Fluorocopolymer-coated Nitinol self-expanding Paclitaxel-eluting stent:
Pharmacokinetics and vascular biology responses in porcine iliofemoral model

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below:


- **Consulting Fees/Honoraria:** None

- **Major Stock Shareholder/Equity:** KCRI, LLC

- **Royalty Income:** None
## Coating Design Specifications

<table>
<thead>
<tr>
<th></th>
<th>Zilver PTX</th>
<th>Eluvia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medicinal Substance</strong></td>
<td>Paclitaxel</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td><strong>Coating Design</strong></td>
<td>No carrier</td>
<td>Proven PROMUS Polymer</td>
</tr>
<tr>
<td><strong>Drug/Total Dose</strong></td>
<td>3µg/mm² 8 x 120mm = 1112 µg</td>
<td>0.167µg/mm² 7 x 150mm = 517 µg</td>
</tr>
<tr>
<td><strong>Size Matrix</strong></td>
<td>6-8mm 40-120mm</td>
<td>6 &amp; 7mm 40-150 mm</td>
</tr>
<tr>
<td><strong>SEM Image 100x</strong></td>
<td><img src="image1.png" alt="SEM Image" /></td>
<td><img src="image2.png" alt="SEM Image" /></td>
</tr>
</tbody>
</table>

The Eluvia Drug-Eluting Vascular Stent is an investigational device, not available for sale in the European Economic Area (EEA).
DES Treatment in a Preclinical Model of Peripheral Artery Restenosis

Fluorocopolymer Coated Self-expanding Low-dose Paclitaxel-eluting Stent in Porcine Ilio-femoral Model

- Paclitaxel was released steadily with limited initial burst phase followed by a sustained controlled release phase.
- The amount of paclitaxel found in the heart, liver, and systemic blood were below quantifiable levels at every time point.

12 pigs, up four 20 mm stents per animal
Arterial, heart, liver and residual stent paclitaxel content were analyzed at 4, 10, 30, 60, 90 and 180 days (n=8 stents/time-point)

Hou, D. TCT 2012.
Porcine model results not necessarily indicative of clinical performance.
DES Treatment in a Preclinical Model of Peripheral Artery Restenosis

Fluorocopolymer Coated Self-expanding Low-dose Paclitaxel-eluting Stent in Porcine Ilio-femoral Model

- Neointimal thickness was significantly inhibited by FP-PES compared to BMS at 30 and 90 days ($P=0.001$, respectively), yielding reductions of in-stent stenosis by 48.1% and 51.9% for FP-PES vs. BMS ($P=0.005$ and $P<0.0001$, respectively).
- No differences in any of the histomorphometric parameters were apparent at 180 days.

- 37 pigs, used two 80 mm stents per animal
- Either FP-PES or BMS (bare metal stent) was implanted with 1.0 to 2.0 mm size up to the baseline vessel diameter. Animals were sacrificed at 30, 90 and 180 days (n=12 stents/time-point) after repeat angiogram.

Hou, D. TCT 2012.
Porcine model results not necessarily indicative of clinical performance.
Lipoprotein Mutations in Pigs Are Associated with Elevated Plasma Cholesterol and Atherosclerosis

Jan Rapacz, Judith Hasler-Rapacz, Katherine M. Taylor, William J. Checovich, Alan D. Attie

Science. 1986 Dec 19;234(4783):1573-7
Concentrations and compositions of plasma lipoprotein subfractions of Lpb5-Lpu1 homozygous and heterozygous swine with hypercholesterolemia

Diana M. Lee,† Tina Mok, * Judith Hasler-Rapacz, ** and Jan Rapacz**
Lipoprotein and Atherosclerosis Research Program,* Oklahoma Medical Research Foundation, and the Department of Biochemistry and Molecular Biology, † University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, and Department of Genetics and Department of Meat and Animal Science,** University of Wisconsin, Madison, WI 53706

Familial Hypercholesterolemia Associated with Coronary Atherosclerosis in Swine Bearing Different Alleles for Apolipoprotein B

Margaret Forney Prescott, Judith Hasler-Rapacz, Jean Von Linden-Reed, and Jan Rapacz
Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, New Jersey 07901
*Department of Genetics and Meat and Animal Science, University of Wisconsin, Madison, Wisconsin 53706

Ann N Y Acad Sci. 1995 Jan 17;748:283-92
Typical Cholesterol Profile
Domestic versus FH Swine

- **Domestic Swine**: 70 mg/dl
- **FH Swine**: 490 mg/dl

- **LDL-Cholesterol**:
  - Domestic Swine: 41.5 mg/dl
  - FH Swine: 410 mg/dl

$p < 0.01$
FHS Swine Predicts Antirestenotic Efficacy of Peripheral DCB in a Dose-Dependent Manner
FHS Swine Predicts Antirestenotic Efficacy of Peripheral DCB in a Dose-Dependent Manner

- All DCBs showed significant inhibition of neointimal formation when compared to the uncoated balloon control.
- The In.Pact DCB provided strongest neointimal inhibition but less complete healing.
- The Ranger DCB provided satisfactory neointimal inhibition and a slightly better healing in comparison to In.Pact.
Study Design and Methods

Mean TC: 389±63 mg/dL 686±94 mg/dL 664±58 mg/dL

Balloon Injury, Stent Implant + baseline imaging (pre & post)

First imaging f/u for all animals

Second imaging prior to termination and histology

High cholesterol diet for 180 days

-7 days Day 0 30 days 90 days 180 days

18 FHS: Eluvia n=12 Zilver n=12 Innova BMS n=12
9 FHS: Eluvia n=6 Zilver n=6 Innova BMS n=6
9 FHS: Eluvia n=6 Zilver n=6 Innova BMS n=6

- 1:1:1 Eluvia : Zilver : Innova randomization
- Imaging: QVA and OCT
- Histology: Histomorphology and histomorphometry
- Histochemistry and Immunohistochemistry
OCT Results at 30 Days (n=12)

- **Lumen Area**
  - BMS: 6.06 mm²
  - Zilver DES: 18.37 mm²
  - Eluvia DES: 19.49 mm²

- **Stent Area**
  - BMS: 17.94 mm²
  - Zilver DES: 22.18 mm²
  - Eluvia DES: 23.15 mm²

- **Neointimal Area**
  - BMS: 11.87 mm²
  - Zilver DES: 3.81 mm²
  - Eluvia DES: 3.67 mm²

- **% Area Stenosis**
  - BMS: 86%
  - Zilver DES: 17%
  - Eluvia DES: 16%
OCT Results: Change from 30 to 90 Days (n=6)

**Lumen Area**
- Control: 4.95, 7.86
- BSC Eluvia DES: 19.88, 17.79
- Zilver PTx DES: 19.31, 10.23

**Stent Area**
- Control: 17.94, 23.45
- BSC Eluvia DES: 23.1, 25.21
- Zilver PTx DES: 22.8, 21.70

**Neointimal Area**
- Control: 12.99, 15.58
- BSC Eluvia DES: 3.22, 7.42
- Zilver PTx DES: 3.51, 11.47

**% AS**
- Control: 81%, 78%
- BSC Eluvia DES: 14%, 30%
- Zilver PTx DES: 15%, 53%
Angio & OCT Images from Day 0 to Day 90

BMS Day 0

Zilver Day 0

Eluvia Day 0
Angio & OCT Images from Day 0 to Day 90

BMS Day 30

Zilver Day 30

Eluvia Day 30
Angio & OCT Images from Day 0 to Day 90

- BMS Day 90
- Zilver Day 90
- Eluvia Day 90
OCT Results: Neointimal Distribution at 30 and 90 Days (n=6)

Neointimal Thickness

<table>
<thead>
<tr>
<th>Stent Segment</th>
<th>Neointimal Distribution - BMS</th>
<th>Neointimal Distribution - Eluvia DES</th>
<th>Neointimal Distribution - Zilver PTX DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC Eluvia DES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilver PTx DES</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>30-Day</td>
<td></td>
<td></td>
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<tr>
<td>90-Day</td>
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Neointimal Thickness (mm)

OCT Results: Neointimal Distribution at 30 and 90 Days (n=6)
In the 30-day imaging data, both Zilver and Eluvia DES achieve profound antirestenotic effect in comparison to the BMS in the porcine model of peripheral atherosclerosis.

Partial, interim 90-day imaging data suggest that in both DES the neointimal proliferation progressed between 30 and 90 days whereas in the BMS it appeared complete. Both DES continued to be superior to BMS in terms of restenosis metrics. However, in contrast to the 30-day data, Eluvia demonstrated significantly lower amount of neointima than Zilver.

The pattern of neointimal coverage appears more uniform longitudinally in Eluvia when compared to Zilver.

We are looking forward to the 90-day imaging data in the remaining 6 animals, as well as to the complete 180-day data. Both 90-day and 180-day animals will also generate histopathologic data which may provide further insight into how these 2 peripheral DES technologies may differ.
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