The Science behind XIENCE™ V

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Summit TCT  April 25
Drug Eluting Stent System Design
Drug Eluting Stent System Design

Mechanical Engineering

Stent

Coating integrity

Matrix

Polymer Chemistry

Mechanical scaffolding

Drug – polymer compatibility
Loading capacity
Release kinetics

Vascular biology

Drug

Vascular biology
Tissue pharmacokinetics
Preclinical models

Tissue

Vascular Biology

Pharmacology
Pharmacology

Preferred Drug

- Mechanism of Action (MOA)
- Functional at µg level
  - Allows for thin drug reservoir coating
- Wide therapeutic window
  - Excellent tissue compatibility
- Drug stability
  - Product yield (manufacturing)
  - Shelf-life
- Proven clinical experience
Polymer Characteristics for Controlled Drug Release

- Physical Properties
  - Polymer Thickness
  - Polymer Flexibility
  - Drug Loading Capacity

- Mechanical Integrity
  - Adhesion to Stent
  - Adhesion to Balloon

- Manufacturability
  - Stability

- Biocompatibility
  - Thrombogenecity
  - Inflammation
  - Proven History

- Controlled Release
XIENCE V DES Components

MULTI-LINK VISION
Stent

MULTI-LINK VISION Stent Delivery System

Everolimus

Fluoropolymer

CAUTION: XIENCE™ V is an investigational device. Limited by Federal (U.S.) law to investigational use only.
Key Product Attributes:

**Excellent acute success**
- Proven Guidant MULTI-LINK VISION Platform
- Coating integrity from delivery to deployment
- Minimal coating thickness

**Commitment to sustainable clinical outcomes**
- Everolimus is a cytostatic proliferation inhibitor that causes cell cycle arrest in the late G1 phase
- Fluoropolymer technology allows for controlled release of Everolimus without sacrificing biocompatibility
- SPIRIT Family of Trials—over 4,000 XIENCE V patients studied by 2007
Excellent Acute Success
MULTI-LINK VISION Platform

Cobalt Chromium Technology
• Allows for thinner struts without compromise to radiopacity or radial strength.¹

Thin Strut Stent Design
• Outstanding flexibility and conformability
• .0032” strut thickness

Low System Profile
• Excellent deliverability

¹. As compared to stainless steel. Source: ASTM International.
XIENCE V Stent Design – MULTI-LINK VISION® Stent

6-crest
• For 2.5 mm and 3.0 mm expansion diameters
• Can be post-dilated to 3.5 mm

9-crest
• For 3.5 mm and 4.0 mm expansion diameters
• Can be post-dilated to 4.5 mm

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XIENCE V Delivery System – MULTI-LINK VISION SDS

• Specifically designed for stent delivery
• Soft, highly flexible Pebax balloon material
• Short abrupt tapers
• 5F guide catheter compatible

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XIENCE V Fluoropolymer

- Fluoropolymers are extremely biocompatible with a proven history in blood contacting applications
  - Haemodialysis machines
  - Cardiac sutures
  - Vascular grafts
  - Guide catheters
- High drug loading
  - Minimize coating thickness
- Good physical coating integrity
  - Excellent adhesion to metal
  - Good ductility and flexibility
Everolimus

- Developed by Novartis

- Immunosuppressant drug
  - Targets primary causes of chronic rejection in heart, renal, and lung transplant patients

- Proliferation inhibitor
  - Inhibits growth factor-stimulated cell proliferation by causing cell cycle arrest in the late G1 stage

- Active ingredient in CERTICAN® (Novartis)
  - Approved for prevention of rejection of heart and kidney transplant in over 60 countries
  - Investigational drug; Novartis received approvable letter from FDA
Proven Pre-clinical Effectiveness

Everolimus and Sirolimus inhibit vascular smooth muscle cell proliferation

Sources: Novartis Pharma AG; Schuler et al. Transplantation. 1997; 64:36-42
DES Release Profiles *(in vivo)*

Source: Medtronic Vascular Data Presentation, TCTMD; TAXUS IV SR Presentation, TCTMD; Cypher Presentation, TCTMD; Data on file at Abbott Vascular.
XIENCE V
Pre-clinical Studies
Safety Data

• *In vivo* animal testing was conducted to demonstrate the safety of the XIENCE V Stent, and the safety of 2 overlapped XIENCE V Stents, in 2 animal models
  • A low injury porcine coronary artery model*
  • A low injury non-atherosclerotic rabbit iliac model**

* Studies conducted with 3.0 x12 mm stents containing 56 µg Everolimus
** Studies conducted with 2.5 x 8 mm stents containing 37 µg Everolimus
The Science of Safety

Acute
- Minimal Injury
- Complete Apposition
- Thromboresistant Materials

Long-Term
- Rapid re-endothelialization
- Functional endothelial layer
- No chronic inflammation
- No persistent fibrin
The Science of Safety

Acute

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Long-Term

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ENDOTHELIAL INJURY AND HEALING POST-STENT IMPLANTATION

- **Endothelial denudation**

  - Small area – little to no intimal hyperplasia observed \(^2,^3\)
  - Large area
    - Focal fibrin deposition + *thrombus formation*
    - Inflammation
    - Activation of SMCs
  - Severe and deeper injury results in delayed re-endothelialisation \(^4\)

- **Subsequent arterial healing process begins immediately** \(^1,^5\)

  - Eventually is essential for restoring normal arterial function
  - In around 15 - 20 % of patients this normal process is exaggerated resulting in re-stenosis
The Science of Acute Safety

Maximizing Acute Safety
- Minimal Injury
- Complete Apposition
- Thromboresistant Materials

Desired Attributes
- Thin Struts
- Low Stent to Shoulder
- Conformable Stent Pattern
- Polymer
- Implant
Minimal Injury
Minimizing Strut and Polymer Thickness

**CYPHER®**
- Strut Thickness: 140 um
- Polymer Thickness: 12.6 um
- Total: 152.6 um

**TAXUS®**
- Strut Thickness: 132 um
- Polymer Thickness: 16 um
- Total: 148 um

**ENDEAVOR**
- Strut Thickness: 91 um
- Polymer Thickness: 5.3 um
- Total: 96.3 um

**XIENCE V**
- Strut Thickness: 81 um
- Polymer Thickness: 7.6 um
- Total: 88.6 um

3.0 mm diameter stents, 500x magnification

Data on file at Abbott Vascular
Minimal Injury
Short, Abrupt Tapers

- Specifically designed for stent delivery
- Soft, highly flexible Pebax balloon material
- Short abrupt tapers
- 5F guide catheter compatible

Photos taken by and on file at Abbott Vascular.
Complete Apposition
Flexible, Conformable Stent Design

Tests performed by and data on file at Abbott Vascular.
3.5 mm x 28 mm XIENCE V, CYPHER Select, and TAXUS® Liberté. 3.5 mm x 30 mm Endeavor
# Thromboresistant Fluoropolymer

## Proven Medical Applications

<table>
<thead>
<tr>
<th>Drug Eluting Stent:</th>
<th>• XIENCE V Everolimus Eluting Coronary Stent System</th>
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<tbody>
<tr>
<td>Other Applications:</td>
<td>• Arterial Prostheses</td>
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<tr>
<td></td>
<td>• Graft Prostheses</td>
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<tr>
<td></td>
<td>• Hemodialysis membrane</td>
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<td></td>
<td>• Vascular suture</td>
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<td>• Guiding Catheter</td>
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<td>• Other blood contacting surfaces</td>
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- The inert and hemocompatible properties of fluoropolymers make it an excellent choice for use in a variety of medical applications.
Thromboresistant Materials
Coating Integrity - XIENCE V Fluoropolymer

- Consistent coating integrity to minimize platelet aggregation and inflammation

Photos taken by and on file at Abbott Vascular
Coating Integrity - TAXUS® Liberté

- Intense webbing of polymer
  - Touch points led to webbing of polymer

Photos taken by and on file at Abbott Vascular
Thromboresistant Materials
Minimal Platelet Aggregation

Chandler Blood Loop Test

Weight of Thrombus (ug) Adhered to Stent

Data on file at Abbott Vascular
Thromboresistant Materials
Ex-Vivo Shunt Study

Low thrombus adherence due to smooth coating integrity and hemocompatibility of the XIENCE V Fluoropolymer.

No reduced flow between 5 minutes and 30 minutes porcine in-vivo.

Data on file at Abbott Vascular
The Science of Safety

**Acute**
- Minimal Injury
- Complete Apposition
- Thromboresistant Materials

**Long-Term**
- Rapid re-endothelialization
- Functional endothelial layer
- No chronic inflammation
- No persistent fibrin
The Science of Long Term Safety

**Maximizing Long-term Safety**
- Rapid Re-endothelialization
- Functional endothelial layer
- Minimal inflammation
- No persistent fibrin

**Desired Attributes**
- Complete coverage
- Decreased VEGF Production
- Presence of CD-31
- No persistent foreign body response
- Lack of medial necrosis
- No positive remodeling
Rapid Re-endothelialization
Porcine Model, XIENCE™ V Stent at 28 Days

Complete luminal endothelialization observed at low and high magnification (SEM)

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Rapid Re-endothelialization
Porcine Stent Healing at 28 & 180 Days

28 Day

Lumen endothelialized
Fibrin
Healthy media

180 Day

CAUTION: XIENCE™ V is an investigational device. Limited by Federal (U.S.) law to investigational use only.
Rapid Re-endothelialization

14-Day Rabbit Iliac Study

Photos on file at Abbott Vascular
Minimal Inflammation
Porcine Safety Study up to 720 days

Inflammation Score

- VISION™
- XIENCE™ V
- CYPHER®

Data on file at Abbott Vascular
Minimal Inflammation
Porcine Safety Study (representative histology)

XIENCE V

CYPHER

Photos taken by and on file at Abbott Vascular
Minimal Inflammation
XIENCE™ V Max Dose Study

Max Dose study (8x XIENCE V Drug Dose):
Patent lumens with stent struts completely covered by a well organized, smooth muscle cell-rich neointima.

Photos taken by and on file at Abbott Vascular
**Minimal Inflammation**

**XIENCE™ V Overlapping Stents**

<table>
<thead>
<tr>
<th>28 Day</th>
<th>180 Day</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="XIENCE™ V" /></td>
<td><img src="image2.png" alt="XIENCE™ V" /></td>
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<tr>
<td><img src="image3.png" alt="ML VISION" /></td>
<td><img src="image4.png" alt="ML VISION" /></td>
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<tr>
<td><img src="image5.png" alt="XIENCE™ V" /></td>
<td><img src="image6.png" alt="XIENCE™ V" /></td>
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*All vessels are widely patent with a smooth muscle cell rich neointima incorporating all stent struts*

Photos on file at Abbott Vascular.

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SE2924433D
Minimal Inflammation & Fibrin
No Medial Necrosis with XIENCE V

XIENCE™ V

28-day Porcine Model:
Overlapping Stents

Photos taken by and on file at Abbott Vascular
The Science of Long Term Safety

Maximizing Long-term Safety

• Rapid Re-endothelialization
• Functional endothelial layer
• Minimal inflammation
• No persistent fibrin

Desired Attributes

✓ Complete coverage
✓ Decreased VEGF Production
✓ Presence of CD-31
✓ No persistent foreign body response
✓ Lack of medial necrosis
✓ No positive remodeling
The pre-clinical data supports the safety of the XIENCE™ V Stent in the animal model

- Neointima characterized by compact smooth muscle cells in proteoglycan / collagen matrix at 28, 90, 180 days
- Completely endothelialized lumens by 28 days
- Widely patent lumens
- No luminal thrombus
- Inflammation within acceptable range in porcine and rabbit models
Family of Trials

- **SPIRIT FIRST**
  - Safety and Performance
  - Europe
  - N = 60

- **SPIRIT II**
  - Clinical Support for CE Launch
  - International
  - N = 300

- **SPIRIT III**
  - U.S. and Japan Approval
  - U.S./Japan
  - N = 1,380
  - (1,292/88)

- **SPIRIT IV**
  - U.S. Peri-approval
  - U.S.
  - N = 1,125

- **SPIRIT V**
  - Post-CE Mark Approval
  - International
  - N = 3,021
  - (Approximate)
  - Diabetic study
  - N = 321
  - Registry
  - N = 2,700
 SPIRIT FIRST: In-Stent Late Loss (mm) per QCA to 12 Months


XIENCE V 6 Mo: 0.12 ± 0.22
Control 6 Mo: 0.89 ± 0.39
XIENCE V 12 Mo: 0.24 ± 0.27
Control 12 Mo: 0.84 ± 0.45
SPIRIT FIRST Key Takeaways

- SPIRIT FIRST met its primary endpoint of in-stent late loss
- Strong 6 month results were sustained to 12 months
- XIENCE V shows promise
  - Late Loss of 0.24 & 0.14 mm (in-stent & in segment)
  - One device-related MACE event (TLR)
  - No acute or late stent thrombosis
  - No late malapposition
International

- PI: Dr Patrick Serruys
- RCT: Prospective, single blind
- Primary end point: in-stent late loss at 6 months
- Stent Size: 2.5 – 4.0 mm; Stent lengths: 8, 18, 28 mm
- Angiographic and IVUS follow-up at 6 months for all patients, and at 2 years for subset of 152 patients at selected sites
- Clinical follow-up at 1, 6, 9 months, 1 and 2 years
- 6 months clopidogrel for all arms

A maximum of two de novo lesions

RCT
2.5 - 4.0 mm
N = 300

3:1

XIENCE V
N = 223

TAXUS® PECS Control
N = 77
Late Loss (mm) – All Lesions

Source: P. Serruys, M.D., WCC 2006

XIENCE™ V  TAXUS®
SPIRIT II In-Stent IVUS Results

Neointimal Volume

<table>
<thead>
<tr>
<th></th>
<th>SPIRIT II</th>
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<tbody>
<tr>
<td>XIENCE™ V</td>
<td>3.8 mm³</td>
</tr>
<tr>
<td>TAXUS®</td>
<td>14.4 mm³</td>
</tr>
</tbody>
</table>

73% reduction, p<0.0001

Volume Obstruction

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<tr>
<th></th>
<th>SPIRIT II</th>
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</thead>
<tbody>
<tr>
<td>XIENCE™ V</td>
<td>2.5%</td>
</tr>
<tr>
<td>TAXUS®</td>
<td>7.4%</td>
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</tbody>
</table>

66% reduction, p<0.0001

NOTE: 124 Patients; 140 lesions
Source: P. Serruys, M.D., WCC 2006
SPIRIT II Conclusions

• SPIRIT II met its Primary Endpoint:

  • XIENCE V was non-inferior to TAXUS® (in-stent late loss 0.11 mm vs 0.36 mm; p<0.0001)

  • XIENCE V proved superior to TAXUS® (in-stent late loss 0.11 mm vs. 0.36 mm; p<0.0001)

• XIENCE V had a statistically significant reduction in volume obstruction and neointimal volume when compared to TAXUS®

• XIENCE V 6M MACE and Stent Thrombosis rates were 2.7% 0.5%, respectively

• SPIRIT II clinical, angiographic and IVUS results confirm the results of SPIRIT FIRST

• US Pivotal Trial Results are pending