FDA ADVISORY PANEL

Zilver® PTX® Drug-Eluting Peripheral Stent

Circulatory Systems Device Panel Meeting
Introduction

Aaron Lottes, PhD
Lead Scientist for Zilver PTX
Director Regulatory Science
PAD Therapies
Cook Medical

Michael Dake, MD
Global Principal Investigator for Zilver PTX
Senior Vice President of Health Sciences,
Professor of Medical Imaging, Medicine,
and Surgery, University of Arizona,
Tucson/Phoenix
Paid consultant of Cook Medical
Cook Medical’s 25 Year History with Paclitaxel

- 1995: Cook begins using PTX on coronary stents
- 2000: First FDA submission for Zilver PTX
- 2002: Zilver coated with PTX
- 2003: Zilver PTX IDE submitted
- 2005: First patient enrolled in PTX study
- 2008: DCB Study Started
- 2009: Renal Study Started
- 2010: 5-year follow-up and US post-approval study
- 2011: CE approval of Zilver PTX and Japan post-approval study
- 2012: US & Japan Zilver PTX approval and Japan post-approval study
- 2013: RCT 5-year follow-up
- 2018: Japan 5-year follow-up study

- No mortality signal in 25 years, across multiple studies and devices
Overview

- **Purest Data on Paclitaxel**
  Because other paclitaxel devices were not yet approved, the Zilver PTX RCT and Japan PMS provide the best data available to look at paclitaxel treatment.

- **Actual Treatment**
  Any analysis that does not consider known paclitaxel treatment is inappropriate for analyzing mortality and simply does not make sense.

- **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.
Durable results through 5 years

- Greater than 40% reduction in restenosis
- Greater than 40% reduction in reinterventions
- Proven clinical benefit in real-world patients
Zilver PTX

Device Overview

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

![Device Image]

RCT Dosage Range

- **DCBs**
  - 0.1 – 21.7 mg

- **Zilver® PTX®**
  - 0.3 – 3.5 mg

- **Eluvia™ DES**
  - 0.1 – 2.4 mg
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

Device Overview

Coating
Low dose, amorphous coating with no polymer or excipient

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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

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1 Ongoing  

>1,000 patients to support US approval  

>2,500 patients in global pre- and post-market studies  

>300,000 stents to treat patients globally  

¹ Ongoing  

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

- Large studies
- Long-term follow-up
- Concurrent comparator groups
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¹ Ongoing ² 77.3% INPact, 21.3% Lutonix, 1.4% Other.

- No exclusion criteria
- All treated patients enrolled
- Pure treatment comparison
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¹ Ongoing ² 77.3% INPact, 21.3% Lutonix, 1.4% Other.

- Trial designed with multidisciplinary physician input and approval from FDA, PMDA, and BfArM
Primary Randomization

Zilver PTX Group

PTA / BMS Group

Zilver PTX Randomized Trial

PTA
n=237

Zilver PTX
n=242
Secondary Randomization

- **Zilver PTX Group**
- **PTA / BMS Group**

**Primary Randomization**
- **PTA**
  - n=237
- **Zilver PTX Randomized Trial**
  - n=242

**Secondary Randomization**
- **Suboptimal PTA**
  - BMS n=56
  - Zilver PTX n=63
- **Optimal PTA**
  - n=118
Early Crossover

Trial Design

Primary Randomization

PTA
n=237

Suboptimal PTA

Zilver PTX Randomized Trial

Zilver PTX
n=242

Optimal PTA
n=118

Median: 183 days

Protocol:
Reintervention in the first year

PTA / BMS Group

Zilver PTX Group

BMS
n=56

Zilver PTX
n=63

Secondary Randomization

One BMS patient received Zilver PTX during reintervention within the first year.
TRIAL DESIGN

Actual Treatment

- Zilver PTX Group
- PTA / BMS Group

**Zilver PTX Randomized Trial**

**Primary Randomization**

**PTA**
- n=237

**Suboptimal PTA**

**Optimal PTA**
- n=118

**Secondary Randomization**

**BMS**
- n=56

**Zilver PTX**
- n=63

Protocol: Reintervention in the first year

- Zilver PTX
  - n=30

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

Primary Randomization

Primary Randomization

Actual Treatment = Primary + Secondary + Crossover

n=242
n=237
n=305
n=174
n=336
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

- 40%
- Zilver PTX
- PTA / BMS
Results

Michael Dake, MD
Global Principal Investigator for Zilver PTX
Primary Randomization

Intent to treat is considered the standard for effectiveness

Based on international standards, to evaluate safety we must analyze how patients were treated\(^1\), not how they were randomized

\(^1\) ICH E9: statistical principles for clinical trials, Section 6.3
Zilver PTX Patients in PTA/BMS Group

- Primary Zilver PTX: n=242
- Secondary + Crossover Zilver PTX: n=94
- PTA / BMS: n=143

40% Zilver PTX Patients in PTA/BMS Group
Zilver PTX Results Attributed to PTA/BMS

- 40% of the PTA/BMS group was treated with Zilver PTX
- Any analysis based on intent to treat is inappropriate for assessing paclitaxel mortality
Secondary Randomization

- Primary: Zilver PTX, n=242
- Secondary: Zilver PTX, n=174
- PTA / BMS, n=63
Early Crossover

- **Primary Zilver PTX**: n=242
- **Secondary Zilver PTX**: n=143
- **PTA / BMS**: n=63
- **Crossover Zilver PTX**: 18%

Crossover Zilver PTX: 18% of the primary group
Analyses by Katsanos, et al and FDA do not account for 18% of patients treated with Zilver PTX.

Zilver PTX mortality results were attributed to PTA/BMS group.
Paclitaxel Mortality Meta-Analysis

- Original analysis including 18% Zilver PTX in Control Group
- Analysis including actual Zilver PTX treatment

- Evaluating all patients treated with Zilver PTX changes the conclusion
- In addition, the result of the meta-analysis becomes non-significant

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Actual treatment is an appropriate assessment of paclitaxel-related mortality.

FDA modified as-treated analysis and Cook analysis include actual treatment.
All patients analyzed by actual treatment

No mortality signal
Includes new patient status for 92% of patients previously lost-to follow-up

Added data confirmed no mortality signal
ZILVER PTX RCT

Randomized Comparison to BMS

- Head-to-head comparison of Zilver PTX to BMS
- No mortality signal
Large, real-world, post-market studies

No increase in rate of mortality after 3 years

No mortality signal

Japan PMS: No Mortality Signal

**Japan PMS: No Mortality Signal**

- **BMS**
  - n=190
  - Died=22
  - 3 year KM=15.3%
  - 5 year KM=N/A

- **Zilver PTX**
  - n=904
  - Died=185
  - 3 year KM=15.6%
  - 5 year KM=25.7%

\[ p = 0.92 \]
Covariate Analysis

- No mortality signal for Zilver PTX when evaluating actual treatment
- What factors were associated with mortality?
Additional non-significant factors included: smoking status, country, CLI/claudication, lesion length, previous MI, BMI
Covariate Analysis

<table>
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<tr>
<th>Covariate</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Tissue Loss</td>
<td>2.277 (1.117, 4.640)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1.962 (1.022, 3.764)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>1.777 (0.962, 3.282)</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.601 (0.979, 2.617)</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Arhythmia</td>
<td>1.527 (0.790, 2.953)</td>
<td>ns</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>1.444 (0.824, 2.532)</td>
<td>ns</td>
</tr>
<tr>
<td>Carotid Disease</td>
<td>1.372 (0.792, 2.378)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.352 (0.739, 2.473)</td>
<td>ns</td>
</tr>
<tr>
<td>Male vs Female</td>
<td>1.272 (0.754, 2.145)</td>
<td>ns</td>
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<tr>
<td>Zilver PTX</td>
<td>1.202 (0.698, 2.070)</td>
<td>p=0.51</td>
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<tr>
<td>Hypertension</td>
<td>1.130 (0.523, 2.441)</td>
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<tr>
<td>Age (yr)</td>
<td>1.062 (1.029, 1.095)</td>
<td>p&lt;0.001</td>
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Additional non-significant factors included: smoking status, country, CLI/claudication, lesion length, previous MI, BMI
Comorbidities common in PAD patients were the significant predictors of mortality.

Zilver PTX not a predictor of mortality.

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<td>Zilver PTX</td>
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<td>Age (yr)</td>
<td>1.045 (1.026, 1.064)</td>
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Additional non-significant factors included: smoking status, lesion length
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### Covariate Analysis

- **Comorbidities common in PAD patients were the significant predictors of mortality**

- **Zilver PTX not a predictor of mortality**

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Covariate Analysis: Dose

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

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Paclitaxel dose **not** a predictor of mortality

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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

- Patient care is being negatively impacted