The Forefront of Drug-Eluting Devices

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Disclosures

Consultant/Advisory Board:

- Abbott
- Bard
- BSCI
- Cordis
- Cook
- CSI
- Endologix
- Gore
- Lombard
- Medtronic/Covidien
- Penumbra
- Spectranetics
Paclitaxel: Properties and Mechanics

• **Hydrophobic**
  – Does not dissolve in water
    ➢ A polymer is not needed to prevent wash-off during tracking & implantation

• **Lipophilic**
  – Attracted to lipids
  – Lipids are found in high concentration in the vessel wall
    ➢ A polymer is not needed for adequate delivery to vessel wall

• **Antiproliferative**
  – Permanently prevents rapid cell division or growth of cells often seen after BMS placement
    ➢ A polymer is not needed for a long lasting effect
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).
FDA Approved Devices

• **Zilver® PTX Drug-Eluting Stent**
  - Cook Medical
    - RCT / Global Registry / Long Lesion Post Market

• **Admiral® Drug-Coated Balloon**
  - Medtronic

• **Moxy® Drug-Coated Balloon**
  - Lutonix/Bard
Drug-Eluting Stents for the Femoropopliteal Segment

Cordis Initiates SIROCCO Trial
Polymer-based Sirolimus-Eluting SmartStent™ vs. non-coated SmartStent™ in A randomized, prospective, multi-center study

Cook Initiates Zilver PTX Trial
Polymer-free Paclitaxel-eluting stent in both an RCT & a Single-arm Global Registry

Cook Medical gains CE Mark for Zilver PTX
1st DES approved for peripheral use after successfully completing Single-arm Global Registry

Cook Medical files PMA
With the FDA after completion of the Zilver PTX RCT demonstrating superiority over PTA & BMS at 12 and 24 months (12mnth PP=89% DES vs. 73% BMS)

Abbott Initiates ESPRIT I Trial
A Zirolimus-eluting, bioresorbable Scaffold evaluated in a single-arm, multi-center study of the iliac & SFA arteries which will include 30 patients at 10 European sites

Cordis II Trial
Results Published
In JVIR & concluded no Statistically significant difference Between the control & study groups at 18 & 24 months. The Sirolimus-Eluting SmartStent™ program was subsequently halted (18mnth PP=80% DES vs. 82% BMS)

Abbott Initiates STRIDES Trial
Polymer-based Everolimus-Eluting Dynalink™ Stent in a prospective, randomized, multi-center study

STRIDES Trial results published
The Everolimus-Eluting Dynalink-E™ Stent fails to demonstrate superiority to BMS at 12 months in a retrospective comparison to the VIENA Absolute Trial. The Dynalink-E™ Stent Program was subsequently halted (12mnth PP=69% DES vs. 63% BMS)

Abbott Initiates Absorb BTK Trial
In a prospective, single-arm, multi-center, European study Of a drug-eluting bioresorbable peripheral stent for treatment of BTK arterial lesions.

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Cook Medical gains FDA approval for Zilver PTX
Polymer-free paclitaxel-eluting Stent indicated for use in the femoropopliteal region

Clinical Evaluation and Regulatory Timeline
Drug-Coated Balloons for the Femoropopliteal Segment

Invatec gains CE Mark approval
1st DCB available for commercial use of the In.Pact™ Amphirion™ with FreePac™ coating (PTX + Urea)

MDT buys Invatec

MDT completes enrollment of In.Pact™ I Trial

Bard buys Lutonix

Bard completes enrollment of LEVANT II Trial
FDA requires 1000 patient PMS

MDT submits IDE with FDA for In.Pact Admiral
Demonstrating superiority over PTA at 12 months in pivotal randomized DCB trial (Patency = 82% vs. 52%) (TLR = 2.4% vs. 20%)


LEVANT I
Begins enrollment
Lutonix initiates DCB study
Enrolling 101 patients with de novo lesions of the fempop segment to evaluate the Moxy® Balloon
(PTX & Polysorbate/Sorbitol)
After predilating with an undersized, uncoated balloon

MDT commences In.Pact SFA I Trial

Lutonix Moxy® DCB Receives CE Mark & begins enrollment in LEVANT II demonstrating superiority in the LEVANT I Trial to standard PTA (TLR = 13% vs. 22%) (LLL = 0.48mm vs. 1.09mm)

MDT initiates In.Pact Global SFA Registry
Scheduled to enroll 1500 patients to gain sufficient data to support a PMA submission for the In.Pact™ Admiral™ DCB

MDT completes enrollment of In.Pact II Trial
FDA requires 1000 patient PMS

MDT Admiral® DCB Gains FDA Approval demonstrating superiority in the LEVANT II Trial to standard PTA (TLR = 2.9% vs. 22.0%) (PP =)

Feb 2014         Nov 2014       Jan 2015

Lutonix Moxy® DCB Gains FDA Approval demonstrating superiority in the LEVANT II Trial to standard PTA (TLR = 12.3% vs. 16.8%) (PP =)

MDT Admiral® DCB Gains FDA Approval demonstrating superiority in the In.Pact SFA Trial to standard PTA (TLR = 2.9% vs. 20.6%) (PP =)

MDT Admiral® DCB Gains FDA Approval demonstrating superiority in the In.Pact SFA Trial to standard PTA (TLR = 2.9% vs. 20.6%) (PP =)

Clinical Evaluation and Regulatory Timeline
Lutonix DCB Catheter 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 II Study Design

- Pivotal IDE Randomized Trial
- 476 Patients
- Moderate Lesions
- Predilatation
LEVANT II

12-Month Treatment Effect

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>MOXY</th>
<th>PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>12.3% (35/285)</td>
<td>16.8% (24/143)</td>
</tr>
<tr>
<td>Primary Patency*</td>
<td>65.2% (172/264)</td>
<td>52.6% (71/135)</td>
</tr>
</tbody>
</table>

*Protocol-defined Primary Patency is reported based on freedom from TLR and restenosis (DUS PSVR 2.5)
*Primary Patency is reported based on freedom from TLR and restenosis (DUS PSVR 2.5)
LEVANT 2 Primary Patency

Primary Patency Kaplan-Meier

$\Delta = 16.7\%$
(29.4% Improvement over PTA)

Survival %

<table>
<thead>
<tr>
<th>Time</th>
<th>Lutonix DCB</th>
<th>Standard PTA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>365 days</td>
<td>73.5%</td>
<td>56.8%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Free from Primary Patency Event (%)

Months from Randomization Date
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 SFA Study Design

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT</th>
<th>PTA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Patency (PSVR ≤ 2.4)</td>
<td>82.2% (157/191)</td>
<td>52.4% (54/103)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinically-driven TLR[^1]</td>
<td>2.4% (5/207)</td>
<td>20.6% (22/107)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All TLR[^2]</td>
<td>2.9% (6/207)</td>
<td>20.6% (22/107)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained Clinical Improv.[^3]</td>
<td>85.2% (167/196)</td>
<td>68.9% (73/106)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABI / TBI[^4]</td>
<td>0.951 ± 0.221</td>
<td>0.886 ± 0.169</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Primary Patency\(^1\) Results through 2 Years

![Graph showing the primary patency results through 2 years with Log-rank \( P < 0.001 \).]

- **1.** Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) or clinically-driven target lesion revascularization through 24 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

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1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR \( \leq 2.4 \)) or clinically-driven target lesion revascularization through 24 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
Freedom from CD-TLR through 2 Years

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 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™ Technology

- Paclitaxel drug-load 3µg / mm²
- Polymer-free delivery
- Highly flexible / Low-fracture rate
- 40mm-100mm Lengths
- Proven paclitaxel effect
Zilver PTX Study Designs

- Pivotal IDE Randomized Trial
- Global “Real World” Registry
- Long Lesion PMS

- 2100+ Patients
- Short / Moderate / Long Lesions
<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>50%</td>
<td>0.11</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></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>0.36</td>
</tr>
<tr>
<td>Stenosed lesion length (mm)&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>53 ± 40</td>
<td>55 ± 41</td>
<td>0.71</td>
</tr>
<tr>
<td>Diameter stenosis (%)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>78 ± 17</td>
<td>80 ± 17</td>
<td>0.38</td>
</tr>
<tr>
<td>Total occlusions</td>
<td>27%</td>
<td>33%</td>
<td>0.20</td>
</tr>
<tr>
<td>De novo lesions</td>
<td>94%</td>
<td>95%</td>
<td>0.68</td>
</tr>
<tr>
<td>Lesion calcification&lt;sup&gt;1&lt;/sup&gt;</td>
<td>None</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Little</td>
<td>38%</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>22%</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>35%</td>
<td>37%</td>
</tr>
</tbody>
</table>

<sup>1</sup> Angiographic core lab assessment
<sup>2</sup> Region with > 20% diameter stenosis
* Statistically significant
At 5 years, Zilver PTX demonstrates a 48% reduction in reintervention compared to standard care.
5-Year Primary Patency (PSVR ≤ 2.0)

Zilver PTX vs. Standard Care

From 1-5 years, the relative separation increases by 35%

<table>
<thead>
<tr>
<th>Years (LESIONS)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zilver PTX</td>
<td>At Risk</td>
<td>318</td>
<td>246</td>
<td>199</td>
<td>163</td>
<td>137</td>
</tr>
<tr>
<td>Failed</td>
<td>1</td>
<td>48</td>
<td>71</td>
<td>83</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>Standard Care</td>
<td>At Risk</td>
<td>183</td>
<td>108</td>
<td>64</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>Failed</td>
<td>0</td>
<td>57</td>
<td>73</td>
<td>79</td>
<td>84</td>
<td>86</td>
</tr>
</tbody>
</table>

p < 0.01 log-rank
At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to BMS.
## 5-Year Zilver PTX 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>1.9%</td>
</tr>
</tbody>
</table>

\(^1\) Kaplan-Meier estimates
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.

* Image provided by Yazan Khatib, MD. First Coast Cardiovascular Institute
Images and Case Review

History

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

Follow-up Image from 2/2015. Tried to repair the R SFA, but unfortunately subintimal and could not re-enter the stent lumen. Zilver PTX Stents were still widely patent.
THANK YOU!

Questions?