Complex Strategies for Peripheral Interventions
What’s on the Horizon with Drug-Eluting Devices?

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Disclosures

Speaker/Trainer/Advisory Board:

• Abbott Vascular
• BARD
• BSCI
• Cardinal Health/Cordis
• Cook Medical
• CSI
• Endologix

• Gore
• Lake Region Medical
• Medtronic
• Penumbra
• Phillips/Volcano
• Spectranetics
• Terumo/Bolton
Paclitaxel: Mechanism of Action

Binds to cellular microtubules to permanently prevent their depolymerization and thereby arrests cell division in the G2/M phase of the cell cycle.

Inhibits cell migration, division, and secretion (involved in cancer and restenosis).
Paclitaxel: Properties and Mechanics

- **Hydrophobic**
  - Does not dissolve in blood or water

- **Lipophilic**
  - Attracted to lipids - found in high concentration in the vessel wall

- **Antiproliferative**
  - Durable prevention of rapid cell division of targeted segment
FDA Approved Peripheral Drug Coated/Eluting Devices

• MOXY® DRUG-COATED BALLOON
  • Lutonix/Bard

• ADMIRAL® DRUG-COATED BALLOON
  • Medtronic

• ZILVER® PTX DRUG-ELUTING STENT
  • Cook Medical
Lutonix DCB Technology

- Low paclitaxel drug-load balloon with 2µg / mm²
- IV approved carriers of polysorbate & sorbitol
- Coating thickness: ±1.3 micron
- Coating applied while balloon is inflated
LEVANT 2 Study Design

- Pivotal IDE Randomized Trial
- 476 Patients
- Moderate Lesions
- Predilatation
LEVANT 2 Primary Patency 12 Month Outcomes

*Primary Patency is reported based on freedom from TLR and restenosis (DUS PSVR ≥ 2.5)
**LEVANT 2 Primary Patency 24 Month Outcomes**

Lutonix DCB Showed Sustained Benefit in Primary Patency at 24 months

<table>
<thead>
<tr>
<th>Efficacy, Primary Patency</th>
<th>Lutonix DCB (N=316)</th>
<th>Standard PTA (N=160)</th>
<th>Difference</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>@730 days</td>
<td>58.6%</td>
<td>53.0%</td>
<td>5.6%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

1 Primary patency is defined as the absence of target lesion restenosis (defined by DUSS peak systolic velocity ratio (PSVR) >2.5) and freedom from target lesion revascularization (TLR).
2 Primary Efficacy reported based on Kaplan-Meier Survival analysis, not pre-specified.
In.Pact Admiral DCB Catheter Technology

- Paclitaxel drug-load balloon with 3.5μg / mm²
- Excipient: Urea
- Freepac hydrophilic coating formulation
- Drug release in 30-60 seconds
- Up to 180 day trace drug retention
In.Pact SFA Study Design

- Pivotal IDE Randomized Trial
- 331 Patients
- Moderate Lesions
- Pre-screened Lesions
In.Pact 12 Month Primary Patency (PSVR ≥ 2.4)
1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)

2. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval

**In.Pact 24 Month Primary Patency (PSVR ≥ 2.4)**

**Log-rank P < 0.001**

- DCB: 69.5%
- PTA: 45.1%

**Time After Index Procedure (Months) vs. Primary Patency**

- DCB
- PTA

**Number at risk**

<table>
<thead>
<tr>
<th>DCB</th>
<th>220</th>
<th>213</th>
<th>192</th>
<th>149</th>
<th>121</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTA</td>
<td>111</td>
<td>108</td>
<td>69</td>
<td>52</td>
<td>41</td>
</tr>
</tbody>
</table>

△ +24.4%
IN.PACT SFA Trial
Effectiveness Outcomes through 2 Years

<table>
<thead>
<tr>
<th>2-Year Outcomes</th>
<th>IN.PACT n = 220</th>
<th>PTA n = 111</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically-driven TLR [1]</td>
<td>9.1% (18/198)</td>
<td>28.3% (30/106)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All TLR [2]</td>
<td>10.1% (20/198)</td>
<td>29.2% (31/106)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Primary Sustained Clinical Improvement [3]</td>
<td>76.9% (133/173)</td>
<td>59.2% (61/103)</td>
<td>0.003</td>
</tr>
<tr>
<td>ABI / TBI [4]</td>
<td>0.924 ± 0.261</td>
<td>0.938 ± 0.184</td>
<td>0.611</td>
</tr>
</tbody>
</table>

1. Clinically-driven TLR adjudicated by an independent Clinical Event Committee, blinded to the assigned treatment based on any re-intervention at the target lesion due to symptoms or drop of ABI of ≥20% or >0.15 when compared to post-procedure baseline ABI
2. All TLR includes clinically-driven and incidental or duplex driven TLR
3. Freedom from target limb amputation, target vessel revascularization (TVR), and increase in Rutherford class
4. TBI allowed in cases of incompressible vessels in IN.PACT SFA II phase

* Unless otherwise indicated, all tests were for superiority using the Fisher’s exact test for binary variables and t-test for continuous variables
Case 1: Short Occlusion
Case 2: Stenosis
Case 3: Long Occlusion
Case 4: Dissection
Case 5: Multiple Stenoses
Zilver  PTX  DES Technology

- Paclitaxel drug-load 3µg / mm²
- Polymer-free
- Low 1% fracture rate
- 40mm-120mm Lengths
- Proven 5yr Drug effect
Zilver PTX Clinical Data Portfolio

Zilver PTX Randomized Trial
- US/Japan/Germany
  - 55 Sites
  - N=479
- Zilver PTX
- PTA
- Suboptimal PTA
- Optimal PTA
- BMS
- Zilver PTX

Zilver PTX Global Registry
- Euro/Can/Korea
  - 30 Sites
  - N=787
- Zilver PTX

Zilver PTX Japan PMS
- Japan
  - Multiple Sites
  - N=907
- Zilver PTX
- Bypass

Zilver-Pass
- Europe/Brazil
  - 18 Sites
  - N=220
- Zilver PTX
At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to BMS
At 5 years, Zilver PTX demonstrates a 48% reduction in reintervention compared to standard care.
**Zilver PTX 5-Year Stent Integrity**

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Number of New Events</th>
<th>Fracture Rate$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>1-year</td>
<td>4</td>
<td>0.9%</td>
</tr>
<tr>
<td>3-year</td>
<td>3</td>
<td>1.9%</td>
</tr>
<tr>
<td>5-year</td>
<td>0</td>
<td><strong>1.9%</strong></td>
</tr>
</tbody>
</table>

$^1$ Kaplan-Meier estimates
Images and Case Review

History

80mm ZPTX (distal) and a 40mm Zilver Bare Metal (proximal) were placed in tandem at baseline (only 80mm ZPTX lengths available at baseline)

Follow-up angio taken within the first year after implant

* Image provided by Yazan Khatib, MD. First Coast Cardiovascular Institute
History

Previous atherectomy and BMS in multiple settings. Multiple recurrences of restenosis at 3-6 month intervals. The patient was a frequent returner.

ZPTX was placed in the proximal SFA (ISR, off-label) where the prior stenosis was most severe while the rest was touched-up with PTA and BMS.

This follow up angio was taken within one year of implant revealing the ZPTX Stent as the only treated segment still widely patent and the patients best outcome to date.
Images and Case Review

History

Two 6mm Zilver PTX stents were placed in the L SFA on 7/2014 and a 6mm BMS placed in the R SFA on 9/2014.

Follow-up Image from 2/2015. Less than 6 months from BMS placement, long total occlusion of BMS was reveal on angio. Attempt to repair the R SFA, but could not cross the ISR segment. Zilver PTX Stents in the opposite limb were still widely patent.
Images and Case Review

History

Proximal SFA stenosis previously treated with a ZPTX Stent remained widely patent while a new diffuse lesion distally was treated with BMS, overlapping the previously placed ZPTX Stent.

Follow-up at 1 year after BMS placement revealed diffuse ISR throughout the entire BMS segment while the ZPTX segment remained widely patent.

DCB’s were then used along the entire BMS segment, while the ZPTX was again left untreated. 9 month follow-up revealed the BMS + DCB segment with long diffuse ISR while the ZPTX segment showed minimal focalized narrowing.
Peripheral Drug Coated/Eluting Devices in IDE Trials

• Stellarex DRUG-COATED BALLOON
  • Spectranetics

• Eluvia DRUG-ELUTING STENT
  • Boston Scientific
Stellarex DCB Technology

- Low paclitaxel drug-load balloon with 2µg / mm²
- Excipient: Polyethylene Glycol
- Next generation EnduraCoat crystalline coating
- Lower particulate count
- High drug-transfer efficiency

*Not currently approved in the U.S.*
• ILLUMENATE Pilot Study

• 50 Patient first-in-human Study

1. Primary Patency defined as freedom from clinically-driven TLR and Duplex stenosis >50% (PSVR≥2.5)
2. KM Survival estimates at upper bound of follow-up intervals = 87.7% (day 390) and 80.3% (day 760)
ILLUMENATE Pivotal Clinical Study

• A prospective, randomized controlled, multicenter study designed to assess the clinical performance of the Stellarex DCB for the treatment of above-the-knee peripheral arterial disease.

• Randomized against standard PTA

• 300 patients at 42 sites in the United States and Austria

• Superficial femoral artery lesions 3 to 14 cm in length.

• Study will assess the safety and efficacy of Stellarex at 12 months, with follow-up to 5 years and will be used to support the company’s premarket approval application with the US Food and Drug Administration

• July 29, 2015—enrollment completed
## Baseline Core Lab Angiographic Data

**ITT Data Set**

<table>
<thead>
<tr>
<th></th>
<th>Stellarex</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Length (cm)</td>
<td>8.0 ± 4.5 (199)</td>
<td>8.9 ± 4.6 (100)</td>
<td>0.105</td>
</tr>
<tr>
<td>Restenotic¹</td>
<td>9.5% (19/200)</td>
<td>18.0% (18/100)</td>
<td>0.035</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>19.0% (38/200)</td>
<td>18.0% (18/100)</td>
<td>0.834</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>43.9% (87/198)</td>
<td>43.0% (43/100)</td>
<td>0.877</td>
</tr>
<tr>
<td>Diameter Stenosis (%)</td>
<td>73.9 ± 16.9 (200)</td>
<td>74.8 ± 17.0 (100)</td>
<td>0.673</td>
</tr>
<tr>
<td>Reference Vessel Diameter (mm)</td>
<td>4.86 ± 0.92 (200)</td>
<td>5.15 ± 1.05 (100)</td>
<td>0.017</td>
</tr>
<tr>
<td>0-1 Patent Run-off Vessels</td>
<td>32.5% (54/166)</td>
<td>30.5% (25/82)</td>
<td>0.745</td>
</tr>
</tbody>
</table>
## Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Stellarex</th>
<th>PTA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pre-dilatation Performed(^1)</td>
<td>100% (200/200)</td>
<td>100% (100/100)</td>
<td>N/A</td>
</tr>
<tr>
<td>Study Device Inflation Time(^1) (min/lesion)</td>
<td>3.9 ± 2.0 (200)</td>
<td>3.7 ± 2.3 (100)</td>
<td>0.557</td>
</tr>
<tr>
<td>Post-DCB/PTA Dissection(^2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade D</td>
<td>20.0% (40/200)</td>
<td>12.0% (12/100)</td>
<td>0.084</td>
</tr>
<tr>
<td>Grade E/F (Flow-limiting)</td>
<td>0.0% (0/193)</td>
<td>0.0% (0/98)</td>
<td>N/A</td>
</tr>
<tr>
<td>Bail-out Stent Placement(^1)</td>
<td>6.0% (12/200)</td>
<td>6.0% (6/100)</td>
<td>1.000</td>
</tr>
<tr>
<td>Post-procedure Diameter Stenosis (%)(^2)</td>
<td>25.2 ± 11.7 (199)</td>
<td>27.4 ± 10.1 (100)</td>
<td>0.107</td>
</tr>
</tbody>
</table>
CD-TLR\textsuperscript{1} Free at 12 Months: 93.6%

ITT Data Set

\begin{itemize}
  \item DCB \textbf{93.6\%} @ day 365
  \item PTA \textbf{87.3\%} @ day 365
  \item 91.0\% @ day 410
  \item 80.0\% @ day 410
\end{itemize}

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\textsuperscript{1} Clinically-driven TLR defined as re-intervention due to PSVR$\geq 2.5$ (or $>50\%$ stenosis via angiography) with an increase in the RCC $>1$ category or deterioration in the ABI by $>0.15$ compared to maximum early post-procedural level. Per subject analysis.
Primary Patency at 12 Months
ITT Data Set

Primary patency is defined as freedom from restenosis (determined by duplex ultrasound PSVR threshold of 2.5) and freedom from clinically-driven TLR at 12 months. Assessed per lesion. KM estimates reported at day 410 to capture all patients and events within the full 360-410 follow-up window. Rates from the middle of the protocol visit window (366 days) reported for consistency and comparative purposes with other trials.
Conclusions

- Stellarex is a low-dose (2 μg/mm²) DCB
  - One of the most complex patient groups studied in DCB IDE trials
  - Severe calcium 43.9%, diabetes 49.5%, 0-1 runoff 32.5%
- 12-Month DCB Primary Patency: 82.3%
- 12-Month DCB Freedom from CD-TLR: 93.6%
- Both primary safety and effectiveness endpoints demonstrated superiority of Stellarex over PTA
- Results reaffirm prior data
  - ILLUMENATE FIH and EU Randomized Trial
Eluvia Drug-Eluting Stent Technology

- CE Mark February 2016
- Innova stent platform
  - Self-expanding nitinol
- Biostable polymer matrix
- Paclitaxel

- 6F Tri-axial SDS, 0.035” guidewire compatible
- Blue Tri-Ax shaft fixed as the clear middle shaft is retracted releasing stent during deployment

*Not currently approved in the U.S.
Eluvia Drug Eluting Stent Technology

Eluvia Drug Eluting Stent:
- **Stent Architecture**: Balanced geometry designed for even stress distribution and optimal radial strength.
- **Spacing of interconnects**: Provides balanced stress distribution for all deformation modes.
- **Width, Length and angles**: Optimized for maximum strength.
- **Radial Force and Flexibility**: Must be matched by excellent Fracture Resistance.

*Stent Fracture rates in studies using the INNOVA Stent platform:*
- SuperNOVA Study (Innova): 2.2% at 24M
- The MAJESTIC Study (Eluvia): 0.0% at 12M

Eluvia Coating Design:
- **Dual Layer System**
- **Conformal coating for both layers**, studied in 20k clinical patients, more than 20M wv implants
- **Primer Layer (PBMA)**: Promotes Adhesion of Active Layer to Stent
- **Active Layer (PTx, PVDF-HFP)**: Controls Release of Paclitaxel
  - 0.167μg PTx/mm² stent surface area
  - PBMA Primer Layer

Paclitaxel/PVDF-HFP Active Layer
# Eluvia™ Drug-Eluting Vascular Stent System for SFA: MAJESTIC Clinical Study

## MAJESTIC Clinical Study

<table>
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<th>Study Overview: MAJESTIC</th>
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<td><strong>Objective</strong></td>
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<td><strong>Study Design</strong></td>
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<td><strong>Follow-up</strong></td>
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<tr>
<td><strong>Primary Endpoint</strong></td>
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</tbody>
</table>
Primary Patency*: 12 Months

- 12-month primary patency was 96.1% (49/51)
- Kaplan-Meier estimate: 96.4%

24 month Freedom from TLR = 91.3%
24 month Patency (PSVR < 2.5) = 78.2%

*Primary patency defined as duplex ultrasound peak systolic velocity ratio ≤2.5 and absence of TLR or bypass.

Note: Kaplan-Meier Estimates.

a. Duplex ultrasound peak systolic velocity ratio ≤2.5 and absence of TLR or bypass.
b. No TLR and those with TLR not for complete occlusion or bypass who were free of restenosis at 24 months.
Eluvia Imperial Randomized Clinical Trial

Currently Enrolling Patients

**Trial Design**
- Prospective, multicenter 2:1 randomized control trial (Eluvia: Zilver™ PTX)
- 485 patients at up to 75 investigational sites worldwide
- 5 year follow-up

**Objective**
Evaluate the safety and effectiveness of the Boston Scientific Eluvia Drug-Eluting Vascular Stent System (Eluvia Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 140 mm in length.
Eluvia vs. Zilver  PTX  DES Technology

- Same drug
- Polymer vs. polymer-free
- Low dose vs. high dose
- Long elution vs. shorter elution times

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<th>Coating Design Specifications</th>
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</thead>
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<tr>
<td></td>
</tr>
<tr>
<td>Medicinal Substance</td>
</tr>
<tr>
<td>Coating Design</td>
</tr>
<tr>
<td>Drug/Total Dose</td>
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</tbody>
</table>
THANK YOU!
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