New Data to Shape the Era of Drug Elution in Peripheral Interventions

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New York
Lower Extremity Endovascular - Interventions

SFA

- PTA

- Atherectomy

- Stents/stent grafts

- Drug coated stents

- Drug Coated Balloons
Adoption of SFA Therapies

- **SFA is a uniquely challenging artery**
  - Long lesions (20+ cm)
  - Mechanical forces twist & bend
  - Frequent presence of hard calcium
  - Many lesions require mechanical scaffold

- **DE clinical data is driving real world adoption**

- **Adjunctive atherectomy + DCB a growing trend**
SFA Lesion Complexity Drives Therapy Selection

* TransAtlantic Inter-Society Consensus (TASC II) Lesion Classification (Type A, B, C, D) for peripheral artery disease
Potential advantages of DES

- Equal/better efficacy in long, real world lesions
- Calcium has not been demonstrated to reduce effectiveness of DES, unlike DCB
- Scaffolding not a question
  - Removes the “art” of judging whether acute result will hold up
  - Reduces/eliminates the acute occlusion risk
- Only long term data available
- May be more cost effective
  - Reduces inventory
Mechanism of Action and Preclinical Data: The Eluvia Drug Eluting Stent Clinical Program
1. Self-expanding nitinol
2. Innova stent platform
3. Biostable polymer matrix
4. Paclitaxel

- 6F Tri-axial SDS, 0.035” guidewire compatible

The Eluvia Drug-Eluting Vascular Stent is an investigational device, not available for sale in the European Economic Area (EEA) or the U.S.
Balanced geometry designed for even stress distribution and optimal radial strength

Spacing of interconnects provides balanced stress distribution for all deformation modes

Width, Length and angles optimized for maximum strength

Stent Fracture rates in studies using the INNOVA Stent platform:
- SuperNOVA Study (Innova): 1.88% at 12M
- The MAJESTIC Study (Eluvia): 0.0% at 12M

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Anti-proliferative Addresses
Restenotic Cascade

Balloon inflation or stent deployment in atherosclerotic vessel
- Crush plaque
- Stretch artery
- De-endothelialization

Platelets and fibrin deposited at injured site
- Signaling cascades
- Inflammatory response

Neointimal Proliferation
- Smooth muscle cell (SMC) migration
- Cellular division

Restenosis
- Extracellular matrix production
- Re-endothelialization

Antiproliferative Agents
- Reduce inflammation
- Arrest mitosis
- Inhibit SMC migration

Immediate
- days
- weeks
- months

Timing of SFA restenosis is longer compared to coronary stenting, which predominantly occurs within 6 months after stenting.

Factors for restenosis in the SFA include the number of runoff vessels, severity of lower limb ischemia, and length of diseased segments.

Clinical Probability of Restenosis Following SFA Stenting

Restenosis following nitinol stenting in the SFA peaks at around 12 months.

Anti-proliferative drug delivery: Polymer-based

Coating Technology:

A variety of stent coatings with differing performance profiles have been studied in clinical trials. Stent coatings can be broadly classified into three types:

– No polymer coatings/surfaces
– Biocompatible (polymer) coatings
– Drug-delivery coatings

Stent coatings influence the thrombogenic activity of metal stents as well as the kinetics of the release of incorporated drugs.

DES Treatment in a Preclinical Model of Peripheral Artery Restenosis

Eluvia 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.
Controlled Drug Release

Drug release from the Eluvia system is sustained over time

- >90% of drug is released at 1 year
- Drug release coincides with the restenotic cascade

*Based on pre-clinical PK analysis. Data on file at Boston Scientific.
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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.
SuperNOVA (BMS) - Prospective, multicentre, single-arm, open label n = 299

MAJESTIC (DES) - Prospective, multicentre, single-arm, open label n = 57

IMPERIAL (DES) - Prospective, multicenter, RCT 2:1 n = ~500

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## MAJESTIC Clinical Study

<table>
<thead>
<tr>
<th>Study Overview: MAJESTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device</strong></td>
</tr>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
</tr>
<tr>
<td><strong>Investigational Centers</strong></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
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The Eluvia Drug-Eluting Vascular Stent is an investigational device, not available for sale in the European Economic Area (EEA) or U.S. Clinicaltrials.gov Identifier: NCT01820637
## MAJESTIC: Lesion Characteristics (Core Lab)

<table>
<thead>
<tr>
<th>Arterial Segments</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Ostial</td>
<td>0.0%</td>
</tr>
<tr>
<td>Proximal</td>
<td>1.8%</td>
</tr>
<tr>
<td>Mid</td>
<td>59.6%</td>
</tr>
<tr>
<td>Distal</td>
<td>77.2%</td>
</tr>
<tr>
<td>Proximal Popliteal</td>
<td>8.8%</td>
</tr>
<tr>
<td><strong>Length (mm)</strong></td>
<td><strong>70.8±28.1</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None/Mild</td>
<td>21.1%</td>
</tr>
<tr>
<td>Moderate</td>
<td>14.0%</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td><strong>64.9%</strong></td>
</tr>
<tr>
<td>Percent Diameter Stenosis</td>
<td><strong>86.3%±16.2%</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occlusions</th>
<th></th>
</tr>
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<td>46%</td>
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| Reference Vessel Diameter (mm) | 5.2±0.8 |

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<tr>
<th>Patency to Foot</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No Infrapopliteal Vessel Patent</td>
<td>5.3%</td>
</tr>
<tr>
<td>1 Vessel Patent</td>
<td>28.1%</td>
</tr>
<tr>
<td>2 Vessels Patent</td>
<td>31.6%</td>
</tr>
<tr>
<td>3 Vessels Patent</td>
<td>22.8%</td>
</tr>
</tbody>
</table>
MAJESTIC: Primary Patency*: 12 Months

- 12-month primary patency was **96.1%** (49/51)
- Kaplan-Meier estimate: 96.4%

*Primary patency defined as duplex ultrasound peak systolic velocity ratio ≤2.5 and absence of TLR or bypass

MAJESTIC: Safety Profile

MAE

- 12-month composite MAE rate was 3.8% (2 TLR events)

<table>
<thead>
<tr>
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<th>Overall</th>
<th>95% CI</th>
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<tr>
<td>12-Month MAE</td>
<td>3.8%</td>
<td>[0.5%, 13.0%]</td>
</tr>
<tr>
<td>All-Cause Death at 1 Month</td>
<td>0.0%</td>
<td>[0.0%, 6.7%]</td>
</tr>
<tr>
<td>Target Limb Major Amputation</td>
<td>0.0%</td>
<td>[0.0%, 6.7%]</td>
</tr>
<tr>
<td>Target Lesion Revascularization (TLR)</td>
<td>3.8%</td>
<td>[0.5%, 13.0%]</td>
</tr>
</tbody>
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Stent Integrity

- No stent fractures observed upon angiographic core lab analysis
MAJESTIC: Patient Outcomes

- 94% of patients classified as Rutherford Category 0-1 at 12 months
- ABI improvement sustained through 12 months

ABI, ankle-brachial index

MAJESTIC: Diabetic Patients

- 100% (14/14) 12-month primary patency
- 0% composite 12-month MAE rate

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<tr>
<th>Safety</th>
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<tr>
<td>12-Month MAE</td>
<td>0% (0/16)</td>
</tr>
<tr>
<td>All-Cause Death at 1 Month</td>
<td>0% (0/16)</td>
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KM curves for SFA DES trials

- Historically, SFA DES studies have demonstrated a pronounced decline in primary patency between 6 and 12M.

- The MAJESTIC study does not show the pronounced loss of patency during this time period.


The Eluvia Stent system is an investigational device. Limited by US law to investigational use only. Not available for sale. Results from different trials are not directly comparable. Information provided for educational purposes.
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### Clinical Study Overview: IMPERIAL

**Title**
A randomized trial comparing the ELUVIA Drug-eluting stent versus Zilver PTX stent for treatment of superficial femoral and/or proximal popliteal arteries

**Primary Investigators**
- **Global:** William A. Gray, MD
- **European:** Prof. Dr. med Stefan Müller-Hülsbeck

**Objective**
To evaluate the safety and effectiveness of the ELUVIA Drug-Eluting Vascular Stent System (ELUVIA Stent) for treating Superficial Femoral Artery (SFA) and/or Proximal Popliteal Artery (PPA) lesions up to 140 mm in length.

**Study Design**
The trial consists of the following:
- A prospective, multicenter, 2:1 randomized (ELUVIA vs Zilver PTX), controlled, single-blind, non-inferiority trial (RCT)
- A concurrent, non-blinded, non-randomized, single-arm, pharmacokinetic (PK) substudy

A subject may be enrolled in the RCT or the substudy; but not in both.
# Boston Scientific Global Pivotal Study
## IMPERIAL Trial

## Clinical Study Overview: IMPERIAL

| **Subjects** | 465 subjects treated with ELUVIA (N=310) or Zilver PTX (N=155)  
| **Investigational Centers** | Up to 75 study centers worldwide:  
| **Primary Efficacy Endpoint** | Primary vessel patency as assessed by duplex ultrasound (DUS) at 12 months post-procedure and adjudicated by an independent core laboratory.  
| **Primary Safety Endpoint** | Major Adverse Event (MAE) rate defined as  
| **First Patient Enrolled** | December 2015

- All cause death through 1 month
- Target limb major amputation through 12 months
- Target lesion revascularization (TLR) through 12 months

The Eluvia Stent system is an investigational device, not available for sale in the European Economic Area (EEA).
Conclusions

• Drug eluting stents and drug coated balloons are expected to make up 50% of the worldwide endovascular market by 2024

• The Eluvia Drug Eluting Stent is designed to optimize flexibility, radial strength, and fracture resistance

• The Eluvia dual layer coating design allows for a sustained drug release that coincides with the restenotic cascade

• The MAJESTIC 12 month results demonstrated:
  • Primary patency of 96.1%
  • TLR rate of 3.8%
  • High patency and excellent safety profile achieved in the challenging subgroup of diabetic patients
  • Zero observed stent fractures

• The IMPERIAL study design will directly compare two DES treatments in the SFA

Ranger is not available for sale in the U.S.
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