RESPONSE ADAPTED COMBINATION THERAPY (REACT): WHEN AND WHERE TO STENT?
CONCEPT FOR A PILOT STUDY

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Disclosure

Speaker name:

Prof Patrice B. Mwipatayi

I have the following potential conflicts of interest to report:

- [x] Consulting: BIOTRONIK
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest
RESPONSE ADAPTED COMBINATION THERAPY

Satisfactory PTA?*

- Passeo-18 Lux

Residual stenosis / flow limiting dissection post-PTA?*

- Passeo-18 Lux + Pulsar 18

- Pulsar-18 + Passeo-18 Lux**

BIOLUX P-III (SFA)
- fcd TLR 94.5%
- PP 84.9%

BIOLUX 4EVER
- fTLR 93.6%
- PP 89.9%

BIOFLEX PEACE
- fTLR 97.1%
- PP 86.2%

DEBAS
- fTLR 94.0%
- PP 94.0%

** The use of Passeo-18 Lux for post-dilatation is not within the indication for the product.
PTA=percutaneous transluminal angioplasty; PP=Primary Patency; fTLR=freedom from Target Lesion Revascularization for BIOFLEX PEACE and BIOLUX 4EVER freedom from clinically driven TLR for BIOLUX P-III and DEBAS

1: Tepe G. Presented at CIRSE 2017, 12-month All-Comers SFA subset data
2: Deloose K. Presented at CX 2017, 12-month data
3: Nolte-Ernsting C. Presented at CIRSE 2017, 12-month data
Leaving Nothing Behind DCB alone can’t fit all

Provisional stenting rate in DCB trial up to 40% in real-world studies

BIOLUX 4EVER
12-months data confirms performance of Passeo-18 Lux and Pulsar

DESIGN:

PRINCIPAL INVESTIGATOR:
Dr. Marc Bosiers, AZ Sint-Blasius, Dendermonde, Belgium

PRIMARY ENDPOINT:
Primary patency\(^1\) at 12 months

SECONDARY ENDPOINT:
Primary patency at 6 and 24 months follow-up
F TLR at 6, 12 and 24 months follow-up
Changes in ABI at 12 and 24 months follow-up

Lesion Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N= 120 /120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length, mm</td>
<td>83.33 mm</td>
</tr>
<tr>
<td>(min-max ± SD)</td>
<td>(6.0 – 190.0; ±49.49)</td>
</tr>
<tr>
<td>Ref. vessel diameter mm</td>
<td>5.26 mm</td>
</tr>
<tr>
<td>(min-max ± SD)</td>
<td>(4.0 – 6.0; ±0.59)</td>
</tr>
<tr>
<td>Mean DCB diameter (min – max; ±SD)</td>
<td>5.15 mm</td>
</tr>
<tr>
<td>Mean stent diameter (min – max; ±SD)</td>
<td>5.78 mm</td>
</tr>
<tr>
<td>Occlusions (n, %)</td>
<td>40 (33.33)</td>
</tr>
<tr>
<td>Calcified lesions (n, %)</td>
<td>60 (50)</td>
</tr>
</tbody>
</table>

Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 120 /120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>79 (65.83)</td>
</tr>
<tr>
<td>Age (min – max; ±SD)</td>
<td>70.8 (43.7 – 92.4 ±10.5)</td>
</tr>
<tr>
<td>Nicotine abuse (n, %)</td>
<td>73 (60.83)</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>76 (63.33)</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>23 (19.17)</td>
</tr>
<tr>
<td>Renal insufficiency (n, %)</td>
<td>15 (12.50)</td>
</tr>
<tr>
<td>Hyperlipidemia (n, %)</td>
<td>66 (55.00)</td>
</tr>
</tbody>
</table>

(1) defined as freedom from >50% restenosis as indicated by an independently verified duplex ultrasound peak systolic velocity ratio (PSVR) <2.5 in the target vessel with no reintervention
Deloose K., Presented at CK  2017, 12-month data
**DEBAS**

Intentional use of Pulsar and Passeo-18 Lux is safe and effective

**DESIGN:**
Physician-Initiated, prospective, multi-center (3), controlled trial investigating safety and efficacy of BIOTRONIK Pulsar-18/35 Stents combined with BIOTRONIK Passeo-18 Lux Drug Coated Balloon in severe Femoropopliteal Arterial Occlusive Disease.

**PRINCIPAL INVESTIGATOR:**
Dr. Patrice Mwipatayi, Perth, Australia

**PRIMARY ENDPOINT:**
Primary patency\(^1\) at 12 and 24 months,

**SECONDARY ENDPOINT:**
Freedom from stent occlusion at 12 and 24 months Freedom from TLR at 12, 18 and 24 months

### Lesion Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N= 51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length, mm (IQR)</td>
<td>200 mm (140-250)</td>
</tr>
<tr>
<td>Ref. vessel diameter mm (min-max ± SD)</td>
<td>6.02 mm +/- 0.33</td>
</tr>
<tr>
<td>TASC C (n,%),</td>
<td>23 (45.1)</td>
</tr>
<tr>
<td>TASC D (n,%),</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Calcified lesion, moderate (n, %)</td>
<td>22 (43.1)</td>
</tr>
<tr>
<td>Calcified lesions, severe (n, %)</td>
<td>12 (23.5)</td>
</tr>
</tbody>
</table>

### Patients Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>32 (72.7)</td>
</tr>
<tr>
<td>Age (min – max; ±SD)</td>
<td>67.6 +/- 10.2</td>
</tr>
<tr>
<td>Nicotine abuse (n,%)</td>
<td>17 (38.6)</td>
</tr>
<tr>
<td>Hypertension (n,%)</td>
<td>31 (70.4)</td>
</tr>
<tr>
<td>Diabetes (n,%)</td>
<td>24 (54.6)</td>
</tr>
<tr>
<td>CAD (n,%)</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>Hyperlipidemia (n,%)</td>
<td>23 (52.3)</td>
</tr>
</tbody>
</table>

Defined as a PSVR at DUS + 2.5 at the stented target lesion with no clinically-driven reintervention within the stented segment.


The use of Passeo-18 Lux for post-dilatation is not within the indication for the product.
**PASSEO-18 LUX PLUS PULSAR SHOW EXCELLENT OUTCOMES IN SFA WHEN COMPARED TO DES**

<table>
<thead>
<tr>
<th>LL (cm)</th>
<th>8.3</th>
<th>20</th>
<th>5.5</th>
<th>14.7</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSVR</td>
<td>2.5</td>
<td>2.5</td>
<td>2</td>
<td>2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**DCB plus BMS**

- **Biolux 4 Ever**
  - Passeo-18 Lux + Pulsar
  - DEBAS
- **Zilver PTX RCT**
  - Zilver PTX RCT
  - Zilver PTX Japanese PMS
- **MAJESTIC**
  - Passeo-18 Lux for post-dilatation is not within the indication for the product.

**DES**

- **BIOLUX 4 EVER**
  - 89.9
  - 93.6
- **DEBAS**
  - 94
  - 94
- **Zilver PTX RCT**
  - 84.4
  - 91.6
- **Zilver PTX Japanese PMS**
  - 86.4
  - 91.4
- **MAJESTIC**
  - 96.4
  - 96.4

**BIOLUX 4 EVER**: Deloose K., Presented at CX 2017, 12-month data (365 days)


**MAJESTIC**: Mueller-Huettelbeck. S. Presented CIRSE 2015

**Zilver PTX RCT**: PMA P100022: FDA Summary of Safety and Effectiveness Data

**Zilver PTX Japan**: Hiroyoshi Yokoi, JACC, Volume 9, Issue 3, February 2016
POBA
Predilation at least 3’
Slow inflation

Satisfactory

Passeo-18 Lux

Mission accomplished

Unsatisfactory

Pulsar-18
As Low as Reasonably Achievable
+ post dilation at the physician discretion

Mission accomplished

A Simple, Flexible and Dynamic treatment with Passeo-18 Lux DCB & Pulsar-18 BMS
when and where needed,
leaving as less metal as possible behind
**DISSECTION CLASSIFICATION**

**Type A** dissections represent minor radiolucent areas within the coronary lumen during contrast injection with little or no persistence of contrast after the dye has cleared.

**Type B** dissections are parallel tracts or a double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance.

**Type C** dissections appear as contrast outside the coronary lumen ("extraluminal cap") with persistence of contrast after dye has cleared from the lumen.

**Type D** dissections represent spiral ("barber shop pole") luminal filling defects, frequently with excessive contrast staining of the dissected false lumen.

**Type E** dissections appear as new, persistent filling defects within the coronary lumen.

**Type F** dissections represent those that lead to total occlusion of the coronary lumen without distal antegrade flow.

**NHLBI Classification of Coronary Artery Dissection**
BIOTRONIK REACT PILOT STUDY RATIONALE

- Consensus on stent requirement to treat elastic recoil and flow limiting dissection
- No clear definition for flow limiting dissection in peripheral artery
- Should a dissection be treated or observed?
- Full lesion stenting or spot stenting?
- Can adjunctive procedural assessments (imaging, ultrasound) improve the stenting approach?
REACT PILOT STUDY DESIGN: REFLECTION QUESTIONS?

- Evaluate the utility of adjunctive procedural assessments to identify flow limiting dissection
  - Procedural DUS?
  - IVUS?
  - Fractional Flow Reserve (FFR)?
- FFR need to be validated
- Feasibility
- Impact on treatment
- Overall impact on procedure costs
# REACT Pilot Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Global Multicenter Prospective Pilot Diagnostic Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Assessing the value of intraoperative <strong>DUS</strong> or <strong>intra-arterial pressure measurement (IAP)</strong> or <strong>intra-arterial pressure measurement associated to IVUS</strong> to identify flow-limiting dissection when 2 projections angiography is inconclusive</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td>▪ Specificity, Sensitivity, Air Under ROC curves</td>
</tr>
</tbody>
</table>
| **Secondary Endpoints** (selected)                                    | ▪ Stenting rate, Nb of stents/lesion, stented length (full, spot)  
▪ Primary Patency, cdTLR, MAE                                      |
| **Study duration**                                                    | ▪ Enrolment: 12 months, FUP: 1 month, 6 months and 12 months |
| **Nb of subjects**                                                    | ▪ 150 subjects ≈ 10 sites globally                 |
CONCLUSION

- DCB alone cannot treat all lesions

- The **BIOTRONIK REACT approach** allows physicians to treat SFA with full-lesion paclitaxel coverage offered by a DCB and stenting *when and where needed*, potentially reducing metal burden rather than the one-fits-all with DES

- The **REACT Pilot Study** will be the first study to look beyond full lesion treatment with DCB and BMS but **investigate a treatment algorithm**
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