New Insights from COMPARE 2-year Low-Dose vs High-Dose DCB

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University Hospital
Leipzig, Germany
Disclosure

I have the following potential conflicts of interest to report:

• Consulting: Bayer
• Research funding: C.R. Bard
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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• Results from case studies are not necessarily predictive of results in other cases. Results in other cases may vary.
Study aim: To compare **high-dose vs. Low-dose paclitaxel-coated balloons** for the treatment of high grade stenotic or occluded femoropopliteal lesions.

Patient population: Patients with Rutherford class 2-4.

Principal investigator: Dierk Scheinert, MD
University of Leipzig.

Sites: German multicenter trial, 15 sites.

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## COMPARE RCT Study Devices

<table>
<thead>
<tr>
<th>Product Image</th>
<th>IN.PACT Admiral Medtronic</th>
<th>Ranger™ Boston Scientific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel Dose</td>
<td>3.5 µg/mm² (“high dose”)</td>
<td>2 µg/mm² (“low dose”)</td>
</tr>
<tr>
<td>Coating Technology</td>
<td>FreePac™ hydrophilic coating (excipient: urea)</td>
<td>TransPax coating (excipient: Citrate ester)</td>
</tr>
<tr>
<td>Guidewire Compatibility</td>
<td>0.035 OTW</td>
<td>0.14/0.18</td>
</tr>
<tr>
<td>Matrix</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>CE Mark</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA Approval</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Efficient drug transfer with RANGER DCB TransPax Coating

Dose Density (2 μg/mm²)

Efficacy
Primary Patency near 90%\(^4,5\)

Drug Loss (Bench model)\(^1\)

Systemic Circulation (RANGER II PK Substudy)\(^3\)

Arterial Tissue Levels (swine model)\(^2\)

<table>
<thead>
<tr>
<th>Balloon Length</th>
<th>Ranger (6mm) PTX μg</th>
<th>In.Pact (6mm) PTX μg</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>1467</td>
<td>3170</td>
<td>0.46</td>
</tr>
<tr>
<td>60</td>
<td>2200</td>
<td>4489</td>
<td>0.49</td>
</tr>
<tr>
<td>80</td>
<td>3108</td>
<td>5809</td>
<td>0.54</td>
</tr>
<tr>
<td>120</td>
<td>4809</td>
<td>8448</td>
<td>0.57</td>
</tr>
</tbody>
</table>

## COMPARE RCT Study Design and Methods

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Investigator-initiated, prospective, multicenter, <strong>non-inferiority</strong> trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>414 patients undergoing 1:1 randomization</td>
</tr>
<tr>
<td></td>
<td>Stratification according to lesion length</td>
</tr>
<tr>
<td></td>
<td>Independent monitoring; 100% source data verification</td>
</tr>
<tr>
<td></td>
<td>Independent corelab for angio and duplex</td>
</tr>
<tr>
<td></td>
<td>Clinical events committee</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Funding</th>
<th>Study sponsor: University of Leipzig</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Funding through a research grant from Boston Scientific</td>
</tr>
<tr>
<td></td>
<td>Funding source not involved in collecting, monitoring and analysing study data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>In-house visits: 6, 12, <strong>24 months (efficacy and safety)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Telephone calls: 1 month, 36, 48, 60 months (safety)</td>
</tr>
</tbody>
</table>

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## Key baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Low dose DCB (n=207)</th>
<th>High dose DCB (n=207)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.2 ± 10.0</td>
<td>68.4 ± 9.3</td>
<td>0.79</td>
</tr>
<tr>
<td>Female gender</td>
<td>79 (38.2)</td>
<td>75 (36.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Rutherford class (RC) ≥ 3</td>
<td>184 (88.9)</td>
<td>176 (85)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63 (30.6)</td>
<td>76 (36.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous/current smoking</td>
<td>160 (77.3)</td>
<td>155 (74.9)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>123.9±97.8</td>
<td>128.3±97.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Total occlusions</td>
<td>84 (40.6)</td>
<td>89 (43)</td>
<td>0.62</td>
</tr>
<tr>
<td>Calcification* PACSS 3-4</td>
<td>105 (50.5)</td>
<td>117 (57.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>0-1 run off vessels</td>
<td>75 (38.5)</td>
<td>71 (36.6)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedural</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total paclitaxel dose (µg)</td>
<td>6971±4026</td>
<td>13035±7483</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bail-out stenting</td>
<td>62 (30.0)</td>
<td>53 (25.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Type E-F Dissection</td>
<td>4 (2.0)</td>
<td>2 (1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Diameter stenosis pp (%)</td>
<td>26.4±12.5</td>
<td>26.1±12.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Residual stenosis ≥ 30%</td>
<td>74 (35.8)</td>
<td>81 (39.1)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

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Data are given as mean±std or number (%).
# Primary endpoint analysis at 12 months

## Efficacy: Primary patency

<table>
<thead>
<tr>
<th></th>
<th>DCB Low dose</th>
<th>DCB High dose</th>
<th>Δ (two-sided 90% lower bound)</th>
<th>( P_{\text{non-inferiority}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>83%</strong></td>
<td>(156/188)</td>
<td><strong>81.5%</strong></td>
<td><strong>1.5%</strong></td>
<td><strong>(-5.2%)</strong></td>
</tr>
</tbody>
</table>

\( \Delta \) Non-inferiority met

## Safety: Freedom from MAE

<table>
<thead>
<tr>
<th></th>
<th>DCB Low dose</th>
<th>DCB High dose</th>
<th>Δ (two-sided 90% lower bound)</th>
<th>( P_{\text{non-inferiority}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>91%</strong></td>
<td>(182/200)</td>
<td><strong>92.6%</strong></td>
<td><strong>-1.6%</strong></td>
<td><strong>(-6.5%)</strong></td>
</tr>
</tbody>
</table>

\( \Delta \) Non-inferiority met

Patient flow diagram through 2 years

414 patients enrolled
47 screen failure
17 general criteria
30 angiographic criteria

**Ranger™ DCB**
207 patients

**In.PACT™ DCB**
207 patients

**Strata**
- ≤ 10 cm: 69 Patients
- >10 and ≤ 20 cm: 70 patients
- >20 and ≤ 30 cm: 68 patients

- 5 deaths
- 2 withdrawals

**12-Month Visit**
200 patients

- 8 withdrawals
- 2 deaths
- 1 lost to FU

**24-Month Visit**
189 patients

- 3 deaths
- 5 withdrawals
- 5 lost to FU
- 1 withdrawal by investigator

**Strata**
- ≤ 10 cm: 69 Patients
- >10 and ≤ 20 cm: 68 patients
- >20 and ≤ 30 cm: 70 patients

**12-Month Visit**
193 patients

- 12 withdrawals
- 1 death
- 3 lost to FU

**24-Month Visit**
177 patients

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Primary patency through 790 days

KM-estimate (95%CI) @ 365days

Low dose DCB: 87.6% (±2.5) 70.6% (±3.4) 64.4% (±3.6)
High dose DCB: 88.7% (±2.4%) 71.4% (±3.5) 63.7% (±3.7)

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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Primary patency – short lesions ≤10cm

Logrank p-value=0.67

KM-estimate (95%CI) @ 365days 730 days 790 days
Low dose DCB 91.5% (±2.5) 76.3% (±5.5) 72.8% (±5.8)
High dose DCB 92.6% (±3.6%) 81.5% (±3.5) 75.9% (±5.8)

Bailout stenting rate:
Low dose: 10.1%
High dose: 15.9%

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

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Primary patency – middle lesions
>10cm - ≤20cm

KM-estimate (95%CI) @ 365days
Low dose DCB 86.2% (±4.5)
High dose DCB 87.3% (±4.5%)

730 days
Low dose DCB 69.0% (±6.1)
High dose DCB 67.3% (±6.3)

790 days
Low dose DCB 65.5% (±6.2)
High dose DCB 58.2% (±6.7)

Logrank p-value=0.46

Bailout stenting rate:
Low dose: 27.1%
High dose: 20.6%

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

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Primary patency – long lesions
>20cm - ≤30cm

KM-estimate (95%CI) @ 365days
Low dose DCB 85.0% (±4.8)
High dose DCB 86.4% (±4.5%)

730 days
Low dose DCB 66.7% (±6.1)
High dose DCB 66.1% (±6.2)

790 days
Low dose DCB 55.0% (±6.4)
High dose DCB 57.6% (±6.4)

Logrank p-value=0.77

Bailout stenting rate:
Low dose: 52.9%
High dose: 40.0%

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

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# Key outcomes through 790 days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low dose DCB (n=207)</th>
<th>High dose DCB (n=207)</th>
<th>P value$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>3.6% (7/196)</td>
<td>2.2% (4/181)</td>
<td>0.6</td>
</tr>
<tr>
<td>Device or procedure-related death</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Major amputation</td>
<td>0% (0/189)</td>
<td>0.6% (1/177)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clinically driven TLR</td>
<td>17.3% (33/191)</td>
<td>13.0% (23/177)</td>
<td>0.3</td>
</tr>
<tr>
<td>All TLR*</td>
<td>17.8% (34/191)</td>
<td>13.0% (23/177)</td>
<td>0.3</td>
</tr>
<tr>
<td>Primary sustained clinical improvement†</td>
<td>69.5% (121/174)</td>
<td>74.3% (124/167)</td>
<td>0.4</td>
</tr>
<tr>
<td>Haemodynamic improvement‡</td>
<td>69.2% (117/169)</td>
<td>67.3% (107/169)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values are percentage (n/N). The numerator is the number of subjects with events prior to the close of the visit window. The denominator includes subjects with events or those without events having follow-up on or past the opening of the visit window.

*Includes clinically-driven TLR and duplex-driven/incidental TLR.
† Defined as improvement in Rutherford classification by one or more categories compared with baseline, without TLR.
‡ Defined as an increase in the ankle-brachial index by ≥0.10 compared with baseline or to an ankle-brachial index ≥0.90, without TLR.
§ P-values based on Fisher’s-exact test.

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Distribution of Rutherford categories

$\approx 70\%$ of patients with no or minimal symptoms @ 2y

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Walking impairment questionnaire

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COMPARE RCT Summary

- First head-to-head comparison of two DCBs with different paclitaxel dosages and coating technologies for femoropopliteal interventions

- Complex real world lesion subset with high proportion of CTO`s >40%

- Low dose DCB (Ranger 2.0μg/mm²) and high dose DCB (IN.PACT 3.5μg/mm²) showing both excellent primary patency and low TLR rates through 2 years

- Low mortality after 2 years; Follow-up ongoing up to 5 years

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CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Instructions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator’s Instructions.

WARNING
A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of repeat paclitaxel coated device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients. See Section 8.1 (in the eIFU) for further information.

INTENDED USE / INDICATIONS FOR USE
The Ranger Drug Coated Balloon (DCB) is indicated for percutaneous transluminal angioplasty (PTA) of de novo or restenotic lesions up to 180 mm in length located in native superficial femoral and proximal popliteal arteries (SFA/PPA) with reference vessel diameters of 4 mm to 7 mm.

CONTRAINDICATIONS
Use of the Ranger DCB is contraindicated in:
• Patients with known hypersensitivity to paclitaxel (or structurally-related compounds).
• Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy.
• Women who are breastfeeding, pregnant, or men intending to father children.
• Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system.
• Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries.

WARNINGS
• To reduce the potential for vessel damage, the inflated diameter of the balloon should approximate the diameter of the vessel segment to be treated. The inflated length of the balloon (shoulder to shoulder) may exceed the length of the lesion/stenosis by approximately 10 mm on either side within the targeted artery.
• The safety of using multiple Ranger DCBs with a total drug dosage exceeding 9266 μg of Paclitaxel in a patient has not been studied.
• Using a drug-eluting stent in conjunction with Ranger DCB at the same treatment site has not been studied.

PRECAUTIONS
• The balloon catheter should be used only by physicians trained in the performance of percutaneous transluminal angioplasty.
• The balloon catheter should be used with caution for procedures involving calcified lesions due to the abrasive nature of these lesions.
• The balloon catheter is not intended for injection of contrast medium.
• Full arterial wall apposition of the Ranger DCB is necessary for proper drug transfer to the vessel.
• Do not touch, wipe, bend, or squeeze the balloon. Do not allow it to contact any liquids including organic solvents such as alcohol or detergents prior to insertion. Damage to the balloon coating or premature release of the drug may occur.
• This product should not be used in patients with uncorrected bleeding disorders or patients who cannot receive anticoagulation or antiplatelet aggregation therapy.
• If treating a long lesion (longer than the maximum balloon length available), each individual segment should be treated only once with a drug-coated balloon. Treat each segment with a new balloon and minimize overlapping of treated segments.

Pregnancy / Lactation
This product has not been tested in pregnant or breastfeeding women or in men intending to father children; effects on the developing fetus have not been studied and the risks and reproductive effects remain unknown.

Drug Information
The mechanism of action by which paclitaxel reduces or reverses neointima formation and proliferation, leading to restenosis, as demonstrated in clinical studies has not been established. It is known that paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

Drug Interaction
Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated. Drug interactions of systemic chemotherapeutic levels of paclitaxel with possible concomitant medications are outlined in the labeling for finished pharmaceuticals containing paclitaxel, such as TAXOL™.

Carcinogenicity, Genotoxicity, and Reproductive Toxicology
No long-term studies in animals have been published in peer-reviewed literature to evaluate the carcinogenic potential of paclitaxel. Paclitaxel interacts with microtubules; this is the major mechanism by which it inhibits cell growth. One consequence is the loss of whole chromosomes via interactions with spindle microtubules during cell division. As such, paclitaxel is defined as an aneugen (agent causing an alteration in chromosome number). This indirect action is consistent with positive responses in in vitro and in vivo micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT. Paclitaxel administered via IV prior to and during mating produced impairment of fertility in male and female rats at doses > 1 mg/kg.

Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day caused embryo- and fetotoxicity. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day; teratogenic potential could not be assessed at higher doses due to extensive fetal mortality. For comparison, the worst-case dose of paclitaxel delivered by the Ranger DCB (assuming maximum size and number of balloons used in a lesion) is 9266 μg, which is approximately 6 and 19 times less than the dose that saw effects in rats and rabbits, respectively, when normalizing to body weight.

Pre and Post Procedure Antiplatelet Therapy
It is strongly advised that the treating physician follow the Inter-Society Consensus (TASC II) Guidelines recommendations (or other applicable country guidelines) for antiplatelet therapy pre- and post-procedure.
Adverse Events
Potential adverse events include, but are not limited to, the following:
• Allergic reaction (device, contrast medium, medications)
• Arteriovenous fistula
• Death
• Hematoma
• Hemorrhage/Bleeding
• Hypotension/Hypertension
• Infection/Sepsis
• Pseudoaneurysm
• Thromboembolic episodes
• Vascular thrombosis
• Vessel injury (e.g., dissection, perforation, rupture)
• Vessel occlusion
• Vessel spasm
Potential adverse events not captured above that may be unique to the paclitaxel drug coating:
• Allergic/immunologic reaction to drug (paclitaxel or structurally-related compounds) or coating or its individual components
• Alopecia
• Anemia
• Blood product transfusion
• Gastrointestinal symptoms
• Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
• Hepatic enzyme changes
• Histologic changes in vessel wall, including inflammation, cellular damage or necrosis
• Myalgia/Arthralgia
• Peripheral neuropathy
Apart from hypersensitivity reactions (allergic/immunologic reactions), the likelihood of paclitaxel related adverse events is low, due to the low exposure.
There may be other potential adverse events that are unforeseen at this time.