PtCr EES, Beyond PROMUS Element™

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Desired Features of Next Generation DES

**Next Generation DES**
Desired Attributes

- **Acute Performance**
  - Deliverable
  - Visible
  - Trackable
  - Conformable

- **Efficacy**
  - Good Clinical Outcomes
  - Low TLR
  - Low Clinical Symptom Recurrence

- **Safety**
  - No Stent Thrombosis
  - Shortened DAPT Requirement
  - Safer for DAPT Interruption

**SYNERGY™ Stent**
Attributes and Design Goals

- **Stent & Delivery System**
  - PtCr Stent Platform
  - Thin Struts
  - Modified Cell Geometry
  - Improved Deliverability

- **Low Drug Load**
  - Drug Load = PROMUS™/Xience™
  - Release kinetics similar to PROMUS™/Xience™

- **Reduced Polymer Load**
  - Bioabsorbable Polymer
  - BMS within 4mo
  - Abluminal Polymer Coating
  - Low Polymer Mass

Presented by Ian Meredith AM, MBBS PhD, TCT 2011 The SYNERGY™ Stent System is an investigational device and not for sale.
Platinum Chromium (PtCr) Stent Material

Biocompatibility

Radial Strength
Bench Test Data

Radiopacity

Flexibility

The ION™ Stent is commercialized as TAXUS™ Element™ outside the US.
### Platinum Chromium (PtCr) Stent Series
Novel alloy with different drug & polymer choices

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Platform</th>
<th>Drug</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMEGA™ Stent</td>
<td>Element</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>TAXUS™ Element™ / ION™ Stent</td>
<td>Element</td>
<td>Paclitaxel</td>
<td>Translute™ (SIBS)</td>
</tr>
<tr>
<td>PROMUS Element™ / PROMUS Element™ Plus</td>
<td>Element</td>
<td>Everolimus</td>
<td>PVDF-HFP PBMA</td>
</tr>
</tbody>
</table>

**Next Generation PtCr Stent Under Development**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Platform</th>
<th>Drug</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNERGY™ Stent with bioabsorbable polymer</td>
<td>Synergy</td>
<td>Everolimus</td>
<td>PLGA</td>
</tr>
</tbody>
</table>

The ION™ Stent is commercialized as TAXUS™ Element™ outside the US.

The SYNERGY™ Stent System is an investigational device limited by law to investigational use. Not for sale.
Stent Design Progression: Drug Delivery

Anti-Restenotic Agents

BMS → DES (Everolimus)

Polymer Coating

Biostable Conformable Polymer → Bioabsorbable Abluminal Polymer
SYNERGY™ Stent Design Goals

Bioabsorbable Polymer Theory
- Polymer only needed for controlling drug release
- Amount of polymer should be minimized
- Polymer should disappear after drug is released

SYNERGY™ Stent Design Goal
Thin abluminal bioabsorbable polymer coating designed to resorb shortly after drug delivery leaving behind a BMS

PtCr Stent Platform
- Biocompatibility, strength, flexibility, and visibility
- Acute performance

Hypothesis
Patient can be managed like BMS—patient after polymer is gone

Modified from Ian Meredith AM, MBBS, PhD at TCT 2011. The SYNERGY™ stent is an investigational device and not for sale.
Early Discontinuation of Anti-platelet Therapy Is Strongest Risk Factor for ST with DES

Overall stent thrombosis = 1.3% (P=0.09, N=2,229)

Incidence (%) of various factors:

- Unstable angina: 1.4%
- Thrombus: 2.0%
- Diabetes: 2.5%
- Unprotected left main: 3.3%
- Bifurcation: 3.6%
- Renal failure: 6.2%
- Prior brachy Rx: 8.7%
- Premature antiplatelet discont’d: 29.0%

Not All Patients are the Same
Patient Risk Profile Makes DAPT Duration Difficult to Optimize

Risk Stratification in ARRIVE 1 & 2

Baran, Am J Cardiol 2008;102:541-545
Increased Adverse Event Rates in Patients Less Responsive to Clopidogrel

Decreased Platelet Inhibition

Clopidogrel Responsiveness
Q1: Highest Responsiveness
Q4: Lowest Responsiveness

Barr et al. JACC 2011
Patients may be prescribed DAPT longer than 12 Mo

“Extending DAPT beyond 1 year is considered reasonable by some practitioners based on observational data analysis”

ACC/AHA Guidelines: Circulation 2011

“Data suggest that certain patient populations (e.g. high risk for thromboembolic events, patients after SES or PES implantation), may benefit from prolonged DAPT beyond 1 year.”

ESC Guidelines: European Heart Journal 2010
Importance of Continued DES Innovation

DAPT Considerations

**DES vs. BMS**
- Delayed healing
- VLST
- Longer DAPT vs. BMS
- Discontinuation #1 ST Risk

**Patient Perspective**
- Quality of life
- Side effects
- Other therapies
- Cost
- Peace of mind

**Physician Perspective**
- Concerns with VLST
- Bleeding complications
- Non-compliance
- DAPT interruption
- DAPT responsiveness
SYNERGY™ Stent
Abluminal Bioabsorbable Polymer

Bioabsorbable polymer
(PLGA)
Applied only to the abluminal surface (rollcoat)
Thin strut PtCr Stent

Durable Permanent Polymer
+ Drug
360° Around Stent

Current Durable Polymer

Abluminal Bioabsorbable Polymer

PLGA Bioabsorbable Polymer
+ Everolimus on Abluminal Side of Stent

Presented by Ian Meredith, MBBS, PhD at TCT 2011. The SYNERGY™ Stent is an investigational device and not for sale.
### Design Goals for SYNERGY™ Stent

Drug released over 3 mo and polymer resorbed within 4 mo

**SYNERGY™ Stent**

<table>
<thead>
<tr>
<th>Schematic</th>
<th>Drug</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image]</td>
<td>Burst release</td>
<td>Hydration &amp; polymer molecular weight reduction begins</td>
</tr>
<tr>
<td></td>
<td>Sustained release</td>
<td>Significant reduction in molecular weight &amp; polymer absorption begins</td>
</tr>
<tr>
<td></td>
<td>Drug release is completed</td>
<td>Molecular weight continues to drop &amp; remaining polymer is absorbed</td>
</tr>
</tbody>
</table>

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**H2O**

Everolimus

Lactic & Glycolic Acid

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**Stent Surface**

**Vessel Wall**

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*IC-76708-AA Apr 2012 Slide 14*

BSC data on file. The SYNERGY™ stent system is an investigational device limited by law for investigational use. Not for sale.
The SYNERGY™ stent is an investigational device limited by law for investigational use. Not for sale.
SYNERGY™ Stent

Designed for polymer resorption within 4 months

Polymer Mass Remaining (%)

Time (Days)

PLGA mass assessed in explanted stent and adjacent tissue

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SYNERGY™ Stent Release Kinetics

In vitro KDR

SYNERGY Stent

PROMUS™ Stent
(in vivo)

SYNERGY Stent
½ Dose

Everolimus Cumulative Release (g)

Time (days)

Presented by Ian Meredith, MBBS, PhD at TCT 2010 • The SYNERGY stent is an investigational device. Not for sale.
## SYNERGY™ Stent
### Design Attributes in Perspective

<table>
<thead>
<tr>
<th>Stent</th>
<th>Coating</th>
<th>Approximate Coating Thickness (μm)</th>
<th>Approximate Drug Load μg/mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYNERGY™</td>
<td>Abluminal</td>
<td>3–5</td>
<td>6</td>
</tr>
<tr>
<td>PROMUS™ / Xience™</td>
<td>Conformal</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Resolute Integrity™</td>
<td>Conformal</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>BioMatrix™ Flex</td>
<td>Abluminal</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

The SYNERGY™ stent is an investigational device limited by law for investigational use. Not for sale.
Clinical Trial Plan for the SYNERGY™ Stent

EVOLVE FHU
291 patients
Control Device
PROMUS Element™
Primary Endpoint
30D TLF
6M Late Loss
TCT 2011

EVOLVE II
1684 patients
Control Device
PROMUS Element™ Plus
Primary Endpoint
12M TLF 2014

Planned
EVOLVE QCA/PK
EVOLVE China
EVOLVE DAPT

EVOLVE FHU: Meredith et al. JACC 2012. The SYNERGY™ stent is an investigational device and not for sale.
Patients with de novo native coronary lesions ≤28 mm in length, RVD ≥2.25 mm ≤3.5, %DS>50 (excluded LM disease, CTO, AMI or recent MI)

Randomized 1:1:1 at 29 sites (EU, Australia, New Zealand)

PROMUS Element™ N=98

SYNERGY™ N=94

SYNERGY ½ Dose N=99

Single-blind, noninferiority design
Primary Clinical Endpoint: TLF (TV–CD, TV–MI, or TLR) at 30 days
Primary Angiographic Endpoint: In-stent late loss at 6 months

Presented by Ian Meredith, MBBS, PhD at TCT 2011. The SYNERGY™ Stent is an investigational device and not for sale.
EVOLVE FHU
Target Lesion Failure

30 Days

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMUS Element™</td>
<td>0</td>
</tr>
<tr>
<td>SYNERGY™ SYN</td>
<td>1.1</td>
</tr>
<tr>
<td>SYNERGY™ ½ Dose</td>
<td>3.1</td>
</tr>
</tbody>
</table>

\[ P = 0.49 \]
\[ P = 0.25 \]

6 Months

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
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<tbody>
<tr>
<td>PROMUS Element™</td>
<td>3.1</td>
</tr>
<tr>
<td>SYNERGY™ SYN</td>
<td>2.2</td>
</tr>
<tr>
<td>SYNERGY™ ½ Dose</td>
<td>4.1</td>
</tr>
</tbody>
</table>

\[ P = 1.00 \]
\[ P = 0.72 \]

Intent-to-treat; \( P \) values are versus PROMUS Element (Fisher exact test)

Meredith et al. *JACC* 2012. The SYNERGY™ Stent is an investigational device and not for sale.
Noninferiority is proven because the upper 95.2% confidence bound of the difference in 6-month late loss is <0.20 for both SYNERGY stents.

Intent-to-treat; *P values for superiority comparison

Meredith et al. JACC 2012. The SYNERGY™ Stent is an investigational device and not for sale.
Evolve FHU
Revascularization and ST at 6 Months

Intent-to-treat; P values are versus PROMUS Element (Fisher exact test)

Meredith et al. JACC 2012. The SYNERGY™ Stent is an investigational device and not for sale.
Patients with atherosclerotic native coronary lesions ≤ 34 mm in length, RVD ≥ 2.25 mm ≤ 4.0, %DS ≥ 50
Up to 3 lesions in 2 vessels
(excluded LM disease, CTO, ISR, STEMI)

Randomized 1:1: at up to 160 global sites

PROMUS Element™ Plus
N=842

SYNERGY™
N=842

Single-blind, noninferiority design
Primary Endpoint: TLF (CD, TV-MI, or TLR) at 12 months
Follow-up: 30 days, 6 months, 12 months, 18 months, annual 2-5 years

The SYNERGY™ Stent is an investigational device and not for sale.
Where Would the SYNERGY™ Stent Sit in the DES Landscape?

**Concerns with DES**
- Late ST
- DAPT Compliance
- DAPT Interruption

**SYNERGY™ Stent Design**
- Reduced Polymer Load
- Minimal Drug Burden
- Short Term Polymer Exposure

**Desired Outcomes**
- Improve late events
- Reduce DAPT duration
- Reduce risk with DAPT interruption

BSC data on file. The SYNERGY™ stent is an investigational device limited by law for investigational use. Not for sale.