Bioresorbable Scaffolds
Moving Forward or Backwards?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse have had a financial interest/arrangement or affiliation with the organization(s) listed below in relation this topic.

Affiliation/Financial Relationship
Consulting Fees or Speaker Honoraria

Company
• Abbott Vascular
### Potential Unique Benefits of BioResorbable Scaffolds

<table>
<thead>
<tr>
<th>CELLS</th>
<th>PATIENT</th>
<th>VESSEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SMC differentiation to contractile phenotype through mechanotransduction</td>
<td>• Stabilization of target lesion events (plaque capping)</td>
<td>• Vessel remodeling allowed in the absence of metallic caging</td>
</tr>
<tr>
<td>• Endothelium lined tissue coverage that responds to stimuli</td>
<td>• Recovery/preservation of epicardial-mediated portion of coronary flow reserve (remodeling/vasomotion)</td>
<td>• Vasomotion recovered through functional cellular tissue formation (mechanotransduction)</td>
</tr>
</tbody>
</table>

- Plaque capping with a “neo-intima” of ~200 μm
- Plaque reduction
Evolution of Vascular Remodeling
As Assumed/Imagined from Animal Models

Stent/scaffold implant

- Procedural Success
  - REPARA
  - GABI-R
  - RAI
  - IT-DISAPPEARS
  - France ABSORB

- Healing comparable to best DES
  - TROFII
  - ESTROFA-BVS

- Efficacy & safety comparable to DES
  - ABSORB III
  - ABSORB Japan
  - ABSORB China
  - ABSORB-FIRST
  - GHOST EU
  - ABSORB II
  - ASSURE
  - PRAGUE-19

1 Month

- Higher risk of Scaffold Thrombosis in aggregate data:
  - Cassese et al
  - Stone et al
  - Lipinski et al

6 Month

- FDA issued a safety alert warning
- Abbott restricts use of Absorb BVS will only in clinical registry settings

1 Year

- Lower Efficacy & Safety comparable to DES
  - ABSORB III
  - ABSORB Japan
  - AIDA
  - ABSORB II

2 Years

- Aggregate Data:
  - Toyota et al
  - Sorrentino et al
  - Collet et al
Everolimus-Eluting Bioresorbable Scaffolds Versus Everolimus-Eluting Metallic Stents

Selected studies: Randomized Clinical Trials (RCTs) in which bioresorbable vascular scaffolds were compared to the best in class everolimus eluting stent

- Median time of follow-up was 2 years (range 2 to 3 years).

* Only studies with at least 2-year of follow up were included
AbsorbBVS 7 trial Meta-Analysis Primary Outcomes

Target Lesion Failure

Definite or Probable Scaffold/Stent Thrombosis (ST)

Sorrentino S; Giustino G; Mehran R, Dangas GD et al
J Am Coll Cardiol. 2017 Apr 12. pii: S0735-1097(17)37013-4
AbsorbBVS 7 Trial Meta-Analysis: Thrombosis across overtime

Sorrentino S; Giustino G; Mehran R, Dangas GD et al
J Am Coll Cardiol. 2017 Apr 12. pii: S0735-1097(17)37013-4
Device Thrombosis: Stratified by Vessel Size

**RVD <2.25 mm**

- HR [95% CI] = 3.34 [0.75, 14.91]
- p=0.09

**RVD ≥2.25 mm**

- HR [95% CI] = 3.08 [0.91, 10.47]
- p=0.06

Stone G. Presented at TCT 2017
Late Series of Human Very Late scaffold thrombosis: The presence of malapposed-uncovered scaffold struts in direct contact with thrombus suggests a potential triggering role (all cases).
AbsorbBVS On-DAPT-status

@ discharge
- DAPT: 97%
- Aspirin: 97%
- P2Y12 inhibitor: 100%

@ VLScT
- DAPT: 83%
- Aspirin: 17%
- P2Y12 inhibitor: 17%

Räber L. Presented at TCT 2017
AbsorbBVS Rates of failure mechanisms

- Underexpansion or scaffold shrinkage: 42%
- Neoatherosclerosis: 18%
- Malapposition: 18%
- Others: 11%
- Scaffold discontinuity: 11%

Räber L. Presented at TCT 2017

n = 38
Presumed specific mechanisms of increased events (ScT) with AbsorbBVS

- Mechanically less strong material
  - Thicker struts/
    - Larger surface area
  - Less embedment/
    - Under-expansion
  - Disturbed microcirculation
  - Predisposition to
    - Early thrombosis
- Late discontinuities/ dismantling without encapsulation
  - Late/ Very Late Thrombosis

Serruys and Onuma, EuroIntervention 2017 Apr 20;12(17):2047-2056
Strut thickness varies among BRS types

<table>
<thead>
<tr>
<th>Scaffold</th>
<th>Absorb BVS 1.1</th>
<th>DESolve</th>
<th>DESolve Cx</th>
<th>Fantom</th>
<th>FORTITUDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td>OCT appearance</td>
<td>157 µm</td>
<td>150 µm</td>
<td>120 µm</td>
<td>125 µm</td>
<td>150 µm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scaffold</th>
<th>Magmaris</th>
<th>ART</th>
<th>MeRES 100</th>
<th>Mirage</th>
<th>Firesorb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td>OCT appearance</td>
<td>150 µm</td>
<td>170 µm</td>
<td>100 µm</td>
<td>125 µm</td>
<td>100-125 µm</td>
</tr>
</tbody>
</table>

Sotomi et al. Circ Res. 2017 Apr 14;120(8):1341-1352
Biodegradation process of CE-mark approved BRS.

<table>
<thead>
<tr>
<th>Material</th>
<th>Hydrolysis</th>
<th>Krebs cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLLA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DESSolve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desaminotyrosine polycarbonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fantom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magmaris</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Onuma Y Presented at Euro PCR 2017
Evolution of the BIOTRONIK Magnesium Scaffold

<table>
<thead>
<tr>
<th>Device generation</th>
<th>AMS 4-month</th>
<th>DREAMS 1G 6-month</th>
<th>DREAMS 2G (Magmaris) 6-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sizes (mm)</td>
<td>Ø 3.0 &amp; 3.5</td>
<td>Ø 3.25 &amp; 3.5</td>
<td>Ø 2.5, 3.0 &amp; 3.5</td>
</tr>
<tr>
<td></td>
<td>Length: 15, 20</td>
<td>Length: 15</td>
<td>Length: 15, 20, 25</td>
</tr>
<tr>
<td>Backbone</td>
<td>Mg alloy</td>
<td>Refined Mg alloy</td>
<td>Refined Mg alloy</td>
</tr>
<tr>
<td>Strut thickness/width</td>
<td>165/80 μm</td>
<td>120/130 μm</td>
<td>120/120 μm (Ø 2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150/150 μm (Ø 3.0 &amp; 3.5)</td>
</tr>
<tr>
<td>Markers</td>
<td>none</td>
<td>none</td>
<td>Ta-composite</td>
</tr>
<tr>
<td>Coating - drug</td>
<td>none</td>
<td>PLGA/PTX</td>
<td>PLLA/SIR</td>
</tr>
<tr>
<td>Crossing profile in mm</td>
<td>1.6</td>
<td>1.5</td>
<td>1.75 (BIOSOLVE-II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.50 (BIOSOLVE-III)</td>
</tr>
<tr>
<td>Drug elution kinetics</td>
<td>n.a.</td>
<td>like Taxus</td>
<td>like Orsiro</td>
</tr>
<tr>
<td>Absorption period in month</td>
<td>1-2</td>
<td>3-4 (Mg)</td>
<td>≈12 (Mg)</td>
</tr>
<tr>
<td>In-segment Late Lumen Loss (mm)</td>
<td>0.83±0.51</td>
<td>0.52±0.48</td>
<td>0.27±0.37 (BIOSOLVE-II)</td>
</tr>
<tr>
<td>TLF* (%)</td>
<td>23.8</td>
<td>4.3</td>
<td>3.3%</td>
</tr>
<tr>
<td>Definite or Probable Scaffold Thrombosis (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG

Waksman R  Presented at TCT 2017
In a porcine arterio-venous shunt model, Magmaris was less thrombogenic than Absorb...

Waksman R et al. Circ CV Interv. 2017 Aug, published online
AMARANTH’S MINIATURIZATION PROCESS

Strut miniaturization maintaining radial force to the <100µm range without compromising biomechanical behavior/properties

Small Studies Ongoing (n<200)

150-µm  FORTITUDE ~20% SA*
115-µm  APTITUDE ~21% SA*
<100-µm  MAGNITUDE ~22% SA*

*Surface Area at RBP, ABSORB BVS currently at ~27% at RBP

*Colombo A. First Report Investigation, TCT2016
DESolve Cx Bioresorbable Coronary Scaffold System

- **120 µm strut thickness**
  - Improved deliverability

- **System crossing profile (0.053” - 1.3mm*)**

- **6 Fr (0.71” – 1.8mm) guide catheter compatible**

- **0.014” wire compatible**
<table>
<thead>
<tr>
<th>Status</th>
<th>Study Description</th>
<th>Countries</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>First-in-human safety study (n=7)</td>
<td></td>
<td>Year 3</td>
</tr>
<tr>
<td>Enrolling</td>
<td>Multi-center safety and performance study (n=240)</td>
<td>Europe, Brazil</td>
<td>Year 2</td>
</tr>
<tr>
<td>Enrolling</td>
<td>Long lesion and multiple vessel, multi-center study (n=50)</td>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>Enrolling</td>
<td>Single center pilot study in STEMI (n=20)</td>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>Planning</td>
<td>European post-market multi-center registry (n=125+)</td>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>Planning</td>
<td>Multi-center RCT vs. metallic DES (n=1,800-2,200)</td>
<td>USA, Europe</td>
<td></td>
</tr>
<tr>
<td>Planning</td>
<td>Multi-center RCT vs. metallic DES (n=350-400)</td>
<td>Japan</td>
<td></td>
</tr>
</tbody>
</table>

J. Hermiller Presented at TCT 2017
MeRes100 (developed in INDIA)
Sirolimus Eluting Bioresorbable Vascular Scaffold
100 micron strut thickness
BRS Era: Conclusions 2017

We hoped for a stent that dissolves (was it too much to ask?)

• After it does its job
• And leaves no mark behind
• 1 was approved early indeed on long term promises...

Yet, our hopes were betrayed - BRS animal models inaccurate...

• DAPT came fast as a savior (sounds familiar?), but a bit too late...

We learnt a lot of lessons:

• Metallic EES may be super tough comparator!
• *Never Underestimate Endovascular Thrombosis*...
• Strut thickness is indeed a very basic factor to get right
• A BRS should, in fact, *Dissolve in time when in human coronaries*

Bio-Engineering principles are improving steadily

A restart is expected – 2\textsuperscript{nd} / 3\textsuperscript{rd} Generation BRS
Bioresorbable Vascular Scaffolds
The fourth revolution in interventional Cardiology?

Indolfi C, De Rosa S, Colombo A. 2016 Dec;13(12):719-729