - Murthy Simhambhatla, PhD, Vice President, Abbott Vascular

• XIENCE V Pre-clinical Program Overview
  - Leslie Coleman, DVM, Director, Abbott Vascular

• XIENCE V Clinical Program Overview and Results
  - Gregg Stone, MD, Professor of Medicine, Columbia University

• XIENCE V Safety Overview
  - Mitchell Krucoff, MD, Professor of Medicine, Duke University Medical Center

• Conclusion
  - Krishna Sudhir, MD, PhD, Director, Abbott Vascular
Expert Consultants

• Stuart Pocock, PhD
  - London School of Hygiene and Tropical Medicine, Professor of Medical Statistics

• Alexandra Lansky, MD
  - Cardiovascular Research Foundation, Angiographic Core Lab

• Peter Fitzgerald, MD, PhD
  - Stanford University, IVUS Core Lab

• Renu Virmani, MD
  - CVPath Institute, Inc., Medical Director

• Ronald Van Valen
  - Novartis, Drug Regulatory Affairs, Immunology and Infectious Diseases, Director
Purpose

- Review XIENCE V Design Goals
- Review XIENCE V comprehensive Pre-Clinical program
- Demonstrate that XIENCE V clinical data in its totality, establishes a reasonable assurance of safety and effectiveness, based on valid scientific evidence
- Review the XIENCE V Post-Approval clinical strategy that augments the Pre-Approval data and is effectively powered to evaluate low frequency events
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 ≤ 28 mm) with reference vessel diameters of 2.5 mm to 4.25 mm.
### XIENCE V

#### System Sizes

- **Diameters:** 2.5, 2.75, 3.0, 3.5, 4.0 mm
- **Lengths:** 8 – 28 mm
- **Platforms:** RX and OTW

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>8 12 15 18 23 28</td>
</tr>
<tr>
<td>2.75</td>
<td>8 12 15 18 23 28</td>
</tr>
<tr>
<td>3.0</td>
<td>8 12 15 18 23 28</td>
</tr>
<tr>
<td>3.5</td>
<td>8 12 15 18 23 28</td>
</tr>
<tr>
<td>4.0</td>
<td>8 12 15 18 23 28</td>
</tr>
</tbody>
</table>

**Drug dose density:** 100 µg/cm² for all sizes
XIENCE V
Major Design Components

• Stent and Delivery System:
  - MULTI-LINK VISION® & MULTI-LINK MINI VISION®
    Coronary Stent Systems (P020047 & P020047/S003)

• Drug Matrix:
  - Fluorinated Copolymer: PVDF-HFP (approved for use in other vascular applications)

• Drug:
  - Everolimus (Novartis Pharmaceutical Corporation)
  - Novartis has received 2 approvable letters from FDA
  - Novartis has granted FDA right to reference IND/NDA
**XIENCE V Marketing History**

- XIENCE V has received regulatory approval and is marketed in 64 countries outside the US
Abbott Vascular worked collaboratively with FDA in 2004 and 2005 to develop the SPIRIT III pivotal clinical trial design.

At the time of initiation of SPIRIT III (May 2005), FDA agreed the pivotal clinical trial and supporting clinical data in the XIENCE V SPIRIT clinical trial program would provide adequate assurance of safety and effectiveness for the XIENCE V Everolimus Eluting Coronary Stent System.
FDA has reviewed the everolimus safety pharmacology, toxicology and ADME studies and has identified no concerns.

FDA considers everolimus to be a well characterized and studied drug therefore, not a New Molecular Entity (NME).

Since everolimus is not an NME, the requirement for 2,000 treated patients in clinical studies with a NME did not apply to the XIENCE V Clinical Program.
# Integrated Pre-Approval and Post-Approval Clinical Program (N > 16,000)

## Pre-approval Clinical Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Comparator</th>
<th>N</th>
<th>Location</th>
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<tbody>
<tr>
<td>SPIRIT First</td>
<td>RCT 1:1 XIENCE V vs. VISION</td>
<td>(n = 60) OUS</td>
<td></td>
<td></td>
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<td>SPIRIT II</td>
<td>RCT 3:1 XIENCE V vs. TAXUS®</td>
<td>(n = 300) OUS</td>
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<td>SPIRIT III</td>
<td>RCT 2:1 XIENCE V vs. TAXUS</td>
<td>(n = 1,002) US</td>
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<td></td>
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<tr>
<td>SPIRIT III 4.0</td>
<td>Registry 4.0 mm</td>
<td>(n = 80) US</td>
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## Ongoing and Planned Clinical Data

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<td>Registry</td>
<td>(n = 88) Japan</td>
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<td>SPIRIT IV</td>
<td>RCT XIENCE V vs. TAXUS 2:1</td>
<td>Continued Access</td>
<td>(n = 3,690) US</td>
<td></td>
</tr>
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<td>SPIRIT V</td>
<td>Registry</td>
<td>(n = 2,700), RCT Diabetics 2:1</td>
<td>(n = 300) OUS</td>
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<td>Registry</td>
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<td>Post-approval Registry – real world</td>
<td>(n ~ 5,000) US</td>
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<td></td>
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<td>XIENCE V USA</td>
<td>Post-approval Registry – real world</td>
<td>(n ~ 1,000) OUS</td>
<td></td>
<td></td>
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<td>XIENCE India</td>
<td>Post-approval Registry – real world</td>
<td>(n ~ 1,000) OUS</td>
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Integrated Pre-Approval and Post-Approval Clinical Program

• Pre-Approval Clinical Studies:
  - All Clinical trials met their pre-specified Primary and Major Secondary Endpoints
  - Showed Non-inferiority and Superiority in LL over BMS
  - Showed Non-inferiority and Superiority in LL over approved DES
  - Showed Non-inferiority in TVF compared to the TAXUS DES
  - Long term follow-up to 5 years

• Ongoing and Planned Clinical Studies:
  - Include real world patients
  - Powered to effectively evaluate low frequency events, 0.5%
  - Designed to potentially support label expansion
  - Long term follow-up to 5 years
SPIRIT II & SPIRIT III
2 Year Analysis

• Abbott Vascular has considered FDA panel comments in December 2006 and has also performed a safety subset analysis of all available 2 year data from SPIRIT II and SPIRIT III

• The results are consistent with the 1 year data from SPIRIT II and SPIRIT III as well as the 3 year data from SPIRIT FIRST
XIENCE V Technology

Murthy Simhambhatla, Ph.D.
Vice President and General Manager, DES
Abbott Vascular
XIENCE V Design Goal
Develop 2nd Generation DES

• Build on proven Multi-Link VISION and MINI VISION Bare Metal Stent (BMS) and Stent Delivery Systems
  - Flexible stent with thin struts
  - Proven deliverability

• Develop thin, biocompatible drug coating
  - Effective with low drug loading
  - Stable polymer
  - Uniform, conformal coating
  - Controlled and complete release of drug
  - Hemocompatibility and vascular compatibility
XIENCE V
Scientific Design & Integration

MULTI-LINK VISION Stent

MULTI-LINK VISION Stent Delivery System

Deliverability
Efficacy
Safety

Everolimus

Fluorinated Copolymer
XIENCE V
Built On The Proven VISION Stent Platform

Cobalt Chromium Technology
- Allows for thinner struts without compromise to radiopacity or radial strength

Thin Strut Stent Design
- Outstanding flexibility and conformability
- .0032” (81 μm) strut thickness

Low System Profile
- Excellent deliverability

VISION Stent Delivery System
- Soft, highly flexible Pebax balloon material
- Short tapers

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1. As compared to stainless steel. Source: ASTM International.
2. Tests performed by and data on file at Abbott Vascular.
XIENCE V
Endothelialization and strut thickness

Endothelial coverage may be impaired for thicker stent struts

XIENCE V
Progression Towards Thinner Struts

<table>
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<tr>
<th>Device</th>
<th>Strut Thickness</th>
<th>Coating Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYPHER</td>
<td>140 µm</td>
<td>12.6 µm</td>
</tr>
<tr>
<td>TAXUS Express</td>
<td>132 µm</td>
<td>19.6 µm</td>
</tr>
<tr>
<td>ENDEAVOR™</td>
<td>91 µm</td>
<td>4.8 µm</td>
</tr>
<tr>
<td>XIENCE V</td>
<td>81 µm</td>
<td>7.8 µm</td>
</tr>
</tbody>
</table>

Abluminal coating thickness represented

Data on file at Abbott Vascular
XIENCE V Deliverability

Maintains Deliverability of Proven VISION BMS

Data on file at Abbott Vascular
Everolimus

Everolimus
IC$_{50}$: 0.9-3.6 nM

Sirolimus
IC$_{50}$: 0.4-3.5 nM

IC$_{50}$ values for Bovine SMCs
XIENCE V
Clinical Dose Selection

• Studied wide range of drug doses in porcine coronary arteries, from 100 µg/cm² to 800 µg/cm²

• Observed sufficient drug effect at 100 µg/cm² with no evidence of toxicity or medial necrosis at 800 µg/cm²

• Lowest effective dose of 100 µg/cm² selected for clinical development
XIENCE V
Reduced Drug Dose

41% Reduced Drug Dose Relative to CYPHER

Achieved effectiveness with reduced drug loading
Consistent and well controlled drug elution *in vivo* with complete elution by 120 days

Data on file at Abbott Vascular
XIENCE V
Coating Design

- Primer and Matrix system enables design optimization for excellent coating integrity and drug release control
- Selection of fluorinated copolymer minimizes unwanted adhesion to delivery balloon
Drug Matrix
Fluorinated Copolymer

- Ultra-pure copolymer composed of VDF and HFP monomers
- Used in cardiovascular, neurological and ophthalmic sutures
- VDF-HFP ratio allows for optimization of coating elasticity and toughness
- Durable C-C backbone and covalent C-F bonds provide outstanding degree of stability and biocompatibility
- Stable molecular weight and mass in vivo
- Excellent hemocompatibility

VDF = vinylidene fluoride
HFP = hexafluoropropylene
**XIENCE V Coating Integrity**

- Coating designed to minimize webbing, bridging, and strut-strut contact in crimped state
- Coating integrity maintained after simulated use, stent expansion and fatigue testing

Photos taken by and on file at Abbott Vascular
XIENCE V  Hemocompatibility  Unheparinized ex vivo Shunt Study

Tested in accordance to ISO 10993-4

Avg. Thrombus Weight (g)

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>VISION BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg. Thrombus Weight (g)</td>
<td>0.00</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Study performed by Dr. Stuart K. Williams, Department of Biomedical Engineering, University of Arizona
XIENCE V
Polymer Compatibility (Porcine Model)

VISION BMS

180 Day
360 Day
720 Day

XIENCE V Fluorinated Copolymer

180 Day
360 Day
720 Day

Polymer response equivalent to VISION BMS

Photos taken by and on file at Abbott Vascular
XIENCE V
Design Summary

- Built on proven VISION Stent and Stent Delivery System
  - ✓ Flexible stent with thin struts
  - ✓ Proven deliverability

- Developed thin, biocompatible drug coating
  - ✓ Effective with low drug loading
  - ✓ Stable polymer
  - ✓ Uniform, conformal coating
  - ✓ Controlled and complete release of drug
  - ✓ Hemocompatibility and vascular compatibility
Pre-Clinical Program Overview

Leslie Coleman, DVM, MS, DACLAM
Director, Preclinical Research
Abbott Vascular
XIENCE V
Pre-Clinical Program Overview

- Biocompatibility
- Pharmacokinetics
- Comprehensive safety assessment
- Endothelial coverage & function
## XIENCE V Biocompatibility Evaluation

<table>
<thead>
<tr>
<th>TEST</th>
<th>XIENCE V</th>
<th>2.6X XIENCE V</th>
<th>Polymer Only</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxicity (<em>in vitro</em>, MEM elution)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Pass</td>
</tr>
<tr>
<td>Sensitization (Guinea Pig)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Pass</td>
</tr>
<tr>
<td>Intracutaneous Reactivity (Rabbit)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Pass</td>
</tr>
<tr>
<td>Systemic Toxicity, Acute (Mouse)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Pass</td>
</tr>
<tr>
<td>Pyrogenicity/BET (LAL)</td>
<td>✓</td>
<td>✓</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Pyrogenicity (Rabbit)</td>
<td>✓</td>
<td>✓</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Hemolysis (<em>in vitro</em>)</td>
<td>✓</td>
<td>✓</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Coagulation (PT, PTT)</td>
<td>✓</td>
<td>✓</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Subchronic Toxicity: 90 day (Rabbit)</td>
<td>NA</td>
<td>✓</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Implantation: 7 day (Rabbit)</td>
<td>NA</td>
<td>NA</td>
<td>✓</td>
<td>Pass</td>
</tr>
<tr>
<td>Genotoxicity (<em>in vitro</em>)</td>
<td>NA</td>
<td>✓</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Teratology (SD Rat)</td>
<td>✓</td>
<td>NA</td>
<td>NA</td>
<td>Pass</td>
</tr>
<tr>
<td>Carcinogenicity (CB61F1-Tg rasH2 Mouse)</td>
<td>✓</td>
<td>NA</td>
<td>NA</td>
<td>Pass</td>
</tr>
</tbody>
</table>
XIENCE V
Pre-Clinical Pharmacokinetics

Porcine model, 6 stents / time point

- **Consistent controlled complete drug release**
- **Effective Arterial Delivery:** Controlled release of everolimus to target tissue
XIENCE V  Clinical Pharmacokinetics

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Oral Dose* (Novartis)</th>
<th>SPIRIT III RCT &amp; 4.0 arm Registry (N=17)</th>
<th>SPIRIT III (Japan) (N=17)</th>
<th>SPIRIT II (OUS) (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage Range</td>
<td>0.75 &amp; 1.5 mg bid</td>
<td>53 – 181 µg</td>
<td>88 – 264 µg</td>
<td>53 – 588 µg</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; Range (ng/mL)</td>
<td>11.1 ± 4.6 &amp; 20.3 ± 8.0</td>
<td>0.17 - 2.40</td>
<td>0.29 - 2.11</td>
<td>0.14 - 2.79</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-last&lt;/sub&gt; Range (ng.hr/mL)</td>
<td>75 ± 31 &amp; 131 ± 59</td>
<td>2.345 - 48.75</td>
<td>2.218 - 54.49</td>
<td>0.453 - 164.1</td>
</tr>
</tbody>
</table>

Results from all PK sub-studies were consistent and showed limited systemic exposure up to a total dose of 588 µg

*Therapeutic window following oral delivery 3-8 ng/mL

Systemic exposure to everolimus is below the minimum therapeutic blood level of 3 ng/mL
### Porcine Coronary Artery Model
- 28, 90, 180 days
- 1, 2 years

### Rabbit Iliac Artery Model
- 28, 90 days

#### XIENCE V Comprehensive Safety Assessment

- 35 Animal Studies; 2 Species; 28 Days to 2 Years

<table>
<thead>
<tr>
<th></th>
<th>28 Day</th>
<th>90 Day</th>
<th>180 Day</th>
<th>1 Year</th>
<th>2 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Porcine Coronary Artery</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rabbit Iliac Artery</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Overlapping Safety</td>
<td></td>
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<tr>
<td>Porcine Coronary Artery</td>
<td>✓</td>
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<td>✓</td>
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<td>Rabbit Iliac Artery</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum Dose (8X) Safety</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Porcine Coronary Artery</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Polymer (1-3X) Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Porcine Coronary Artery</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</table>
Goal of DES Safety

- Effective drug delivery with rapid vessel healing
  - Smooth muscle cell rich neointima
  - Minimal persistent fibrin
  - Minimal long term inflammation
  - Rapidly endothelialized lumen
XIENCE V Porcine Safety Study
28 Days to 2 Years

Minimal long term inflammation consistent with vessel healing

Inflammation score
0-1= background

Inflammation score
4
3
2
1
0
28 Days 90 Days 180 Days 1 Year 2 Years
Resolution of fibrin consistent with vessel healing
XIENCE V Endothelialization

28 Day Porcine Coronary Artery

Luminal endothelialization complete by 28 days
XIENCE V
Safety Response

**Short term response**
28, 90 days
Active Phase (drug elution)

- Fully endothelialized
- Neointimal coverage of struts
  - Peri-strut fibrin consistent with drug elution
  - Inflammation comparable to VISION BMS
  - No to minimal mineralization
  - No medial necrosis

**Long term response**
≥180 days
Post drug elution

- Fully endothelialized
- Quiescent healed vessel wall
  - Minimal to no peri-strut fibrin
  - Minimal inflammation comparable to VISION BMS
  - No to minimal mineralization
  - No medial necrosis

Safety consistent with vessel healing
XIENCE V Safety

- XIENCE V safety has been demonstrated in 2 animal models with data out to 2 years

- Goal of DES safety program has been met
  - ✓ Smooth muscle cell rich neointima
  - ✓ Minimal persistent fibrin
  - ✓ Minimal long term inflammation
  - ✓ Rapidly endothelialized lumen
Comprehensive Endothelial Cell Coverage and Function Evaluation

- Qualitative and Quantitative Scanning Electron Microscopy evaluation of endothelial cell coverage
- Confocal microscopy evaluation of specific endothelial markers
- Molecular quantification of specific endothelial markers

Comparison of Endothelialization following Implantation of CYPHER, TAXUS, ENDEAVOR™ and XIENCE V Stents in Rabbit Iliac Arteries

Qualitative Assessment of Endothelial Cell Coverage: 14-day Rabbit Iliac
Quantitative Assessment of Luminal Endothelialization by SEM

Error bar = ± 1 SE

14 Days Rabbit Iliac
Endothelial Cell Integrity and Functionality Assessed

- Platelet endothelial adhesion molecule (PECAM-1)
  - A membrane glycoprotein that is constitutively expressed by endothelial cells at cell borders, platelets and other cells; inhibits aggregation of platelets

- Vascular endothelial growth factor (VEGF)
  - Endothelial cell specific mitogen, and regulator of vascular permeability; upregulated in absence of confluent endothelial growth and down regulated with complete endothelialization
PECAM-1 Expression: XIENCE V Consistent with Endothelialization

14 Days Rabbit Iliac

Error bar = ± 1 SE
VEGF Production: VISION and XIENCE V Levels Consistent with Endothelialization

Protein Levels (ELISA)

Gene Expression (RT-PCR)

14 days Rabbit Iliac

Error bar = ± 1 SE
XIENCE V
Endothelial Cell Coverage & Function

- XIENCE V demonstrates rapid re-endothelialization compared to other DES
- XIENCE V demonstrates enhanced endothelial cell function compared to other DES

Rapid endothelial cell coverage and function is consistent with vessel healing
SPIRIT Clinical Program

Gregg W. Stone, MD
Professor of Medicine, Columbia University Medical Center
Chairman, The Cardiovascular Research Foundation
Disclosure Slide

• Gregg W. Stone, MD
• Research support from Abbott Vascular and Boston Scientific
## Integrated Pre-Approval and Post-Approval Clinical Program (N > 16,000)

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XIENCE V vs. VISION
DES vs. BMS

SPIRIT FIRST
Randomized Controlled Trial
SPIRIT FIRST: Study Design (DES vs. BMS)

- Prospective, single blind, randomized trial in 60 pts
- Angiographic and IVUS follow-up at 180 days and one year
- Clinical follow-up up to 5 yrs
- Primary endpoint: Angiographic in-stent late loss (LL) at 180 days
- Major secondary endpoint: IVUS volume obstruction (% VO) at 180 days
- Both endpoints powered for superiority
- PI: Patrick W. Serruys, MD
SPIRIT FIRST: 6 Month Results
In-Stent LL and % VO

DES vs. BMS

Primary Endpoint
In-stent Late Loss

0.85 ± 0.36

-0.76 [-0.93, -0.59]
P < 0.0001

88% Reduction

XIENCE V
N = 23

VISION BMS
N = 27

Major Secondary Endpoint
IVUS % Volume Obstruction (%VO)

28.1 ± 14.0

-20.2 [-27.5, -12.8]
P < 0.0001

72% Reduction

XIENCE V
N = 21

VISION BMS
N = 24
SPIRIT FIRST: 3 Year Results

Event Rates

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Cardiac death</th>
<th>MI</th>
<th>TLR</th>
<th>MACE</th>
<th>TVR remote</th>
<th>TVF</th>
<th>Stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES</td>
<td>7.7</td>
<td>0.0</td>
<td>25.0</td>
<td>25.0</td>
<td>0.0</td>
<td>32.1</td>
<td>0.0</td>
</tr>
<tr>
<td>BMS</td>
<td>0.0</td>
<td>2/26</td>
<td>7/28</td>
<td>7/28</td>
<td>4/28</td>
<td>4/26</td>
<td>0.0</td>
</tr>
</tbody>
</table>

MACE = Cardiac death, MI, or ischemic TLR
TVF = Cardiac death, MI, or ischemic TVR

All p-values = NS
Conclusions
SPIRIT FIRST

The SPIRIT FIRST Trial met both its pre-specified primary and major secondary endpoints, demonstrating superiority of the XIENCE V stent compared to the bare metal ML VISION stent in reducing late loss and % volume obstruction.
XIENCE V vs. TAXUS
DES vs. DES

SPIRIT II
Randomized Controlled Trial
SPIRIT II: Study Design (DES vs. DES)

- Prospective, single blind, randomized trial in 300 pts
- Angiographic and IVUS follow-up: 180 days (all pts), and 2 years (152 pts)
- Clinical follow-up up to 5 years
- Primary endpoint: Angiographic in-stent late loss at 180 days (powered for sequential non-inferiority and superiority)
- Powered secondary endpoint: Angiographic in-segment late loss at 180 days (powered for non-inferiority)
- PI: Patrick W. Serruys, MD
SPIRIT II: Angiographic Patient Flow at 6 Months

Randomized (N=300)

XIENCE V (N = 223)  

6 month angio F/U (N=275; 91.7%)  

XIENCE V (N = 202)  

TAXUS (N = 77)  

TAXUS (N = 73)
SPIRIT II: 6 Months Results
In-Stent and In-segment LL

**Primary Endpoint**
In-stent Late Loss

- **XIENCE V**
  - 201
  - 0.11 ± 0.27
  - 69% Reduction
- **TAXUS**
  - 73
  - 0.36 ± 0.39

**Secondary Endpoint**
In-segment Late Loss

- **XIENCE V**
  - 237
  - 0.07 ± 0.33
  - 53% Reduction
- **TAXUS**
  - 86
  - 0.15 ± 0.38

**Des vs. DES**

- **Diff [95% CI]**
  - 0.24 [-0.34, -0.15]
  - **P<NI <0.0001**
  - **P<Sup <0.0001**

- **In-Stent Late Loss**
  - 0.36 ± 0.04
  - 69% Reduction

- **In-segment Late Loss**
  - 0.15 ± 0.08
  - 53% Reduction
SPIRIT II: 6 Months Results
IVUS % Volume Obstruction

DES vs. DES
IVUS Percent
% Volume Obstruction

Diff [95% CI]
-4.9 [-7.3, -2.4]
66% Reduction

2.5% ±4.7
99
XIENCE V

7.4% ±7.1
40
TAXUS
SPIRIT II: Clinical Follow-up
Patient Flow at One Year

Randomized (N=300)

XIENCE V
N=223

12 month follow-up (N=298; 99.3%)

XIENCE V
N=222

TAXUS
N=77

TAXUS
N=76
SPIRIT II: One Year Results
Event Rates

**DES vs. DES**

<table>
<thead>
<tr>
<th>Event</th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis per protocol</td>
<td>1/220 (0.5%)</td>
<td>1/76 (1.3%)</td>
</tr>
<tr>
<td>Stent thrombosis per ARC</td>
<td>0/0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0/0</td>
<td>0.0%</td>
</tr>
<tr>
<td>MI</td>
<td>2/220 (0.9%)</td>
<td>3/76 (1.3%)</td>
</tr>
<tr>
<td>TLR</td>
<td>4/220 (1.8%)</td>
<td>5/76 (2.7%)</td>
</tr>
<tr>
<td>MACE</td>
<td>6/220 (2.7%)</td>
<td>7/76 (4.5%)</td>
</tr>
<tr>
<td>TVR remote</td>
<td>4/220 (1.8%)</td>
<td>10/220 (4.5%)</td>
</tr>
<tr>
<td>TVF</td>
<td>1/76 (1.3%)</td>
<td>7/76 (4.5%)</td>
</tr>
</tbody>
</table>

**RR [95% CI]**

- **Stent thrombosis per protocol**: RR 0.28 [0.08, 1.00]
- **Cardiac death**: RR 0.30 [0.10, 0.85]
- **MI**: RR 0.49 [0.19, 1.25]

*M Confidence Intervals are for descriptive purposes only and not adjusted for multiple comparisons.

MACE = Cardiac death, MI, or ischemic TLR
TVF = Cardiac death, MI, or ischemic TVR
Conclusions

SPIRIT II

The SPIRIT II Trial met its pre-specified primary endpoint, demonstrating superiority of the XIENCE V stent compared to the TAXUS stent in reducing in-stent angiographic late loss.
XIENCE V vs. TAXUS DES vs. DES

Pivotal U.S. SPIRIT III Randomized Controlled Trial
SPIRIT III: RCT (DES vs. DES)

- Prospective, single blind, randomized trial in 1,002 pts
- Angiographic and IVUS follow-up at 8 months in pre-specified subsets
- Clinical follow-up up to 5 years in all patients
- Primary endpoint: Angiographic in-segment late loss at 8 months (powered for non-inferiority and superiority) (N = consecutive 564 patients)
- Major secondary (co-primary) endpoint: Ischemia-driven target vessel failure (TVF) at 9 months (cardiac death, MI, TVR) (powered for non-inferiority)
- Both endpoints required to be met for regulatory approval
- PI: Gregg W. Stone, MD
SPIRIT III: 4.0 mm Stent Registry

- Prospective, single blind, 4.0 mm registry (RVD 3.75 - 4.25 mm) compared to concurrent TAXUS control from Spirit III, with angiographic follow-up at 8 months and clinical follow-up up to 5 years in all patients
- Primary endpoint for regulatory approval: Angiographic in-segment late loss at 8 months (powered for non-inferiority compared to TAXUS from Spirit III)

Up to two de novo lesions, maximum of one lesion per epicardial vessel

RVD: 3.75 – 4.25 mm
LL: ≤ 28 mm
N = 80
at 65 US sites

XIENCE V
SPIRIT III: Angiographic Patient Flow at 8 Months

Randomized (N = 564)

- XIENCE V (N = 376)
- TAXUS (N = 188)

8 month angio F/U (N = 436; 77%)

- XIENCE V (N = 302)
- TAXUS (N = 134)
SPIRIT III: Primary Endpoint
In-segment LL at 8 Months

Des vs. DES

Late loss, mm

Diff [95% CI]
-0.14 [-0.23, -0.05]

P_NI < 0.0001
P_Sup = 0.004

50% Reduction

0.14 ±0.41
301*

0.28 ±0.48
134

Analysis Lesion

* 1 additional patient had angiographic follow-up but baseline angiography was not available
SPIRIT III - 4.0: Primary Endpoint
In-segment LL at 8 Months*

**Diff [95% CI]**
-0.11 [-0.24, -0.03]

**P_NI = 0.0001**

39% Reduction

Analysis Lesion

**XIENCE V**
- 0.17
- ±0.38
- 49

**TAXUS RCT**
- 0.28
- ±0.48
- 134

* Interim analysis
SPIRIT III: IVUS In-stent Measures at 8 Months

**NIH Volume**

- **XIENCE V**
  - Diff [95% CI]*: 10.1 ±11.4
  - Reduction: 52% Reduction
- **TAXUS**
  - Diff [95% CI]*: 20.9 ±31.5
  - Reduction: 20.9
- **Diff [95% CI]***:
  - XIENCE V vs. TAXUS: -10.7 [-20.9, -0.6]

**% Volume Obstruction**

- **XIENCE V**
  - Diff [95% CI]*: 6.9% ±6.4
  - Reduction: 38%
- **TAXUS**
  - Diff [95% CI]*: 11.2% ±9.9
- **Diff [95% CI]***:
  - XIENCE V vs. TAXUS: -4.3 [-7.7, -0.9]

*Confidence Intervals are for descriptive purposes only and not adjusted for multiple comparisons.*
SPIRIT III: IVUS In-stent Measures at 8 Months

**EEL volume**
post-procedure and at 240 days

- **XIENCE V post procedure**
  - 269 ±100
- **XIENCE V at 8 months**
  - 273 ±100
- **TAXUS post procedure**
  - 278 ±119
- **TAXUS at 8 months**
  - 305 ±127

- **Diff [95% CI]**
  - 4 [-5, 12]
  - 26 [17, 36]

**Late Acquired Incomplete Apposition**

- **XIENCE V**
  - 1/90
  - 1.1%

- **TAXUS**
  - 1/43
  - 2.3%

P=NS
### SPIRIT III: Clinical Follow-up

<table>
<thead>
<tr>
<th>Group</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 1,002)</td>
</tr>
</tbody>
</table>

- **9 month follow up**
  - XIENCE V (N = 669)
  - TAXUS (N = 333)
  - (N = 980; 97.8%)

- **12 month follow up**
  - XIENCE V (N = 658)
  - TAXUS (N = 322)
  - (N = 976; 97.4%)

- XIENCE V (N = 655)
  - TAXUS (N = 321)
SPIRIT III (Co-Primary Endpoint): TVF at 9 Months

**DES vs. DES**

RR [95% CI]  
0.79 [0.51, 1.20]

P<sub>NI</sub> <0.0001

- **XIENCE V**: 7.6%  
  50/657

- **TAXUS**: 9.7%  
  31/320

75
SPIRIT III: TVF at One Year

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>669</td>
<td>332</td>
</tr>
<tr>
<td>90</td>
<td>649</td>
<td>311</td>
</tr>
<tr>
<td>180</td>
<td>636</td>
<td>308</td>
</tr>
<tr>
<td>270</td>
<td>611</td>
<td>289</td>
</tr>
<tr>
<td>393</td>
<td>597</td>
<td>283</td>
</tr>
</tbody>
</table>

TVF, %

- **XIENCE V**: 8.5%
- **TAXUS**: 11.1%

HR = 0.75

[0.49, 1.14]

$P_{\text{logrank}} = 0.18$
SPIRIT III: MACE at One Year

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>669</td>
<td>332</td>
</tr>
<tr>
<td>90</td>
<td>651</td>
<td>312</td>
</tr>
<tr>
<td>180</td>
<td>642</td>
<td>309</td>
</tr>
<tr>
<td>270</td>
<td>626</td>
<td>292</td>
</tr>
<tr>
<td>393</td>
<td>613</td>
<td>286</td>
</tr>
</tbody>
</table>

MACE, %

- HR = 0.57 [0.36, 0.90]
- $P_{\text{logrank}} = 0.015$

Days

- 10.2%
- 5.9%
SPIRIT III: One Year Results
Event Rates

**Event Rates**

<table>
<thead>
<tr>
<th>Event</th>
<th>XIENCE V (N = 653)</th>
<th>TAXUS (N = 320)</th>
<th>RR [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis per protocol</td>
<td>5/647</td>
<td>7/648</td>
<td>0.60 [0.33, 1.10]</td>
</tr>
<tr>
<td>Stent thrombosis per ARC</td>
<td>5/653</td>
<td>6/317</td>
<td>0.58 [0.37, 0.90]</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2/653</td>
<td>3/320</td>
<td>0.76 [0.51, 1.13]</td>
</tr>
<tr>
<td>MI</td>
<td>18/653</td>
<td>13/320</td>
<td>10.3%</td>
</tr>
<tr>
<td>TLR</td>
<td>22/653</td>
<td>18/320</td>
<td>0.60 [0.33, 1.10]</td>
</tr>
<tr>
<td>MACE</td>
<td>39/653</td>
<td>33/320</td>
<td>6.0%</td>
</tr>
<tr>
<td>TVR remote</td>
<td>20/653</td>
<td>14/320</td>
<td>3.1%</td>
</tr>
<tr>
<td>TVF</td>
<td>55/363</td>
<td>36/320</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

**Notes**
- MACE = Cardiac death, MI, or ischemic TLR
- TVF = Cardiac death, MI, or ischemic TVR

* Confidence Intervals for TLR and MACE are for descriptive purposes only and not adjusted for multiple comparisons
Conclusions
SPIRIT III

The pivotal SPIRIT III Trial met both its pre-specified primary and major secondary (co-primary) endpoints, demonstrating superiority of the XIENCE V stent compared to the TAXUS stent in reducing angiographic in-segment late loss, and non-inferiority with regard to the 9 month endpoint of target vessel failure.
XIENCE V vs. TAXUS
DES vs. DES

SPIRIT II & III
Pooled Meta-Analysis
Rationale for the SPIRIT II & III Pooled Analysis

• At the time the SPIRIT III trial was designed, the regulatory burden that was agreed upon with FDA for approval of the XIENCE V stent was the demonstration of non-inferiority for angiographic late loss and target vessel failure compared to TAXUS, which required randomization of 1,002 patients.

• Since that time interest has shifted to examination of lower frequency safety and efficacy endpoints, such as death, MI, stent thrombosis and TLR.
  - SPIRIT III was not powered to examine the rates of these endpoints.
Rationale for the SPIRIT II & III Pooled Analysis

- Thus, at the request of FDA, to provide more power to examine infrequent events, we have combined SPIRIT II and III in a true patient level pooled meta-analysis
  - In SPIRIT II and III, patients with similar inclusion and exclusion criteria were randomized in 2 consecutive randomized trials to XIENCE V vs. TAXUS – follow-up has been completed to 1 year in both trials
Similar inclusion and exclusion criteria:
Up to two de novo lesions, maximum of one lesion per epicardial vessel
RVD: 2.5 – 3.75 mm*
LL: ≤ 28 mm

Pooled analysis of patient level data
N = 1,302 patients
N = 1,506 lesions

SPIRIT II & III Pooled Analysis

- Two prospective, single blind trials with similar inclusion and exclusion criteria in 1,302 pts with 1,506 lesions
- Independent pooled analysis by academic statisticians at the Cardiovascular Research Foundation
- Pre-specified superiority testing on all endpoints
- All analyses are exploratory and hypothesis generating

*3 patients in SPIRIT II received 4.0 mm stents
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SPIRIT II (N = 892 pts)</th>
<th>SPIRIT III (N = 410 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.9 ± 10.5</td>
<td>62.6 ± 10.1</td>
</tr>
<tr>
<td>Male</td>
<td>70.3%</td>
<td>68.2%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27.9%</td>
<td>27.1%</td>
</tr>
<tr>
<td>- treated with insulin</td>
<td>7.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74.0%</td>
<td>72.3%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>72.8%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>25.3%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>23.7%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>20.8%</td>
<td>26.5%</td>
</tr>
<tr>
<td>Dual vessel treatment</td>
<td>15.7%</td>
<td>15.9%</td>
</tr>
</tbody>
</table>
### SPIRIT II & III Meta-Analysis
### Angiographic Characteristics (N = 1,506 lesions)*

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>XIENCE V (N = 1,028 lesions)</th>
<th>TAXUS (N = 473 lesions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>41.1%</td>
<td>43.8%</td>
</tr>
<tr>
<td>LCX</td>
<td>28.0%</td>
<td>26.4%</td>
</tr>
<tr>
<td>RCA</td>
<td>30.7%</td>
<td>29.6%</td>
</tr>
<tr>
<td>LMCA</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>2.75 ± 0.47</td>
<td>2.77 ± 0.48</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.88 ± 0.43</td>
<td>0.89 ± 0.41</td>
</tr>
<tr>
<td>DS (%)</td>
<td>67.7 ± 13.6</td>
<td>67.5 ± 13.6</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>14.3 ± 5.7</td>
<td>14.5 ± 5.9</td>
</tr>
</tbody>
</table>

* Information on 5 lesions was not available
SPIRIT II & SPIRIT III Meta-Analysis
Event Rates at 30 (±7) Days

<table>
<thead>
<tr>
<th>Event</th>
<th>XIENCE V (N = 890)</th>
<th>TAXUS (N = 407)</th>
<th>RR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>0.0%</td>
<td>1.0%</td>
<td>0.34 [0.15, 0.81]</td>
<td>0.02</td>
</tr>
<tr>
<td>MI</td>
<td>1.0%</td>
<td>1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>2.9%</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>0.3%</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>1.2%</td>
<td>3.2%</td>
<td>0.39 [0.17, 0.86]</td>
<td>0.02</td>
</tr>
<tr>
<td>TVR remote</td>
<td>0.2%</td>
<td>0.7%</td>
<td>0.42 [0.20, 0.90]</td>
<td>0.03</td>
</tr>
<tr>
<td>TVF</td>
<td>3.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MACE = Cardiac death, MI, or ischemic TLR
TVF = Cardiac death, MI, or ischemic TVR
SPIRIT II & III Pooled Analysis NQMI (CKMB Rises) through 37 Days

Results for subjects with post-procedure CKMB values available
Note: Three XIENCE V subjects had NQMI within 37 days post procedure but did not have post-procedure CKMB value, therefore they are excluded from this analysis.
SPIRIT II & III Meta-Analysis
Stent Thrombosis Through One Year

Per Protocol

HR = 0.91
[0.23, 3.65]
\( P_{\text{logrank}} = 0.90 \)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>90</td>
<td>881</td>
<td>401</td>
</tr>
<tr>
<td>180</td>
<td>878</td>
<td>400</td>
</tr>
<tr>
<td>270</td>
<td>867</td>
<td>394</td>
</tr>
<tr>
<td>393</td>
<td>861</td>
<td>390</td>
</tr>
</tbody>
</table>
SPIRIT II & III Meta-Analysis
Stent Thrombosis Through One Year

ARC Definite or Probable

HR = 1.06
[0.28, 4.12]

$P_{logrank} = 0.93$

Number at Risk

<table>
<thead>
<tr>
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<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>270</td>
<td>867</td>
<td>394</td>
</tr>
<tr>
<td>393</td>
<td>861</td>
<td>390</td>
</tr>
</tbody>
</table>

Stent thrombosis, %

0.8% for both XIENCE V and TAXUS at 393 days.
SPIRIT II & III Meta-Analysis
All-Cause Death at One Year

HR = 0.71
[0.28, 1.84]

Plogrank = 0.48

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 Days</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>180 Days</td>
<td>884</td>
<td>401</td>
</tr>
<tr>
<td>270 Days</td>
<td>881</td>
<td>400</td>
</tr>
<tr>
<td>393 Days</td>
<td>871</td>
<td>394</td>
</tr>
<tr>
<td></td>
<td>865</td>
<td>389</td>
</tr>
</tbody>
</table>
SPIRIT II & III Meta-Analysis
Cardiac Death at One Year

HR = 0.57
[0.15, 2.11]
P_{\text{logrank}} = 0.39
SPIRIT II & III Meta-Analysis
MI at One Year

- **HR = 0.56**
- **[0.29, 1.09]**
- **$P_{\text{logrank}} = 0.08$**

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at Risk</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>90</td>
<td>875</td>
<td>390</td>
</tr>
<tr>
<td>180</td>
<td>871</td>
<td>389</td>
</tr>
<tr>
<td>270</td>
<td>857</td>
<td>382</td>
</tr>
<tr>
<td>393</td>
<td>848</td>
<td>378</td>
</tr>
</tbody>
</table>
SPIRIT II & III Meta-Analysis
Cardiac Death or MI at One Year

HR = 0.60
[0.33, 1.11]
$P_{\text{logrank}} = 0.10$

Cardiac death or MI, %

Days

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>90</td>
<td>875</td>
<td>390</td>
</tr>
<tr>
<td>180</td>
<td>871</td>
<td>389</td>
</tr>
<tr>
<td>270</td>
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<td>382</td>
</tr>
<tr>
<td>393</td>
<td>848</td>
<td>378</td>
</tr>
</tbody>
</table>
SPRINT II & III Meta-Analysis
TLR at One Year

HR = 0.53
[0.30, 0.92]

P-logrank = 0.02

Number at Risk

<table>
<thead>
<tr>
<th>Days</th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>90</td>
<td>879</td>
<td>397</td>
</tr>
<tr>
<td>180</td>
<td>869</td>
<td>393</td>
</tr>
<tr>
<td>270</td>
<td>851</td>
<td>376</td>
</tr>
<tr>
<td>393</td>
<td>840</td>
<td>369</td>
</tr>
</tbody>
</table>
SPIRIT II & III Meta-Analysis
Key Angiographic Endpoints

In-stent late loss

<table>
<thead>
<tr>
<th>Diff [95% CI]</th>
<th>58% Reduction</th>
<th>P &lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.19 [-0.25, -0.12]</td>
<td>0.14 ±0.36</td>
<td>579</td>
</tr>
<tr>
<td>0.33 ±0.48</td>
<td>244</td>
<td>TAXUS</td>
</tr>
</tbody>
</table>

In-segment late loss

<table>
<thead>
<tr>
<th>Diff [95% CI]</th>
<th>50% Reduction</th>
<th>P = 0.0004</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.11 [-0.18, -0.05]</td>
<td>0.11 ±0.37</td>
<td>580</td>
</tr>
<tr>
<td>0.22 ±0.44</td>
<td>244</td>
<td>TAXUS</td>
</tr>
</tbody>
</table>

Angiographic follow-up was at 6 months in SPIRIT II and 8 months in SPIRIT III
SPIRIT II & III Meta-Analysis
Key Angiographic Endpoints

In-stent binary restenosis

1.9% 11/580

XIENCE V

RR [95% CI]: 0.39 [0.17, 0.86]
P = 0.021

61% Reduction

4.9% 12/244

TAXUS

In-segment binary restenosis

4.1% 24/581

XIENCE V

RR [95% CI]: 0.53 [0.30, 0.95]
P = 0.039
47% Reduction

7.8% 19/244

TAXUS

Angiographic follow-up was at 6 months in SPIRIT II and 8 months in SPIRIT III
SPIRIT II & III Meta-Analysis
MACE at One Year

HR = 0.51
[0.33, 0.78]

$P_{\text{logrank}} = 0.002$

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>90</td>
<td>870</td>
<td>386</td>
</tr>
<tr>
<td>180</td>
<td>859</td>
<td>382</td>
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<tr>
<td>270</td>
<td>840</td>
<td>364</td>
</tr>
<tr>
<td>393</td>
<td>826</td>
<td>356</td>
</tr>
</tbody>
</table>
SPIRIT II & III Meta-Analysis
TVR Remote at One Year

HR = 0.72
[0.38, 1.37]

\[ P_{\text{logrank}} = 0.32 \]

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>892</td>
<td>881</td>
</tr>
<tr>
<td></td>
<td>409</td>
<td>397</td>
</tr>
</tbody>
</table>
SPIRIT II & III Meta-Analysis
TVF at One Year

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>892</td>
<td>409</td>
</tr>
<tr>
<td>90</td>
<td>867</td>
<td>385</td>
</tr>
<tr>
<td>180</td>
<td>851</td>
<td>381</td>
</tr>
<tr>
<td>270</td>
<td>821</td>
<td>361</td>
</tr>
<tr>
<td>393</td>
<td>806</td>
<td>353</td>
</tr>
</tbody>
</table>

TVF, %

- XIENCE V: 7.6%
- TAXUS: 10.7%

HR = 0.70
[0.47, 1.02]

\( P_{\text{logrank}} = 0.062 \)
SPIRIT II & III Pooled Analysis
Pre-Specified Subgroups: In-stent LL

Late loss, mm

59% Reduction
50% Reduction
40% Reduction

<table>
<thead>
<tr>
<th>RVD (mm)</th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.5</td>
<td>0.16 ± 0.37</td>
<td>0.39 ± 0.48</td>
</tr>
<tr>
<td>2.5 – 3.0</td>
<td>0.14 ± 0.37</td>
<td>0.31 ± 0.49</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>0.13 ± 0.38</td>
<td>0.29 ± 0.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion length (mm)</th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.11 ± 0.26</td>
<td>0.35 ± 0.45</td>
</tr>
<tr>
<td>10 – 20</td>
<td>0.14 ± 0.36</td>
<td>0.30 ± 0.49</td>
</tr>
<tr>
<td>&gt;20</td>
<td>0.12 ± 0.31</td>
<td>0.20 ± 0.49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes</th>
<th>XIENCE V</th>
<th>TAXUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>0.12 ± 0.31</td>
<td>0.32 ± 0.50</td>
</tr>
<tr>
<td>YES</td>
<td>0.14 ± 0.31</td>
<td>0.33 ± 0.44</td>
</tr>
</tbody>
</table>

Lesion length (mm) Diabetes

XIENCE V TAXUS

≤2.5 53 148 430 149 =N
2.5 – 3.0 326 148 97 37
>3.0 430 191 149 52

Lesion length (mm) Diabetes

XIENCE V TAXUS

≤2.5 53 148 430 149 =N
2.5 – 3.0 326 148 97 37
>3.0 430 191 149 52
SPIRIT II & III Pooled Analysis
Pre-Specified Subgroups: In-segment LL

RVD (mm) | XIENCE V | TAXUS
---|---|---
<2.5 | 0.09 ±0.35 | 0.23 ±0.40
2.5 – 3.0 | 0.15 ±0.38 | 0.21 ±0.43
>3.0 | 0.08 ±0.38 | 0.23 ±0.51

Lesion length (mm) | XIENCE V | TAXUS
---|---|---
<10 | 0.06 ±0.27 | 0.21 ±0.39
10 – 20 | 0.11 ±0.37 | 0.22 ±0.49
>20 | 0.18 ±0.56 | 0.26 ±0.42

Diabetes | XIENCE V | TAXUS
---|---|---
NO | 0.09 ±0.34 | 0.22 ±0.46
YES | 0.15 ±0.46 | 0.22 ±0.38
# Perspectives from the “New DES” vs. TAXUS RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Stent</th>
<th>In-stent LL</th>
<th>In-seg LL</th>
<th>In-seg ABR</th>
<th>TLR</th>
<th>TVR</th>
<th>MACE</th>
<th>TVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zomaxx 1</td>
<td>Zomaxx vs. TAXUS</td>
<td>↑49%</td>
<td>↑80%</td>
<td>↑140%</td>
<td>↑95%</td>
<td>↑129%</td>
<td>↑31%</td>
<td>↑43%</td>
</tr>
<tr>
<td>Costar II</td>
<td>Costar vs. TAXUS</td>
<td>↑67%</td>
<td>↑200%</td>
<td>↑152%</td>
<td>↑113%</td>
<td>↑188%</td>
<td>↑60%</td>
<td>–</td>
</tr>
<tr>
<td>Endeavor IV</td>
<td>Endeavor vs. TAXUS</td>
<td>↑60%</td>
<td>↑57%</td>
<td>↑47%</td>
<td>↑41%</td>
<td>↑6%</td>
<td>↓2%</td>
<td>↓8%</td>
</tr>
<tr>
<td>SPIRIT III</td>
<td>XIENCE V vs. TAXUS</td>
<td>↓48%</td>
<td>↓50%</td>
<td>↓47%</td>
<td>↓46%</td>
<td>↓29%</td>
<td>↓43%</td>
<td>↓22%</td>
</tr>
</tbody>
</table>

1) Zomaxx I trial results are on file with sponsor, Abbott Vascular
2) Costar II; EUROSTAR II Trial presented by M. Krucoff at PCR 2007
3) Endeavor IV results presented by M. Leon at TCT 2007
4) Clinical event rates for XIENCE V calculated from 284 day data
XIENCE V Stent: Conclusions from Clinical Studies

- With follow-up complete through 1 year, the XIENCE V everolimus-eluting stent compared to the TAXUS paclitaxel-eluting stent results in:
  - Significant reductions in angiographic in-stent and in-segment late loss and binary restenosis
  - Significant reduction in IVUS percent volume obstruction, without positive remodeling or late acquired incomplete apposition
  - Significant reductions in MI, MACE and TVF at 30 days, with non-significant numerical trends toward less composite cardiac death and MI, and TVF at 1 year
  - Significant reductions in TLR and MACE at 1 year
  - Comparable rates of stent thrombosis
The clinical and angiographic benefits of the everolimus-eluting XIENCE V stent compared to the widely utilized paclitaxel-eluting TAXUS stent have been consistent in 2 consecutive randomized trials in 2 different geographies; as such, these findings may be considered especially robust.

Every pre-specified primary and major secondary endpoint from the SPIRIT FIRST randomized trial, the SPIRIT II randomized trial, and the SPIRIT III randomized trial were successfully met.
Mitchell W. Krucoff MD
Professor of Medicine / Cardiology
Duke University Medical Center
Director, Cardiovascular Devices Unit
Duke Clinical Research Institute
Conflict of Interest

- No equity holding or significant conflict
- Consulting* and/or research grants from the following:
  - Cordis J&J
  - Medtronic
  - Boston Scientific
  - Biosensors
  - Affinergy
  - Abbott
  - St. Jude Medical
  - OrbusNeich
  - Conor
  - Terumo

* Moderate: < $10,001 per annum
Reasonable Assurance of XIENCE V Safety: Presentation Overview

- Prospective study analyses: safety context
- 2 year safety subset
- Continued Access/Post-approval Program
Safety Context for 1 Year Pooled SPIRIT II & III Analysis
Consistency Across The Spectrum of Prospective Safety & Effectiveness

### XIENCE V vs. TAXUS

<table>
<thead>
<tr>
<th>Study</th>
<th>In-stent LL</th>
<th>In-seg LL</th>
<th>In-stent ABR</th>
<th>In-seg ABR</th>
<th>TLR @ 1 yr</th>
<th>MACE @ 1 yr</th>
<th>TVF @ 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIRIT II</td>
<td>↓ 69%</td>
<td>↓ 53%</td>
<td>↓ 63%</td>
<td>↓ 41%</td>
<td>↓ 73%</td>
<td>↓ 71%</td>
<td>↓ 51%</td>
</tr>
<tr>
<td>SPIRIT III</td>
<td>↓ 47%</td>
<td>↓ 50%</td>
<td>↓ 60%</td>
<td>↓ 47%</td>
<td>↓ 39%</td>
<td>↓ 42%</td>
<td>↓ 24%</td>
</tr>
<tr>
<td>SPIRIT II and III Pooled</td>
<td>↓ 58%</td>
<td>↓ 50%</td>
<td>↓ 61%</td>
<td>↓ 47%</td>
<td>↓ 47%</td>
<td>↓ 48%</td>
<td>↓ 29%</td>
</tr>
</tbody>
</table>
Late Stent Thrombosis & DES Safety

- Contemporary focus: Fall 2006 (ESC)
- Rare events: $\leq 0.6\%$ per annum
- Complex substrate issue:
  - Patient
  - Procedure
  - Platform
  - Plavix
- Statistical certainty:
  - Large patient cohorts
  - Long term follow up
Over 15 meta-analyses comparing DES to BMS


When used for the approved indications, safety and effectiveness of DES, when used, is indicated to be equivalent to bare metal stents. The special FDA panel on DES and thrombosis, December 2006, noted:

“On-label use of TAXUS DES is safe and effective relative to BMS.”

2 Year Pooled Spirit II & III Safety Subset

New DES vs. Approved DES
SPIRIT II & III Pooled Analysis: 2 Year Safety Subset

- 2 year Safety Data analysis
  - Not a prospective analysis plan for either SPIRIT II or SPIRIT III
  - Statistical Analysis Plan (SAP) developed based on discussions with FDA
  - 2 year safety subset subjects “inclusion” criterias specified in the SAP:
    - Subjects must have completed 2 year follow-up by or must have terminated prior to Oct. 30, 2007 (e.g. “all available” as of Oct 30, 2007)
    - All data must be monitored (100% source verification)
    - All events must be adjudicated by independent blinded CECs
SPIRIT II & III 2 Year Safety Subset: Clinical Follow-up Patient Flow

SPIRIT II & III RCT (N = 1,302)

2 year safety subset data monitored and events adjudicated (N = 603*)

Patients not reached 2 year follow-up or data collection on-going (N = 699)

* Include 74 early terminators (Patients died = 30, LTFU = 29, or withdrew = 15)
SPIRIT II & III Pooled Analysis Early Terminators in 2 Year Safety Subset

- Among the 74 monitored early terminators:
  - 43 terminated before 1 year
  - 31 terminated between year 1 and 2
  - The range of denominators for 0-2 year analysis is 534 - 563
### SPIRIT II & III Pooled 2 Year Analysis Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Complete Cohort</th>
<th>2 Year Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIENCE V (n = 892 pts)</td>
<td>TAXUS (n = 410 pts)</td>
</tr>
<tr>
<td>Age (mean) (years)</td>
<td>62.9</td>
<td>62.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>70.3</td>
<td>68.2</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27.9</td>
<td>27.1</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>74.0</td>
<td>72.3</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>72.8</td>
<td>72.1</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>25.3</td>
<td>23.8</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>23.7</td>
<td>19.3</td>
</tr>
<tr>
<td>Unstable Angina (%)</td>
<td>20.8</td>
<td>26.5</td>
</tr>
<tr>
<td>Dual vessel treatment (%)</td>
<td>15.7</td>
<td>15.9</td>
</tr>
</tbody>
</table>
### SPIRIT II & III Pooled 2 Year Analysis

**Angiographic Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Complete Cohort</th>
<th></th>
<th>2 Year Subset</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIENCE V</td>
<td>TAXUS</td>
<td>XIENCE V</td>
<td>TAXUS</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lesions</strong></td>
<td>1,032</td>
<td>474</td>
<td>494</td>
<td>211</td>
</tr>
<tr>
<td><strong>LAD (%)</strong></td>
<td>41.1</td>
<td>43.8</td>
<td>40.5</td>
<td>44.1</td>
</tr>
<tr>
<td><strong>LCX (%)</strong></td>
<td>28.0</td>
<td>26.4</td>
<td>28.3</td>
<td>25.1</td>
</tr>
<tr>
<td><strong>RCA (%)</strong></td>
<td>30.7</td>
<td>29.6</td>
<td>31.2</td>
<td>30.3</td>
</tr>
<tr>
<td><strong>LMCA (%)</strong></td>
<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>RVD (mean) (mm)</strong></td>
<td>2.75</td>
<td>2.77</td>
<td>2.72</td>
<td>2.76</td>
</tr>
<tr>
<td><strong>MLD (mean) (mm)</strong></td>
<td>0.88</td>
<td>0.89</td>
<td>0.91</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>%DS (mean)</strong></td>
<td>67.7</td>
<td>67.5</td>
<td>66.2</td>
<td>66.2</td>
</tr>
<tr>
<td><strong>Lesion Length (mean) (mm)</strong></td>
<td>14.3</td>
<td>14.5</td>
<td>14.3</td>
<td>14.7</td>
</tr>
</tbody>
</table>
### SPIRIT II & III Pooled 2 Year Analysis

#### Antiplatelet Agent Utilization

<table>
<thead>
<tr>
<th></th>
<th>Complete Cohort</th>
<th>2 Year Completers*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIENCE V</td>
<td>TAXUS</td>
</tr>
<tr>
<td></td>
<td>n=892 pts</td>
<td>n=410 pts</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months (%)</td>
<td>97.3</td>
<td>95.8</td>
</tr>
<tr>
<td>At 9 months (%)</td>
<td>96.5</td>
<td>94.6</td>
</tr>
<tr>
<td>At 1 year (%)</td>
<td>95.4</td>
<td>92.9</td>
</tr>
<tr>
<td>At 2 years (%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Thienopyridine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months (%)</td>
<td>93.4</td>
<td>92.9</td>
</tr>
<tr>
<td>At 9 months (%)</td>
<td>67.8</td>
<td>70.6</td>
</tr>
<tr>
<td>At 1 year (%)</td>
<td>63.3</td>
<td>64.5</td>
</tr>
<tr>
<td>At 2 years (%)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Excluding early terminators
SPIRIT II & III 2 Year Safety Subset: All Death

DES vs DES

RR [95% CI]*
0.72 [0.35, 1.47]

6.7%

4.8%

19/398

11/165

XIENCE V

TAXUS

* Confidence Intervals are for descriptive purposes only and not adjusted for multiple comparisons
SPIRIT II & III 2 Year Safety Subset: Cardiac Death

DES vs DES

RR [95%CI]
0.71 [0.21, 2.41]

1.8% vs 2.5%

7/387 vs 4/158
SPIRIT II & III 2 Year Safety Subset: MI

DES vs DES

RR [95% CI]
0.61 [0.26, 1.47]

3.1%
12/387
XIENCE V

5.1%
8/158
TAXUS
SPIRIT II & III 2 Year Safety Subset: Cardiac Death or MI

<table>
<thead>
<tr>
<th></th>
<th>DES vs DES</th>
<th>RR [95%CI]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>XIENCE V</td>
<td>4.7%</td>
<td>0.73 [0.35, 1.56]</td>
<td>18/387</td>
</tr>
<tr>
<td>TAXUS</td>
<td>6.3%</td>
<td></td>
<td>10/158</td>
</tr>
</tbody>
</table>
SPIRIT II & III 2 Year Safety Subset: Stent Thrombosis

Stent Thrombosis Per Protocol

- XIENCE V: 1.6% (6/379)
- TAXUS: 1.9% (3/155)

RR [95%CI] = 0.82 [0.21, 3.23]

Stent Thrombosis Per ARC (Definite + Probable)

- XIENCE V: 1.3% (5/379)
- TAXUS: 1.3% (2/155)

RR [95%CI] = 1.02 [0.20, 5.21]
SPIRIT II & III 2 Year Safety Subset: Late/Very Late Stent Thrombosis (31 days – 2 yrs)

Per Protocol

- **XIENCE V**: 1.1% (4/378)
- **TAXUS**: 1.9% (3/155)

Per ARC (Definite + Probable)

- **XIENCE V**: 0.8% (3/378)
- **TAXUS**: 1.3% (2/153)

Relative Risk (RR) [95% CI]

- **Per Protocol**: 0.55 [0.12, 2.41]
- **Per ARC**: 0.62 [0.10, 3.65]
SPIRIT II & III 2 Year Safety Subset: MACE

DES vs DES

RR [95%CI]
0.52 [0.31, 0.88]

13.9%

7.2%

28/387
XIENCE V

22/158
TAXUS

MACE: Cardiac Death, MI or TLR
SPIRIT II & III 2 Year Safety Subset: TVF

DES vs DES

RR [95%CI]
0.72 [0.46, 1.13]

TVF: Cardiac Death, MI or TVR
SPIRIT II & III
Pooled Analysis: Observations

- 2 year Safety Subset Analysis from SPIRIT II and SPIRIT III shows:
  - Similar baseline and angiographic data compared to the total cohort
  - Slightly lower long term clopidogrel use (≥ 9 Months) in the safety subset compared to the entire study population
  - Directionality of endpoints at 2 years in safety subset consistent with outcomes at 1 year in entire cohort
  - No evidence of any safety signal at 2 years based on all available monitored data
XIENCE V Safety: Reasonable Assurance of Safety

• Design objectives met or exceeded:
  – Second generation stent platform
  – Advanced polymer design
  – Well characterized drug entity
  – Preclinical models through 2 years

• Human trials:
  – Non inferior or superior in all prospective angiographic and clinical safety and efficacy endpoints at one year
  – Two year directionality of safety endpoints very consistent with 1 year
  – No evidence for safety concerns apparent compared to TAXUS based on all available monitored data at 2 year follow-up
## Sample Size for Rare Endpoints

<table>
<thead>
<tr>
<th>Assumed Rate (per year)</th>
<th>0.3%</th>
<th>0.4%</th>
<th>0.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta (RR = 1.5)</td>
<td>0.15%</td>
<td>0.2%</td>
<td>0.25%</td>
</tr>
<tr>
<td>80% Power* Alpha = 0.025</td>
<td>11,926</td>
<td>8,944</td>
<td>7,156</td>
</tr>
<tr>
<td>90% Power* Alpha = 0.025</td>
<td>16,610</td>
<td>12,458</td>
<td>9,966</td>
</tr>
</tbody>
</table>

* Sample size determined using NCSS PASS using Post Market Surveillance
XIENCE V
Continued Access/Post Approval Program
### Integrated Pre-Approval and Post-Approval Clinical Program (N > 16,000)

#### Pre-approval Clinical Data

<table>
<thead>
<tr>
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<td>Registry</td>
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#### Ongoing and Planned Clinical Data

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<td>Registry</td>
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<td>(n = 1,550) RCT 2:1 vs. CYPHER</td>
<td>(n = 450)</td>
</tr>
<tr>
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<td>Post-approval Registry – real world</td>
<td></td>
<td>(n ~ 5,000)</td>
<td>US</td>
</tr>
<tr>
<td>XIENCE India</td>
<td>Post-approval Registry – real world</td>
<td></td>
<td>(n ~ 1,000)</td>
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</table>
SPIRIT IV

**Main US RCT**

- RVD 2.5 – 4.25 mm
- LL ≤ 28 mm
- N = 3,690 at up to 70 sites

**XIENCE V**

- (N = 2,460)

**TAXUS Control**

- N = 1,230

- Up to three de novo lesions, maximum of two lesions per epicardial vessel

- Prospective, single blind, randomized, continued access trial in 3,690 patients
- Expanded multi-vessel treatment
- Primary endpoint: MACE at 1 year*
- Clinical follow-up to 5 years
- Currently enrolling (2,225 patients enrolled by November 26, ‘07)
- 3 DSMB meetings – No safety-related issues reported to date
- PI: Gregg Stone

* Under discussions with FDA
SPIRIT V

- Registry: n = 2,700
  - Primary endpoint: adjudicated composite rate of death, MI and TVR at 30 days
  - Clinical follow-up to 5 years
- Diabetic study: n = 300
  - Primary endpoint: In-stent LL at 270 d, compared to TAXUS, 2:1
  - Angiographic follow up at 9 months, clinical follow-up to 5 years
- Enrollment complete in registry, 2,700 patients enrolled
- 3 DSMB meetings – no safety related issues reported to-date
- PI: Eberhard Grube, MD
SPIRIT Women

- **Single Arm Registry**: n = 1,550
  - Primary endpoint: Composite rate of all Death, all MI & TVR at 1 year
  - Clinical follow-up to 5 years
- **RCT**: n = 450 vs. CYPHER, 2:1
  - Primary endpoint: Composite rate of all Death, all MI & TVR at 1 year
  - Clinical follow-up to 5 years
  - Angiographic follow-up at 9 months
- **Currently enrolling** (enrollment commenced July 2007)
- **PI**: Marie-Claude Morice, MD  **Co-PI**: Stephan Windecker, MD
XIENCE V India

- Post market registry in ~ 1,000 real world patients
- Primary endpoint: ARC defined stent thrombosis through 5 years
- Co-primary endpoint: Composite endpoint of death and MI at 1 year and through 5 years
- Clinical follow-up to 5 years
- Procedural success during commercial use
- Health status by the Seattle Angina Questionnaire
- Patient compliance with adjunctive antiplatelet therapy and major bleeding complications
- PI: Ashok Seth, MD
Post Market Study in the USA

Consecutively enrolled patients in a real world setting
N ~ 5,000 at up to 275 sites

XIENCE V (N ~ 5,000)

- Post-approval registry in ~ 5,000 real world patients
- Primary Endpoint: ARC defined stent thrombosis through 5 years
- Secondary Endpoint: Composite death and MI at 1 year and through 5 years
- Procedural success during commercial use
- Health status by the Seattle Angina Questionnaire
- Evaluate compliance with adjunctive antiplatelet therapy, management of interruption and major bleeding complications
- Abbott Vascular Considerations:
  - Composite Death and MI as co-primary
  - Optimal dual anti-platelet therapy duration
- Co-PI’s: James Hermiller, MD & Mitchell Krucoff, MD
SPIRIT/XIENCE V
Integrated Post-Approval Strategy

Post-Approval Trials N=14,690; (Randomized: 4,440)

Adding Certainty (On Label)

- SPIRIT IV N~3,690
  - ~80%
- SPIRIT V N~3,000
  - ~36%
- SPIRIT Women N~2,000
  - ~40%
- XIENCE V USA N~5,000
  - ~40%
- XIENCE V INDIA N~1,000
  - ~30%

~ 7,000

Advance Knowledge (Real World)

- 3 vessel CAD: N=738
  - ~20%
- Real world (EU): N=1620
diabetics: N=300
  - ~64%
- Gender specific N~1,200
  - ~60%
- Real world (US) N~3,000
  - Optimal DAP
  - ~60%
- Real world (India) N~700
  - ~70%
XIENCE V Continued Access/Post Approval Program: Conclusions

- Evaluates continued safety and performance over 5 years
  - ~14,690 patients worldwide
  - ~8,600 patients in US
  - ~4,900 already enrolled (without DSMB modifications)
- Integrated, committed post approval program utilizing systematic, high quality science delivered from post-market research landscape
- Will prospectively provide additional statistical certainty about on-label XIENCE V safety
- Will prospectively provide new knowledge regarding off-label and real world XIENCE V use
Conclusions

Krishna Sudhir, MD, PhD
XIENCE V Design

- Built on the well established ML VISION and MINI-VISION Stent and Stent Delivery System
  - Flexible stent with thin struts
  - Proven deliverability
- Thin, biocompatible drug coating
  - Durable polymer, used in other Cardiovascular applications
  - Long term biocompatibility similar to VISION BMS
- Well studied drug, not a new molecular entity
Pre-clinical Program

- Comprehensive pre-clinical evaluation with 35 studies, 2 species, 28 days to 2 years
- Rapid re-endothelialization
- Smooth muscle cell rich neointima
  - No persistent fibrin
  - Minimal long term inflammation
- Hemocompatibility comparable to VISION BMS
- Pre-clinical safety profile equivalent to VISION BMS
# Integrated Pre-Approval and Post-Approval Clinical Program (N > 16,000)

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Robust Evidence of Effectiveness

Consistent clinical and angiographic benefits of the XIENCE V stent compared to TAXUS, in 2 consecutive randomized trials (SPIRIT II and III) in multiple geographies.

All pre-specified primary and major secondary endpoints from the SPIRIT FIRST randomized, SPIRIT II randomized, SPIRIT III randomized trials were successfully met.
XIENCE V demonstrates reasonable assurance of safety, with comparable 1 year death, MI and Stent thrombosis rates to TAXUS.

No differences apparent in safety events at 2 years between treatment groups based on all available monitored data.

Thus, no safety concerns apparent as compared to TAXUS based on all available data to date.
Summary

- Clinical results consistent with design intent and pre-clinical observations
- SPIRIT FIRST, II and III all met their primary and major secondary endpoints; SII and SIII results confirmed in pooled analysis
- Superiority in angiographic endpoint (Late Loss), and non-inferiority in clinical endpoint (Target Vessel Failure), compared to TAXUS
- Reasonable assurance of safety as demonstrated by similar rates of Death, MI and Stent Thrombosis compared to TAXUS up to 2 years.
Post-Approval Considerations

- In post-market surveillance programs, sample sizes for low frequency events (< 0.5% per year) can vary from ~7,000 - 16,000 patients.

- Abbott Vascular has a comprehensive, integrated pre-approval and post-approval plan with >16,000 patients, and five year follow-up.

- A robust post-approval program with 14,690 patients worldwide and 5 year follow-up has been presented today, designed to detect the true incidence of low frequency adverse events.