Inhibiting Intimal Vessel Hyperplasia through Local Delivery of Anti-Proliferative Drug: Medtronic Drug-Coated Balloon

CLAUDIO SILVESTRO
Research & Development
Medtronic Aortic and Peripheral Vascular
Medtronic Drug Coated Balloon (DCB) group

Part of *Medtronic Aortic and Peripheral Vascular (APV)*

Headquarters: Santa Rosa, CA

Other sites:
- Galway, IRL (manufacturing)
- Brescia, IT (catheter design)

**Peripheral segment**

Stents and balloon catheters for the interventional treatment of narrowed arteries beyond the heart and brain, carrying blood throughout the body to the lower extremities

APV: $895 million - 5% of Medtronic $17 billion total revenue in FY2014
Medtronic’s history with DCB

Medtronic has worked with the original inventors of DCB, building on our combination device expertise from Drug Eluting Stents to develop next generation technology.

First DCB: Paccocath™ 2001

Supported by Schering, Prof. Speck from the University of Berlin combines his contrast media Ultravist with Paclitaxel to develop the “Paccocath™” clinical prototype DCB.

Results by Dr. Scheller show reduced restenosis vs. POBA.

Invatec/Inventors Optimize Coating 2008

Prof. Speck collaborates with Invatec on optimized coating technology, selects organic molecule, urea, as drug excipient.

Medtronic Acquires Invatec 2010

Medtronic leverages 10 years of advanced combination product expertise to advance DCB manufacturing and coating characterization.
Medtronic DCB technology

Medtronic Drug Coated Balloon catheters: The combination of 4 main components

- **Platform**: Admiral PTA balloon
- **Drug**: Paclitaxel (Hydrophobic, lipophilic, anti-proliferative drug, 3.5 µg/mm²)
- **Excipient**: Urea (Facilitates drug transfer to vessel wall. Hydrophilic, naturally occurring, non-toxic)
- **Coating process**: Medtronic (Reliable, scalable, uniform drug coating process)
DCB mechanism of action

IN.PACT Admiral balloon matrix coating:
- Paclitaxel
- Urea - excipient that controls drug release

DCB inflation:
- Matrix coating contact with the blood
- Urea hydrates causing the release of paclitaxel
- Paclitaxel binds to the wall due to its hydrophobic and lipophilic properties

Paclitaxel penetration:
- Through vessel wall deep into the media and adventitia
- Interferes with the causes of restenosis
- Can remain in the vessel wall for over 180 days at therapeutic levels

¹Data on file at Medtronic (GLP Study FS208; GLP Study PS516)
Mechanism of action (video)

- Stenotic lesion
- Anti-proliferative Paclitaxel coating
- PTA balloon catheter
- Guide wire
Mechanism of action (video)
THE CATHETER
IN.PACT Admiral

*Medtronic Drug-Coated Balloon catheter for the treatment of SFA*

- FDA-approved for US commercialization: Dec 2014
- Based on PTA balloon catheter platform commercialized in the US since 2006
- On the market in Europe since June 2009
- Used in close to 100,000 patients (out-of-US) prior to FDA clearance

*Indications for Use*

Percutaneous transluminal angioplasty, after pre-dilatation, of *de novo* or restenotic lesions up to 180 mm in length in native superficial femoral or popliteal arteries with 4-7 mm vessel diameters
THE DRUG
The drug: Paclitaxel

- Lipophilic and is retained well in tissues (up to 6 months)
- Eliminates cells that cause restenosis (triggers apoptosis, durable effect)

Paclitaxel (Cytotoxic) *Interferes with cell division*

Rapamycin/Sirolimus (Cytostatic) *Interferes with cell growth*

Cytotoxic drugs stabilize microtubules, preventing division in the final stages of the cellular replication cycle and leading to cell death (apoptosis)

Cytostatic drugs hold a cell in G₀ phase, arresting growth but allowing cell to continue functioning.
Differences with Limus compounds

- Limus compounds have low stability (susceptible to oxidation) so require a durable implant and stabilizers to be effective over time
  - When used in coronary DES, limus drugs are often combined with BHT antioxidant and protected within a polymer matrix

- Limus compounds have a minimal long-term biological effect, temporarily inhibiting cell growth.
  - Paclitaxel fully blocks cell division and triggers cell death (apoptosis)

- Paclitaxel is highly stable and potent so can function alone without a durable implant over a long period of time
Identifying optimal drug dose

- Dose-dependent response up to 3-4 µg/mm² (effective dose)
- Wide, stable therapeutic window with no statistically significant differences in neointimal inhibition or local toxic effects up to 10 µg/mm²
- Clinically effective drug levels transfer within 60 seconds, with no negative clinical effects from longer inflation time

THE EXCIPIENT
The excipient: urea

- **Hydrophilic molecule**

- **Naturally produced by the body**
  - One of most common substances in human serum (100–500 mg/l)
  - Synthesized in the liver (18–35 g/day)
  - Used by the body to detoxify and excrete nitrogen derived from proteins
  - Has very low toxicity and no hypersensitivity reactions

- **Maximum amount of urea on a balloon: 1.2 mg**
  - 20,000 times less than what the body produces in a single day

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2. Internal White Paper, IN.PACT™ Admiral, Paclitaxel-eluting PTA Catheter, Justification for Urea and Paclitaxel use in Coating Formulation with Respect to Reproductive Toxicity, Genotoxicity and Carcinogenicity
3. Image: Copyright © Benjamin Cummings, an imprint of Addison Wesley Longman, Inc.
The excipient’s role

- Facilitates the transfer of paclitaxel deep into vessel tissue
- Acts as a molecular spacer to increase paclitaxel surface exposure
- Facilitates paclitaxel transfer through its hydrophilic properties

**Tissue Concentration**

<table>
<thead>
<tr>
<th>Time</th>
<th>PTX only (no carrier)</th>
<th>PTX + Iopromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td>2000</td>
<td>3000</td>
</tr>
<tr>
<td>24 hrs</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>72 hrs</td>
<td>0</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Blood Concentration**

<table>
<thead>
<tr>
<th>Time</th>
<th>PTX only (no carrier)</th>
<th>PTX + Iopromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>3346.7</td>
<td>712.8</td>
</tr>
<tr>
<td>30 min</td>
<td>11.0</td>
<td>7.6</td>
</tr>
<tr>
<td>1 hr</td>
<td>6.2</td>
<td>5.1</td>
</tr>
<tr>
<td>3 hrs</td>
<td>2.4</td>
<td>3.4</td>
</tr>
<tr>
<td>24 hrs</td>
<td>0.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

R. Virmani – CIRSE 2012 Oral Presentation
THE COATING TECHNOLOGY
Medtronic’s coating technology

Provides reliable and uniform drug delivery

**DESIGN OBJECTIVE:**
**DURABLE / SCALABLE COATING**

Balloon coating in semi-inflated shape:

~ 60-70% of dose protected within balloon folds

**DESIGN OBJECTIVE:**
**UNIFORM COATING**

Longitudinal Coating Thickness

Circumferential Coating
ASSESSING DCB CATHETER PERFORMANCE
How to assess performance

- *in-vitro* testing

- *in-vivo* animal studies

- Clinical studies
## Functional Testing
- Complete PTA Balloon testing on finished product
  - Dimensional (length, profile, etc.)
  - Balloon Preparation
  - Balloon Rated Burst Pressure
  - Balloon Fatigue
  - Balloon Compliance (Diameter vs. Pressure)
  - Balloon Inflation / Deflation Time
  - Tensile Strength
  - Catheter Kink
  - Torque Strength

## Biocompatibility
- Standard ISO10993 Testing

## Coating Integrity and Analytical Testing
- Submerge and Deploy (S&D) Particulate
- Acute Track and Deploy (AT&D) Particulate (Simulated Use)
- Coating Uniformity
- Related Substances
- Residual Solvents
- Urea
- Elution (Drug Release)

## CMC Information
- Potency
- Related Substances
- Residual Solvents
**In-vitro testing: coating uniformity**

Drug uniformity verified both length-wise and circumferentially.

**Potency Along the Length (UPLC)**

- Balloon section definition
- 20 mm, 20 mm, 20 mm, 20 mm

**Circumferential Uniformity**
- ±2% for 6.0x120 mm

**Coating Thickness Uniformity**
- ±6% for 6.0x120 mm
Preclinical animal studies: drug levels

The vast majority of the particulate transfers to the arterial tissue.

Drug in Plasma

- Levels found in plasma were low
- 50% decline in first 30 min
- No detectable levels at day 7

Drug in Distal Muscle Tissue

- 1-2 orders of magnitude lower than arterial tissue
- No detectable levels after 90 days

*Porcine ilio-femoral model* - Data on file at Medtronic Inc.
Preclinical animal studies: drug levels

Drug in arterial tissue

- Nominal (1X) and safety margin (3X) doses were assessed by animal study.
- Detectable levels of paclitaxel were seen up to 180 days in both arms.
- No drug was quantified at 320 days post-treatment with the nominal dose.

Porcine ilio-femoral model - Data on file at Medtronic Inc.
Clinical studies

Different levels of evidence depending on:

• Study design:
  • single vs multicenter
  • retrospective vs prospective
  • randomized vs single-arm

• Patients demographics

• Primary endpoints
Medtronic DCB clinical studies

- **IN.PACT SFA**: 2-phase randomized clinical trial assessing the safety and efficacy of Medtronic device as compared to standard PTA in the treatment of SFA and proximal popliteal disease

- **IN.PACT Global**: single-arm study evaluating a more complex patient population including in-stent restenosis, longer lesions, more chronic total occlusions and popliteal involvement, and a higher Rutherford classification

### Key Population Differences

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IN.PACT SFA (DCB Arm) n = 220</th>
<th>IN.PACT Global n = 655</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Lesion Length</td>
<td>8.9 cm</td>
<td>12.2 cm</td>
</tr>
<tr>
<td>Chronic Total Occlusion (CTO)</td>
<td>25.8%</td>
<td>35.8%</td>
</tr>
<tr>
<td>In-Stent Restenosis (ISR)</td>
<td>0.0%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Baseline Rutherford Classification (RC) &gt; 3</td>
<td>5.0%</td>
<td>14.6%</td>
</tr>
</tbody>
</table>
# Medtronic DCB clinical studies

<table>
<thead>
<tr>
<th>IN.PACT SFA</th>
<th>IN.PACT GLOBAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Type</strong></td>
<td><strong>Single-Arm Study</strong></td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td></td>
</tr>
<tr>
<td>Efficacy: Primary Patency(^1)</td>
<td>Efficacy: Freedom from CD-TLR (All Subjects)(^3)</td>
</tr>
<tr>
<td>Safety: Safety Composite(^2)</td>
<td>Efficacy: Primary Patency (Imaging Cohort)</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Rigor + Quality</strong></td>
<td><strong>Prospective, Multicenter</strong></td>
</tr>
<tr>
<td>Independent adjudication by Clinical Events Committee and Imaging Core Labs*</td>
<td>External Monitoring</td>
</tr>
<tr>
<td><strong># Patients</strong></td>
<td></td>
</tr>
<tr>
<td>331 patients</td>
<td>1500+ patients</td>
</tr>
<tr>
<td><strong># Sites &amp; Location</strong></td>
<td></td>
</tr>
<tr>
<td>57 sites (US, EU)</td>
<td>~67 sites Global</td>
</tr>
<tr>
<td><strong>Key Eligibility Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Single lesions ≤18 cm, CTO ≤10 cm</td>
<td>Single or multiple lesions ≥ 2 cm</td>
</tr>
<tr>
<td>TASC A-C</td>
<td>All TASC</td>
</tr>
<tr>
<td>SFA + Proximal Popliteal</td>
<td>SFA + Full Popliteal</td>
</tr>
<tr>
<td>No ISR, Ca++</td>
<td>ISR, Ca++, CTO (including ≥ 10 cm)</td>
</tr>
</tbody>
</table>

*IN.PACT Global Study: Only imaging cohort Core Lab Adjudicated (Long lesions, CTO, ISR)
1. Freedom from CD-TLR and DUS-derived restenosis (PSVR ≤2.4) at 12m
2. Composite 30-day freedom for device-and procedure-related mortality and 12-month freedom from major target limb amputation and CD-TVR
3. Defined as TLR due to symptoms or drop of ABI/TBI of >20% or >0.15 when compared to post-procedure baseline ABI/TBI
Patients demographics

IN.PACT SFA and IN.PACT Global Patient Population Comparison

<table>
<thead>
<tr>
<th>Category</th>
<th>IN.PACT SFA (DCB Arm)</th>
<th>IN.PACT Global (First 655 Subjects)</th>
</tr>
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<tbody>
<tr>
<td>Mean Lesion Length (cm)</td>
<td>8.9</td>
<td>25.8</td>
</tr>
<tr>
<td>CTO (%)</td>
<td>12.2</td>
<td>35.8</td>
</tr>
<tr>
<td>ISR (%)†</td>
<td>0.0</td>
<td>21.4</td>
</tr>
<tr>
<td>Popliteal (%)</td>
<td>6.8</td>
<td>29.4</td>
</tr>
<tr>
<td>Baseline RC &gt;3 (%)</td>
<td>5.0</td>
<td>14.5</td>
</tr>
<tr>
<td>Baseline ABI/TBI (mmHg ratio)</td>
<td>0.769</td>
<td>0.675</td>
</tr>
</tbody>
</table>

† ISR indication is not approved in the US by the FDA.

*Qualitative Comparison. Not Meant for Head-to-Head Comparison.
1. Primary patency is defined as freedom from clinically-driven TLR and freedom from restenosis as determined by DUS PSVR ≤2.4.
2. Clinically-driven TLR defined as any re-intervention due to symptoms or drop of ABI/TBI of >20% or >0.15 compared to post-procedure ABI/TBI.
IN.PACT Global results reinforce outcomes from the IN.PACT SFA trial

Weighted Average of 12-Month Reported TLR Rates

- **PTA**: 26.4%
- **BMS**: 14.3%
- **DES**: 10.2%
- **IN.PACT Global**: 8.7%
- **IN.PACT SFA**: 2.4%

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7. Tepe, G Charing Cross Symposium 2014; London, UK
17. Dake MD et al. J Endovasc Ther 2011; 18:613-23
18. Ansel, G. TCT 2014; Washington, DC
## DCB clinical trials 12-month results summary

### Results

<table>
<thead>
<tr>
<th>Results</th>
<th>IN.PACT SFA (DCB Arm, N=220)</th>
<th>IN.PACT Global N=655</th>
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<tr>
<td>CD-TLR</td>
<td>2.4%</td>
<td>8.7%</td>
</tr>
<tr>
<td>CD-TVR</td>
<td>4.3%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Target Limb Major Amputation</td>
<td>0.0% (0)</td>
<td>0.3% (2)</td>
</tr>
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### Baseline Lesion and Clinical Characteristics

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*ISR indication is not approved in the US*
CHALLENGES AND FUTURE DEVELOPMENT
Calcified lesions

- Objective: Assess effect of calcium on IN.PACT DCB efficacy
- 60-patient registry
- SFA de-novo: average Lesion Length 6.1 cm
- Chronic Total Occlusion: 31.7%
- Systematic PTA pre-dilatation followed by IN.PACT DCB

- Calcium distribution and severity affect Late Lumen Loss and Primary Patency
- Severe calcium may represent a barrier to drug absorption

F. Fanelli  LINC 2013  Calcium distribution evaluation by CTA (circumferential) and DSA (longitudinal)