“Paclitaxel-Eluting PTCA-Balloon in Combination with the Coroflex Blue Stent vs the Sirolimus Coated Cypher Stent in the Treatment of Advanced Coronary Artery Disease”
Consulting or speaker honorarium

- Braun
- Cordis
- Medtronic
- Abbott
**Drug-Eluting Balloon (DEB)**

### Drug Eluting Stent
- Slow release
- Persistent exposure
- ~ 100 - 200 µg dose
- Polymer

### Drug Eluting Balloon
- Immediate release
- Short-lasting exposure
- ~ 300 - 600 µg dose
- No polymers

- **Treatment of coronary in-stent restenosis**
  - Superior to POBA and DES

- **De-novo and restenotic lesions in SFA**
  - Superior to conventional PTA

- **Coronary de-novo lesions: DEB with BMS?**
Objective and Study Design

Comparison of the combination of a Paclitaxel-Coated Balloon + Bare-Metal Stent (DEB+BMS, ‘Coroflex® DEBlue’) with the Sirolimus-Eluting Cypher® (DES) stent in the treatment of de-novo stenoses in native coronary arteries.

Prospective, randomized, multi-center, two-armed phase-II pilot study conducted in Europe.

Design: non-inferiority versus Cypher®
Inclusion and Exclusion Criteria

- **Inclusion Criteria**
  - Patients with stable or unstable angina or documented ischemia due to a significant lesion in a native coronary artery
  - Intention to treat one lesion with one stent
  - Significant stenoses in native coronary arteries with nominal stent diameters between $\geq 2.5$ mm and $\leq 3.5$ mm and < 24 mm in length

- **Exclusion Criteria**
  - Unprotected left main
  - In stent restenosis
  - PCI 6 months prior to enrolment
  - Indication for more than one lesion to treat
  - Intended bifurcational stenting
  - Chronic total occlusions
  - Art. / vein grafts
  - Chronic anticoagulation required
  - Acute MI (STEMI, NSTEMI)
  - Cardiogenic shock
Primary and Secondary Endpoints

Primary Endpoint
• Late lumen loss (in stent) at 9 months*

Secondary Endpoints
• Procedural success
• 30-day complication rate (by phone)
• Percent diameter stenosis at 9 months
• Binary restenosis rate at 9 months
• MACE rate at 9 months, 1 & 3 years
• Indication for premature follow-up

* Assessed by an independent, blinded Core-Lab (U. Dietz).
Medication

Medication before Intervention
- ASA
- loading dose Clopidogrel of 300 mg > 6 hours before or 600 mg < 6 hours before the procedure

Medication during Intervention
- Heparin according to ESC guidelines
- GP IIb/IIIa and bivalirudin local clinical routine

Medication post intervention
- ASA 100mg to 325 mg 1x daily
- Clopidogrel 75 mg/d for 6 months
Patients randomized
N = 637

N = 312
DEB+BMS: Paclitaxel-coated balloon + Bare-Metal Stent Coroflex DEBlue ®

N = 296 (95.5%)
Follow-up 9 months

N = 269 (86.8%)
Angiography

N = 325
DES: Sirolimus-eluting stent Cypher ®

N = 313 (96.6%)
Follow-up 9 months

N = 273 (84.3%)
Angiography
## Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DEB+BMS Coroflex DEBlue®</th>
<th>DES Cypher®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.9 ± 10.2</td>
<td>65.1 ± 9.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Female</td>
<td>28.2 %</td>
<td>21.8 %</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.1 %</td>
<td>27.7 %</td>
<td>0.87</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74.8 %</td>
<td>80.1 %</td>
<td>0.11</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>66.8 %</td>
<td>66.5 %</td>
<td>0.93</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>61.3 %</td>
<td>58.3 %</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>49.7 %</td>
<td>37.3 %</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>75.0 %</td>
<td>73.1 %</td>
<td>0.59</td>
</tr>
<tr>
<td>Prior MI</td>
<td>15.1 %</td>
<td>14.8 %</td>
<td>0.93</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>21.5 %</td>
<td>22.2 %</td>
<td>0.82</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6.5 %</td>
<td>6.2 %</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Intention-to-treat analysis
# Angiographic Baseline Characteristics

<table>
<thead>
<tr>
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<th>DEB+BMS Coroflex DEBlue®</th>
<th>DES Cypher®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Vessel</td>
<td>60.1 %</td>
<td>55.6 %</td>
<td>0.08</td>
</tr>
<tr>
<td>2-Vessel</td>
<td>23.8 %</td>
<td>21.3 %</td>
<td></td>
</tr>
<tr>
<td>3-Vessel</td>
<td>16.1 %</td>
<td>23.1 %</td>
<td></td>
</tr>
<tr>
<td>Prox. LAD</td>
<td>14.8%</td>
<td>15.1%</td>
<td>0.91</td>
</tr>
<tr>
<td>TIMI flow 3</td>
<td>84.2%</td>
<td>86.1%</td>
<td>0.51</td>
</tr>
<tr>
<td>% Diameter Stenosis</td>
<td>83.7 ± 10.2</td>
<td>83.0 ± 10.1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Intention-to-treat analysis
## Stent Implantation

<table>
<thead>
<tr>
<th></th>
<th>DEB+BMS Coroflex DEBlue®</th>
<th>DES Cypher®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent length [mm]</td>
<td>16.5 ± 4.0</td>
<td>16.5 ± 4.6</td>
<td>0.24</td>
</tr>
<tr>
<td>Stent diameter [mm]</td>
<td>3.1 ± 0.4</td>
<td>3.1 ± 0.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Inflation pressure [bar]</td>
<td>14.1 ± 2.0</td>
<td>14.6 ± 2.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Inflation duration [sec]</td>
<td>51.9 ± 20.7</td>
<td>25.0 ± 14.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Direct Stenting</td>
<td>46.6 %</td>
<td>44.4%</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Intention-to-treat analysis
## Quantitative Coronary Angiography

<table>
<thead>
<tr>
<th></th>
<th>DEB+BMS Coroflex DEBlue®</th>
<th>DES Cypher®</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter</td>
<td>2.87 ± 0.38</td>
<td>2.87 ± 0.37</td>
<td>0.68</td>
</tr>
<tr>
<td>MLD before</td>
<td>0.67 ± 0.37</td>
<td>0.67 ± 0.38</td>
<td>0.97</td>
</tr>
<tr>
<td>MLD final In-stent</td>
<td>2.59 ± 0.40</td>
<td>2.62 ± 0.36</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>2.16 ± 0.48</td>
<td>2.16 ± 0.43</td>
<td>0.98</td>
</tr>
<tr>
<td>MLD final In-segment</td>
<td>2.62 ± 0.36</td>
<td>2.16 ± 0.43</td>
<td></td>
</tr>
<tr>
<td>MLD 9 months In-stent</td>
<td>2.17 ± 0.63</td>
<td>2.46 ± 0.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.95 ± 0.62</td>
<td>2.05 ± 0.50</td>
<td>0.07</td>
</tr>
<tr>
<td>MLD 9 months In-segment</td>
<td>2.46 ± 0.49</td>
<td>2.05 ± 0.50</td>
<td></td>
</tr>
<tr>
<td>Late Lumen Loss In-stent</td>
<td>0.41 ± 0.51 mm</td>
<td>0.16 ± 0.39 mm</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.20 ± 0.52 mm</td>
<td>0.11 ± 0.40 mm</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Per protocol analysis
Late Lumen Loss

Difference LLL Coroflex DEBlue® and Cypher®

Non-inferiority margin $\delta = 0.1$ mm

Per protocol analysis
MLD Distribution

In-Stent

Cumulative Percent (per protocol population)

Minimal lumen diameter [mm] in-stent

Pre F/U Post

In-Segment

Cumulative Percent (per protocol population)

Minimal lumen diameter [mm] in-segment

Pre F/U Post

Per protocol analysis
### Angiographic 2\textsuperscript{nd} Endpoints

<table>
<thead>
<tr>
<th></th>
<th>DEB+BMS Coroflex DEBlue\textsuperscript{®}</th>
<th>DES Cypher\textsuperscript{®}</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binary Restenosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent\textsuperscript{*}</td>
<td>10.0 %</td>
<td>2.9 %</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>In-segment\textsuperscript{*}</td>
<td>13.8 %</td>
<td>4.9 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TVR\textsuperscript{**}</td>
<td>13.8 %</td>
<td>6.9 %</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TLR\textsuperscript{**}</td>
<td>10.5 %</td>
<td>4.7 %</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Per protocol analysis

\textsuperscript{**}Intention-to-treat analysis
## Safety Endpoints

<table>
<thead>
<tr>
<th></th>
<th>DEB+BMS Coroflex DEBlue® N = 310</th>
<th>DES Cypher® N = 324</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural Success</strong></td>
<td>91.6%</td>
<td>94.1 %</td>
<td>0.22</td>
</tr>
<tr>
<td>Stent placed + expanded</td>
<td>QCA: TIMI3 + In-stent stenosis &lt; 30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death (9 months)</strong></td>
<td>1.0 %</td>
<td>0.3 %</td>
<td>0.29</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0.7 %</td>
<td>0.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>MI (9 months)</strong></td>
<td>4.6 %</td>
<td>0.3 %</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STEMI</td>
<td>3.0 %</td>
<td>0.3 %</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>2.0 %</td>
<td>0.3 %</td>
<td></td>
</tr>
<tr>
<td><strong>Stent Thrombosis (ARC)</strong></td>
<td>2.0 %</td>
<td>0.3 %</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Definite</td>
<td>1.3 %</td>
<td>0.3 %</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>0.6 %</td>
<td>0.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Intention-to-treat analysis
Summary / Conclusions

- This first Drug-Eluting Balloon / Stent system did not meet the non-inferiority criteria versus Cypher®
- Safety aspects need to be investigated
- However,
  - Late lumen loss comparable to published data on Paclitaxel® eluting stents
  - In-segment analysis demonstrates efficacy at the stent margins
  - Further design evolution is warranted to improve this new approach
Study Centers

- Scheller B., Homburg / Saar, Germany (93)
- Hamm Ch., Bad Nauheim, Germany (64)
- Möbius-Winkler S., Leipzig, Germany (58)
- Zeymer U., Ludwigshafen, Germany (56)
- Vrolix M., Genk, Belgium (46)
- Heuer H., Dortmund, Germany (43)
- Huret B., Caen, France (31)
- Vallbracht Ch., Rotenburg a.d. Fulda, Germany (27)
- Schieffer B., Hannover, Germany (24)
- Janek B., Prague, Czech Republic (23)
- Wijns W., Aalst, Belgium (23)
- Kuck K.H., Hamburg, Germany (23)
- Brachmann J., Coburg, Germany (20)
- Bocksch W., Berlin, Germany (19)
- Appelman Y., Amsterdam, Netherlands (16)
- Hehrlein Ch., Freiburg, Germany (15)
- Nienaber Ch., Rostock, Germany (11)
- Haase K. K., Reutlingen, Germany (11)
- Angevaeren W., Arnhem, Netherlands (10)
- Kähler J., Hamburg-Eppendorf, Germany (9)
- Barragan P., Ollioules, France (7)
- Eeckhout E., Lausanne, Switzerland (6)
- Hoffmann R., Aachen, Germany (3)
- Coste P., Pessac, France (3)
Thank you!
Statistical Hypothesis

Non-inferiority test problem: margin $\delta = 0.1$ mm

Hypothesis: LLL Coroflex – LLL Cypher $=> \delta$

Alternative: LLL Coroflex – LLL Cypher $< \delta$

Test niveau $\alpha = 5%$

Power $1 - \beta = 90%$

Sample Size: 198 per group
300 per group regarding drop-outs
Survival free of MACE (MI, Revasc)

Kaplan-Meier survival curves:
Survival free of MI / any Revasc

p-log-rank < 0.001

Days after PCI

Cumulative survival

CYPHER
Coroflex

Intention-to-treat analysis
637 patients randomized

Randomized for PEB (n=312)
- Withdrawal of IC before PCI (n=1)
- Randomisation done by mistake (n=1)
- Intention to treat (n=310)
  - Received PEB (n=302)
  - Did not receive PEB (n=8)
    - Reasons see extra chart

Randomized for SES (n=325)
- Withdrawal of IC before PCI (n=0)
- Randomisation done by mistake (n=1)
- Intention to treat (n=324)
  - Received SES (n=322)
  - Did not receive SES (n=2)
    - Reasons see extra chart

Lost to follow-up (fu) with regard to primary endpoint (n=31)
- Reasons:
  - Deaths (n=2)
  - Lost to fu (n=1)
  - Withdrawal of IC (n=1)
  - No premature angio or regular fu angio done (n=27)

Lost to follow-up (fu) with regard to primary endpoint (n=48)
- Reasons:
  - Deaths (n=1)
  - Lost to fu (n=1)
  - Withdrawal of IC (n=4)
  - No premature angio or regular fu angio done (n=42)

Excluded from analysis (n=39)
- No QCA data available (n=22)
- Other major protocol violators (n=17)

Excluded from analysis (n=30)
- No QCA data available (n=11)
- Other major protocol violators (n=19)

Analyzed per protocol (n=232)

Analyzed per protocol (n=244)