Zilver® PTX® Drug-Eluting Peripheral Stent

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Actual Treatment

Analysis of mortality must consider known treatment with paclitaxel devices

Current Status

Cook will continue working collaboratively with regulatory authorities, clinicians, and our industry partners to provide the data needed to make informed decisions for patient treatment

Patient Impact

There is no mortality signal with Zilver PTX and the current situation is limiting patient access to the proven benefits of paclitaxel devices
Zilver PTX Stent Overview

- **Coating**
  Low dose, amorphous coating with no polymer or excipient

![Diagram showing coating types and dosage ranges]

- **RCT Dosage Range**
  - DCBs
    - 0.1 – 21.7 mg
  - Zilver® PTX®
    - 0.3 – 3.5 mg
  - Eluvia™ DES
    - 0.1 – 2.4 mg
Zilver PTX Stent Overview

Coating
Low dose, amorphous coating with no polymer or excipient

Local Drug Delivery
Short-term drug delivery, no long-term paclitaxel exposure, only BMS remains
Zilver PTX Stent Overview

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Low dose, amorphous coating with no polymer or excipient

Local Drug Delivery
Short-term drug delivery, no long-term paclitaxel exposure, only BMS remains

Long-term data
Only peripheral DES with long-term safety data
### Zilver PTX Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>Follow-up</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Zilver PTX</td>
<td>5 years</td>
<td>336</td>
</tr>
<tr>
<td></td>
<td>PTA/BMS</td>
<td></td>
<td>143</td>
</tr>
<tr>
<td>Japan PMS</td>
<td>Zilver PTX</td>
<td>5 years</td>
<td>904</td>
</tr>
<tr>
<td></td>
<td>BMS</td>
<td>3 years</td>
<td>190</td>
</tr>
<tr>
<td>EU BMS</td>
<td>BMS</td>
<td>5 years</td>
<td>110</td>
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<tr>
<td>US PAS</td>
<td>Zilver PTX</td>
<td>5 years(^1)</td>
<td>200</td>
</tr>
<tr>
<td>Single-arm Study</td>
<td>Zilver PTX</td>
<td>2 years</td>
<td>787</td>
</tr>
<tr>
<td>French Reimbursement</td>
<td>Zilver PTX</td>
<td>2 years</td>
<td>119</td>
</tr>
<tr>
<td>China</td>
<td>Zilver PTX</td>
<td>1 year</td>
<td>178</td>
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<tr>
<td>REAL PTX</td>
<td>Zilver PTX</td>
<td>3 years</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>DCB(^2)</td>
<td></td>
<td>75</td>
</tr>
</tbody>
</table>

- Large studies
- Long-term follow-up
- Concurrent comparator groups

\(^1\) Ongoing  \(^2\) 77.3% INPact, 21.3% Lutonix, 1.4% Other.
TRIAL DESIGN

Primary Randomization

- Zilver PTX Group
- PTA / BMS Group

Zilver PTX Randomized Trial

PTA
n=237

Zilver PTX
n=242
Secondary Randomization

PTA n=237
Suboptimal PTA
BMS n=56
Zilver PTX n=63
Optimal PTA n=118
Zilver PTX
Secondary Randomization
Primary Randomization
Zilver PTX Group
PTA / BMS Group

TRIAL DESIGN
Early Crossover

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TRIAL DESIGN

One BMS patient received Zilver PTX during reintervention within the first year.
One BMS patient received Zilver PTX during reintervention within the first year.
Treatment Results

- Actual Treatment = Primary + Secondary + Crossover
- Primary Randomization
  - Zilver PTX: n=242
  - PTA / BMS: n=237
- Primary + Secondary Randomization
  - Zilver PTX: n=305
  - PTA / BMS: n=174
- Actual Treatment = Primary + Secondary + Crossover
  - Zilver PTX: n=336
  - PTA / BMS: n=143
Treatment Results

- Zilver PTX
- PTA / BMS

40% of patients initially randomized to PTA were actually treated with Zilver PTX.

Actual Treatment = Primary + Secondary + Crossover
### RCT Actual Treatment

<table>
<thead>
<tr>
<th>Survival</th>
<th>Years</th>
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<tr>
<td>100%</td>
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</tr>
<tr>
<td>90%</td>
<td>1</td>
</tr>
<tr>
<td>80%</td>
<td>2</td>
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<tr>
<td>70%</td>
<td>3</td>
</tr>
<tr>
<td>60%</td>
<td>4</td>
</tr>
<tr>
<td>50%</td>
<td>5</td>
</tr>
<tr>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

#### PTA/BMS
- n=143
- Died=23
- KM=17.1%

#### Zilver PTX
- n=336
- Died=61
- KM=19.1%

- p=0.60

- 5-year vital status for 94% of patients
- All patients analyzed by actual treatment
- No mortality signal
Japan Post-Market Studies

- Large, real-world; no exclusion criteria
- No increase in rate of mortality after 3 years
- No mortality signal
Covariate Analysis

• No mortality signal for Zilver PTX when evaluating actual treatment
• What factors were associated with mortality?
Comorbidities common in PAD patients were the significant predictors of mortality.

- Zilver PTX not a predictor of mortality.
Comorbidities common in PAD patients were the significant predictors of mortality.

Zilver PTX not a predictor of mortality.
Covariate Analysis: Dose

- Paclitaxel analyzed by dose (mg) per patient
- Significant predictors same as treatment arm analysis
  - RCT: Age, tissue loss, CHF
  - Japan: CLI, renal failure, gender, age, hypercholesterolemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>1.034 (0.718, 1.490)</td>
<td>0.86</td>
</tr>
<tr>
<td>Japan</td>
<td>1.201 (0.987, 1.461)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

- Paclitaxel dose not a predictor of mortality
Conclusion

- Analysis must be based on actual treatment
  Protocol defined secondary randomization and crossover must not be ignored

- No mortality signal with Zilver PTX
  When data are appropriately analyzed
Paclitaxel-Coated Zilver PTX Drug-Eluting Stent Treatment Does Not Result in Increased Long-Term All-Cause Mortality Compared to Uncoated Devices

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The patient-level data used for the analyses presented here is available on the following website:

https://www.cookmedical.com/peripheral-intervention/paclitaxel/