Randomised Control Trial Data. The Pinnacle of Proof

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Medical University of Graz, Austria
Disclaimer

• IMPORTANT INFORMATION: These materials are intended to describe common clinical considerations and procedural steps for the on-label use of referenced technologies as well as current standards of care for certain conditions. Of course, patients and their medical circumstances vary, so the clinical considerations and procedural steps described may not be appropriate for every patient or case. As always, decisions surrounding patient care depend on the physician’s professional judgment in light of all available information for the case at hand.

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The power of RCTs

• After bench testing and pilots, properly powered, randomised controlled trials are essential to prove device performance against current standard of care with clinically accepted primary endpoints.

• Registry data should be used to confirm findings in real world populations to compliment, and not replace, RCTs
<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from at least one randomised controlled trial or from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>
Standing on Evidence in SFA Intervention

>10,000 patients in >15 countries

**Meta-analysis**

**Head to Head RCT**

- IMPERIAL RCT N=465
- EMINENT RCT N=750
- SPORTS* RCT N=222 to be reported
- COMPARE RCT N=414
- RANGER II SFA RCT N=396
- RANGER SFA RCT N=105
- MAJESTIC N= 57
- DESAFINADO N= 64
- Aukland N= 51
- Muenster* N= 132
- REGAL N=291
- CAPSICUM N= 1079
- K-Eluvia N=100
- RANGER SFA Registry* N= 172
- POPCORN N~1000
- Jetstream LL* N= 162
- Jetstream ISR* N= 113
- J-SUPREME I+II* N= 81

**Cohort/Registry (single-arm)**

- PRECISE N= 2000
- BRIGHTER N= 500

**Case Series/Case-Control**

- ELEGANCE N = 5000

**Mechanism-based Reasoning**

- Preclinical and bench

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# RANGER II SFA Global Study Overview

| Principal Investigators | Global: Prof. Thomas Zeller, MD  
United States: Ravish Sachar, MD, FACC |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td></td>
</tr>
</tbody>
</table>
RCT  
(Ranger™ DCB vs Standard PTA)  
• 3:1 randomized  
• Single-blind  
• Superiority design for effectiveness | Pharmacokinetics Sub-study  
(Ranger DCB)  
• Single-arm | Long Balloon Sub-study  
(Ranger DCB)  
• Single-arm |
| **Patients** | N=376  
(Ranger DCB N=278 vs PTA N=98)  
• Symptomatic PAD (Rutherford 2-4)  
• Stenotic lesions of the femoropopliteal segment, up to 180 mm | N=12  
• Symptomatic PAD (Rutherford 2-4)  
• Stenotic lesions of the femoropopliteal segment, up to 180 mm | N=52  
• Occlusion up to 150 mm |
| **Balloon Sizes** | Diameter  
4-8 mm  
30-100 mm |  
4-7 mm  
120-200 mm |  
 |
| **Investigational Centers** | 67 study centers: United States, Japan, New Zealand, Europe, Canada | United States | 7 study centers: Belgium, Austria, New Zealand |
RANGER II SFA RCT: Primary Endpoint
Primary Patency at 12 Months

Kaplan-Meier Analysis

Log rank
P=0.0005

Primary Patency Rate (%)

Ranger DCB 89.8%
Standard PTA 74.0%

Error bars are SE.
• Primary safety endpoint met (non-inferiority $P<0.0001$)

• 12-month MAE-free rate

94.1% (241/256) Ranger DCB vs 83.5% (76/91) PTA; $P=0.002$

• Significantly lower MAE and TLR rates for Ranger DCB vs PTA

<table>
<thead>
<tr>
<th></th>
<th>Ranger DCB (N=256)</th>
<th>Standard PTA (N=91)</th>
<th>Difference [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-Month MAE</td>
<td>5.9% (15/256)</td>
<td>16.5% (15/91)</td>
<td>-10.6% [-18.8%, -2.5%]</td>
<td>0.002</td>
</tr>
<tr>
<td>All Causes of Death at 1 Month</td>
<td>0.4% (1/256)</td>
<td>0.0% (0/91)</td>
<td>0.4% [-0.4%, 1.2%]</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Target Limb Major Amputation</td>
<td>0.0% (0/256)</td>
<td>0.0% (0/91)</td>
<td>0.0% [NA, NA]</td>
<td>Undef</td>
</tr>
<tr>
<td>Clinically-Driven TLR</td>
<td>5.5% (14/256)</td>
<td>16.5% (15/91)</td>
<td>-11.0% [-19.1%, -2.9%]</td>
<td>0.001</td>
</tr>
</tbody>
</table>

PTA: Percutaneous transluminal angioplasty; DCB: Drug-coated balloon; MAE: major adverse events; TLR: target lesion revascularization; CI: confidence interval

MAEs were adjudicated by a Clinical Events Committee.

3-Year Primary Patency in Pivotal DCB Trials

Primary patency estimates reported in Kaplan-Meier analysis at 1095 days (36 months).

Results from different clinical investigations are not directly comparable. Information provided for educational purposes only. All trademarks are the property of their respective owners.


<table>
<thead>
<tr>
<th></th>
<th>LEVANT II (N=476)</th>
<th>ILLUMENATE (N=300)</th>
<th>IN.PACT SFA (N=331)</th>
<th>RANGER II SFA (N=376)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>63.2</td>
<td>89.0</td>
<td>88.1</td>
<td>79.9</td>
</tr>
<tr>
<td>Occlusions</td>
<td>21.9%</td>
<td>18%</td>
<td>19.5%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>8.1%</td>
<td>43.0%</td>
<td>6.2%</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

Primary patency estimates reported in Kaplan-Meier analysis at 1095 days (36 months). *Mean. Results from different clinical investigations are not directly comparable. Information provided for educational purposes only. All trademarks are the property of their respective owners.
Estimates of freedom from CD-TLR reported at 48 months from Kaplan-Meier analyses. Results from different clinical investigations are not directly comparable. Information provided for educational purposes only. All trademarks are the property of their respective owners.

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<tr>
<td>Standard PTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>63.2</td>
<td>62.7</td>
<td>89.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Occlusions</td>
<td>21.9%</td>
<td>20.6%</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>8.1%</td>
<td>10.4%</td>
<td>43.0%</td>
<td>43.9%</td>
</tr>
</tbody>
</table>

**COMPARE RCT (Ranger vs IN.PACT) (n = 414)**

<table>
<thead>
<tr>
<th>Primary efficacy endpoint</th>
<th>Primary patency at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined absence of clinically driven TLR or restenosis with PVR &gt; 2.4 evaluated by Duplex Ultrasound)</td>
<td></td>
</tr>
<tr>
<td>Non-inferiority margin: -10%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary safety endpoint</th>
<th>Freedom from major adverse events at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined as device and procedure-related deaths through 1 month, major amputations and clinically driven target lesion revascularization through 12 months</td>
<td></td>
</tr>
<tr>
<td>Non-inferiority margin: -10%</td>
<td></td>
</tr>
</tbody>
</table>

| Follow-up | In-house visits: 6, 12, 24 months (efficacy DUS and safety) Telephone calls: 1 month, 36, 48, 60 months (safety) |
## COMPARE RCT Study Devices

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT Admiral Medtronic</th>
<th>Ranger™ Boston Scientific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Image</strong></td>
<td><img src="image1" alt="IN.PACT Admiral Medtronic Product Image" /></td>
<td><img src="image2" alt="Ranger™ Boston Scientific Product Image" /></td>
</tr>
<tr>
<td><strong>Paclitaxel Dose</strong></td>
<td>3.5 µg/mm² (&quot;high dose&quot;)</td>
<td>2 µg/mm² (&quot;low dose&quot;)</td>
</tr>
<tr>
<td><strong>Coating Technology</strong></td>
<td>FreePac™ hydrophilic coating (excipient: urea)</td>
<td>TransPax coating (excipient: Citrate ester)</td>
</tr>
<tr>
<td><strong>Guidewire Compatibility</strong></td>
<td>0.035 OTW</td>
<td>0.14/0.18</td>
</tr>
<tr>
<td><strong>Matrix</strong></td>
<td>SFA: 4-7 mm; 40-150 mm</td>
<td>SFA: 4-8 mm; 30-200 mm BTK: 2-4 mm; up to 150 mm</td>
</tr>
<tr>
<td><strong>CE Mark</strong></td>
<td>✓ ✓</td>
<td>✓ ✓</td>
</tr>
<tr>
<td><strong>FDA Approval</strong></td>
<td>✓ ✓</td>
<td>✓ ✓</td>
</tr>
</tbody>
</table>
### Efficacy: Primary patency

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>( \Delta ) (two-sided 90% lower bound)</th>
<th>( P_{\text{non-inferiority}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low dose (Ranger)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83% (156/188)</td>
<td>1.5% (5.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>High dose IN.PACT</strong></td>
<td>81.5% (141/173)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary endpoint for non-inferiority met

### Safety: Freedom from MAE

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>( \Delta ) (two-sided 90% lower bound)</th>
<th>( P_{\text{non-inferiority}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low dose (Ranger)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>91% (182/200)</td>
<td>-1.6% (-6.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>High dose (IN.PACT)</strong></td>
<td>92.6% (175/189)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary endpoint for non-inferiority met
COMPARE Primary Patency through 790 days

Logrank p-value=0.96

Patients without an event at 790 days of follow-up or later were censored at 790 days.

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Steiner S et al. Eur Heart J 2020;41: 2541–2552
Drug release with ELUVIA and ZILVER PTX

- Drug release from the Eluvia system is sustained over time >90% of drug is released at 1 year

- Drug release from the Zilver PTX is achieved at 60 days

Restenosis predominantly occurred within a year following nitinol stenting in the SFA

**Study Design**

- **RCT (2:1) N=465**
- **Non inferiority (effectiveness) – Superiority post-oc analysis**
- **Single-blind**
- 2 sub-studies:
  - *Long Lesion (Eluvia): single arm - lesion length 140 mm-190 mm – N=50*
  - *Pharmacokinetic (Eluvia): sigle arm – N=13*

**Intervention**

- Study arm: **Eluvia DES**
- Control arm: **ZILVER PTX DES**

**Primary Endpoint**

**12-Month Primary Patency**

- **Investigational Centers**: 65 study centers: US, Canada, New Zealand, Belgium, Germany, Austria, Japan
- **Principal Investigators**:
  - Global: William A. Gray, MD
  - European: Stefan Müller-Hülsbeck

Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings assessed by an independent core laboratory.

DES, drug-eluting stent; PPA, proximal popliteal artery; RCT, randomized controlled trial; SFA, superficial femoral artery.
## IMPERIAL Study Devices

<table>
<thead>
<tr>
<th></th>
<th><strong>Eluvia™ DES</strong></th>
<th><strong>Zilver® PTX®</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent Platform</strong></td>
<td>Innova</td>
<td>Zilver Flex</td>
</tr>
<tr>
<td><strong>Material</strong></td>
<td>Nitinol</td>
<td>Nitinol</td>
</tr>
<tr>
<td><strong>Polymer</strong></td>
<td>Biostable Fluorinated Polymer Matrix (PROMUS polymer)</td>
<td>None</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>Paclitaxel</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td><strong>Dose Density</strong></td>
<td>0.167µg/mm²</td>
<td>3 µg/mm²</td>
</tr>
<tr>
<td><strong>Deployment</strong></td>
<td>Self-expanding</td>
<td>Self-expanding</td>
</tr>
<tr>
<td><strong>Sizes</strong></td>
<td>Diameter 6-7 mm, Length 40-150 mm</td>
<td>Diameter 6-8 mm, Length 40-120 mm</td>
</tr>
</tbody>
</table>

Primary patency defined as duplex ultrasound PSVR ≤2.4, in the absence of clinically-driven target lesion revascularization or bypass of the target lesion, as assessed by the DUS core lab.

**Superior primary patency for Eluvia vs Zilver PTX**

<table>
<thead>
<tr>
<th>Eluvia</th>
<th>Zilver PTX</th>
<th>Δ (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=309)</td>
<td>(N=156)</td>
<td>9.3% (1.4%, 17.3%)</td>
<td>0.0144</td>
</tr>
</tbody>
</table>

86.8% (243/280) vs 77.5% (110/142)

**IMPERIAL RCT Primary endpoint: Primary Patency 12m**

Pre-specified superiority analysis on primary endpoint

IMPERIAL RCT – Repeat Interventions Through 2 Years

Significantly fewer Eluvia TLRs vs paclitaxel-coated stent

Overall clinical trial population

Eluvia DES (N=275) vs Zilver PTX (N=134)

- **Eluvia DES**: 12.7%
- **Zilver PTX**: 20.1%

**p=0.0495**

Intention to treat.

Eluvia DES vs Zilver PTX TLR time course

• First CD-TLR occurred later for patients treated with Eluvia
• Significant difference at 3 years horizon.

Mean Number of Days to First CD-TLR

3-year Time Horizon

Eluvia DES
Mean time to first CD-TLR and 95%CI for those undergoing CD-TLR within the specified time horizon.

1 Year
2 Years

P=0.0058
Difference 166 days (5.5 months)

Zilver PTX
414

Eluvia DES
581

5-year Time Horizon

Eluvia DES
Mean time to first CD-TLR and 95%CI for those undergoing CD-TLR within the specified time horizon.

1 Year
2 Years

P=0.3099
Difference 92 days (3.1 months)

Zilver PTX
645

Eluvia DES
737

CD-TLR, clinically-driven target lesion revascularization.
Eluvia DES vs Zilver PTX IMPERIAL 5-year results

<table>
<thead>
<tr>
<th></th>
<th>Eluvia DES (N=309)</th>
<th>Zilver PTX (N=156)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause Mortality(^a)</td>
<td>18.8% (58/309)</td>
<td>17.9% (28/156)</td>
<td>0.8294</td>
</tr>
<tr>
<td>Target Limb Major Amputation</td>
<td>3.4% (8/232)</td>
<td>2.6% (3/114)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Clinically-Driven TLR</td>
<td>29.3% (68/232)</td>
<td>34.2% (39/114)</td>
<td>0.3540</td>
</tr>
</tbody>
</table>

- No significant differences in 5-year safety measures

\(^a\)Crude rate including all vital status assessments regardless of CEC adjudication.

[Image: Log-rank p=0.4764]
# EMINENT RCT Study Overview

## Study Design
- **RCT (2:1)**
- **N=775**
- **Superiority** (effectiveness)
- Single-blind

## Intervention
- **Study arm:** Eluvia DES
- **Control arm:** Bare nitinol stent

## Primary Endpoint
- **12-month Primary Patency**

## Investigational Centers
- **58 centers in 10 European countries**

## Principal Investigators
- **Prof. Dr. Yann Gouëffic**
  Groupe Hospitalier Paris St. Joseph, Paris, France
- **Prof. Dr. Giovanni Torsello**
  Sint-Franziskus-Hospital GmbH, Münster, Germany

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Primary vessel patency is defined as a binary endpoint and will be determined to be a success when the duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) is ≤ 2.4 at the 12-month follow-up visit in the absence of clinically-driven TLR or bypass of the target lesion. All DUS readings assessed by an independent core laboratory.

DES, drug-eluting stent; PPA, proximal popliteal artery; RCT, randomized controlled trial; SFA, superficial femoral artery.
EMINENT RCT Primary endpoint: Primary Patency 12m

Statistically significantly greater primary patency in patients treated with Eluvia DES vs BMS

83.2% [337/405] vs 74.3% [165/222]; p=0.0077

Superior primary patency for Eluvia DES vs BMS

Intention to treat. Primary patency defined as core-lab assessed duplex ultrasound peak systolic velocity ratio (PSVR) ≤ 2.4 at 12 months in the absence of clinically-driven TLR or bypass of the target lesion.

8.9% (95%CI 2.1%, 15.7%)
Primary patency defined as a binary rate based on core-lab assessed duplex ultrasound peak systolic velocity ratio (PSVR) ≤ 2.4 at 12 months in the absence of clinically-driven TLR or bypass of the target lesion. Primary endpoint analysis showed the observed, binary 12-month primary patency for patients treated with Eluvia DES was significantly greater than for patients treated with BMS (83.2% [337/405] vs 74.3% [165/222]; p=0.0077).

Significantly greater rate of clinical improvement without TLR for Eluvia DES vs BMS.

Primary sustained clinical improvement is defined as improvement (decrease) in Rutherford classification by one or more categories as compared to baseline, without TLR.
RCTs – Primary endpoints analysis

COMPARE RCT- Ranger vs IN.PACT non-inferiority efficacy and safety. SUCCESS.
Similar Primary Patency with ~ half the PTX dose out to 2 years.

Ranger II SFA RCT- Ranger vs PTA: superiority efficacy and non-inferiority safety. SUCCESS.
Confirming findings of smaller Ranger SFA First in Human RCT. SUCCESS

IMPERIAL RCT- Eluvia vs Zilver PTX: non-inferiority efficacy and safety. SUCCESS
Demonstrated superior patency for Eluvia at 12m, significant TLR advantage at 24 months, longer time to re-intervention at 3 years horizon and similar safety outcomes to 5 years.

EMINENT RCT- Eluvia DES vs BMS: superiority efficacy, non inferiority safety. SUCCESS
The first and only DES to do so in SFA intervention.
Standing on Evidence in SFA Intervention

>10,000 patients in >15 countries

#### Meta-analysis
- IMPERIAL RCT N=465
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- RANGER SFA RCT N=105

#### Head to Head RCT
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- RANGER SFA Registry* N=172
- POPCORN N~1000
- Jetstream LL* N=162
- Jetstream ISR* N=113
- J-SUPREME I+II* N=81

#### Cohort/Registry (single-arm)
- DES ELEGANCE N = 5000
- DCB
- Primary endpoints met

#### Case Series/Case-Control
- ELEGANCE N = 5000

#### Mechanism-based Reasoning
- Preclinical and bench

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Thank You
Randomised Control Trial Data. The Pinnacle of Proof

Prof. Marianne Brodmann, MD
Head of Division of Angiology and Department of Clinical Research
Medical University of Graz, Austria