The Zilver PTX® Randomized Trial of Paclitaxel-Eluting Stents for Femoropopliteal Disease: 24-Month Update

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*On behalf of the Investigators*
Overview

• Background
  – Drug-eluting stents for SFA treatment
  – Zilver PTX® drug-eluting stent
  – Trial design
  – Patient demographics/lesions

• Zilver PTX Randomized Trial – 24-month update
  – Safety
  – Effectiveness – Primary Patency
    • **81.2% Zilver PTX® vs. 62.7% BMS**
SFA Treatment Overview

- **Medical therapy** – small population
- **Exercise** – effective when supervised; not reimbursed
- **Surgery** – invasive
- **PTA** – limited effectiveness (12-mo. patency rates ≈35%)
- **BMS** – more effective than PTA (12-mo. patency rates ≈70%)
- **Atherectomy** – no randomized data
- **Cryoplasty** – no randomized data
- **Previous DES (polymer-based, limus drug coatings)** – no sustained difference from BMS
- **Paclitaxel-coated balloons** – promising in short, simple lesions
What is Driving Increased Device Use?

1996 - 2006

Endovascular Interventions
RR = 3.3;
95% CI 2.9-3.8

Major Lower Extremity Amputation
RR = 0.71;
95% CI 0.7-0.8

Lower Extremity Bypass Surgery
RR = 0.58;
95% CI 0.5-0.7
Zilver PTX® Drug-Eluting Stent

- Designed for the SFA
- CE Marked
  - Investigational in the US and Japan
- Dual therapy stent
  - **Mechanical support:**
    Zilver Flex® Stent Platform
  - **Drug coating:** Paclitaxel only
    - No polymer or binder
    - 3 µg/mm² dose density
- **Sponsor:** Cook Medical
Complementary Zilver PTX® Clinical Studies

55 sites in US, Japan, and Germany

Zilver PTX® Randomized Trial

PTA
n = 238

Optimal PTA
n = 118

Suboptimal PTA
(>30% residual stenosis)

n = 120

Primary Randomization

Bare Zilver®
n = 59

Zilver PTX®
n = 61

Secondary Randomization

>1000 patients
>2000 stents

Zilver PTX®
n = 236

Zilver PTX®
n = 236

Zilver PTX®
n = 787

30 sites in Europe, Canada, and Korea

Zilver PTX® Single-Arm Study
# Complementary Studies

<table>
<thead>
<tr>
<th>Zilver PTX®</th>
<th>Single-Arm Study</th>
<th>Randomized Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol</strong></td>
<td>Prospective, detailed case report forms, extensive monitoring</td>
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<tr>
<td><strong>Antiplatelets</strong></td>
<td>Clopidogrel for 60 days, aspirin indefinitely</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>Patency by ultrasound, stent integrity by X-ray, clinical benefit</td>
<td></td>
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<tr>
<td><strong>Patients</strong></td>
<td>Symptomatic PAD with Rutherford score ≥ 2</td>
<td></td>
</tr>
<tr>
<td><strong>Control Group(s)</strong></td>
<td>None</td>
<td>PTA ± provisional BMS</td>
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</table>
| **Lesions** | **Real-world:**  
• Unlimited per limb  
• Included in-stent restenosis  
• Length not limited  
• Unlimited Zilver PTX® stents per lesion* | **Controlled/Moderate:**  
• One lesion per limb  
• No prior stent in study vessel  
• Length ≤ 14 cm  
• Maximum of 2 Zilver PTX® stents per lesion* |
| **Imaging Analysis** | Site-based | Core laboratories (duplex ultrasound, angiography, X-ray) |
| **Primary Analysis** | | 12 months |
| **Ongoing Follow-up** | 2 years | 5 years |

* Maximum four per patient
Zilver PTX® Randomized Trial

- **Prospective, multinational trial**
  - Protocol approved by FDA, PMDA and German regulatory authorities

- **CEC and DSMB oversight, and imaging Core Lab analyses**

- **Key inclusion/exclusion criteria**
  - Rutherford classification ≥ 2
  - Reference vessel diameter 4-9 mm
  - Lesion length ≤ 14 cm
  - *De novo* or restenotic lesions (no in-stent restenosis)
  - > 50% diameter stenosis
  - One lesion per limb (bilateral treatment allowed)
Zilver PTX® Randomized Trial

• **12-month event-free survival** – Primary safety endpoint
  – Per patient freedom from death, amputation, target lesion revascularization, or worsening Rutherford score (by 2 classes or to class 5 or 6)

• **12-month primary patency** – Primary effectiveness endpoint
  – Per lesion patency by duplex ultrasonography, patent = PSVR < 2.0 (or angiography if available, patent = diameter stenosis < 50%)
  – One lesion per limb, bilateral treatment allowed

• **5 year ongoing follow-up**
  – 2, 3, 4, and 5 year patency evaluations for all stent patients and a randomly selected subset of patients with acutely successful PTA
  – 3 and 5 year stent radiographs
# Patient Demographics and Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>Zilver PTX®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>238</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 ± 11</td>
<td>68 ± 10</td>
<td>0.88</td>
</tr>
<tr>
<td>Male</td>
<td>64%</td>
<td>66%</td>
<td>0.70</td>
</tr>
<tr>
<td>Height (in)</td>
<td>66 ± 4</td>
<td>67 ± 4</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>179 ± 44</td>
<td>180 ± 40</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42%</td>
<td>49%</td>
<td>0.13</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>70%</td>
<td>76%</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82%</td>
<td>89%</td>
<td>0.02*</td>
</tr>
<tr>
<td>Past/current smoker</td>
<td>84%</td>
<td>86%</td>
<td>0.70</td>
</tr>
</tbody>
</table>

* Statistically significant
## Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th>Lesion Characteristic</th>
<th>PTA</th>
<th>Zilver PTX®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>251</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>Normal-to-normal lesion length (mm)</td>
<td>63 ± 41</td>
<td>66 ± 39</td>
<td>0.35</td>
</tr>
<tr>
<td>Stenosed lesion length (mm)&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>53 ± 40</td>
<td>54 ± 41</td>
<td>0.76</td>
</tr>
<tr>
<td>Diameter stenosis (%)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>78 ± 17</td>
<td>80 ± 17</td>
<td>0.44</td>
</tr>
<tr>
<td>Total occlusions</td>
<td>25%</td>
<td>30%</td>
<td>0.20</td>
</tr>
<tr>
<td>De novo lesions</td>
<td>94%</td>
<td>95%</td>
<td>0.69</td>
</tr>
<tr>
<td>Lesion calcification&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Little</td>
<td>38%</td>
<td>26%</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>Moderate</td>
<td>22%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>35%</td>
<td>37%</td>
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</tbody>
</table>

<sup>1</sup> Angiographic core lab assessment
<sup>2</sup> Region with > 20% diameter stenosis
*Statistically significant
Safety
Event-free Survival

Primary Randomization

Enrollment

PTA

Zilver PTX

Failed PTA

Successful PTA

Secondary Randomization

Provisional Bare Zilver

Provisional Zilver PTX
24-Month Safety
Event-free Survival

Event-free Survival: Freedom from CEC-adjudicated death, amputation, and target lesion revascularization, or worsening Rutherford score (by 2 classes or to class 5 or 6)
Low Stent Fracture Rate

- 546 stents implanted
  - 453 Zilver PTX (average of 1.5 stents per patient)
  - 93 Zilver BMS

- X-ray core laboratory analysis of 457 stents at 12 months

- Four stent fractures
  - No associated adverse events

**0.9% stent fracture rate through 12 months (next evaluations at 3 and 5 years)**
12-Month Effectiveness
Primary Patency (PSVR < 2.0): Zilver PTX vs. PTA

- Zilver PTX vs. PTA (All)
  - Zilver PTX: p < 0.01
  - Successful PTA: p < 0.01

12-month Primary Patency Rate (Kaplan-Meier Estimate)
- PTA (All): 32.4%
- Successful PTA: 64.5%
- Zilver PTX: 83.1%
24-Month Effectiveness
Primary Patency (PSVR < 2.0): Zilver PTX vs. PTA

- Zilver PTX: 83.1% (Successful PTA 116 Lesions)
- PTA: 74.8% (Successful PTA 187 Lesions)
- Overall: 32.4% (All PTA 241 Lesions)

1 Excludes patients with a clinically unacceptable acute PTA result (~50% of initial PTA cohort)
2 A randomly selected subset of 56 acutely successful PTA patients assigned to long term (>12 mo) follow-up

p = 0.029
12-Month Paclitaxel Effect
Patency (PSVR < 2.0): Provisional Zilver PTX vs. BMS

- Patency Rate
  - Provisional Zilver PTX: 89.9%
  - Bare Zilver: 73.0%

- Kaplan-Meier Estimate

- p < 0.01
24-Month Paclitaxel Effect
Patency (PSVR < 2.0): Provisional Zilver PTX vs. BMS

<table>
<thead>
<tr>
<th>Provisional Group</th>
<th>24-month Restenosis Rate</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zilver PTX</td>
<td>18.8%</td>
<td>50%</td>
</tr>
<tr>
<td>Bare Zilver</td>
<td>37.3%</td>
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</tbody>
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Conclusions

• **24-month results** support sustained safety and effectiveness
  
  – Primary Zilver PTX significantly better patient safety than PTA ($p < 0.01$)
  
  – Primary Zilver PTX patency of 74.8%
  
  – Provisional Zilver PTX patency (81.2%) significantly higher than provisional BMS patency (62.7%, $p < 0.01$)
  
  – PTX coating reduces 24-month restenosis rates by 50%