Next Generation TAVI Systems

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Stanford University, Palo Alto, California, USA
Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Physician Name</th>
<th>Company/Relationship</th>
</tr>
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<tbody>
<tr>
<td>Eberhard Grube, MD</td>
<td>Medtronic, CoreValve: C, SB, AB, OF</td>
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<tr>
<td></td>
<td>Sadra Medical: E, C, SB, AB</td>
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<tr>
<td></td>
<td>Direct Flow: C, SB, AB</td>
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<td></td>
<td>Mitralign: AB, SB, E</td>
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<td>Maya Medical: E, AB</td>
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<td>Abbott Vascular: AB</td>
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<td>Capella: SB, C, AB</td>
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<td>Valtec: E, SB</td>
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<td>Claret, SB</td>
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</table>
TAVI – Current Issues

• Device related Issues
  – Lack in Control and Accuracy in Positioning
  – Lack of Retrievability
  – Paravalvular Leack
  – Access Site Complications
  – Stroke
  – Pacemaker Need
  – Profile size
New TAVI valves are coming to the market in a few year’s time

Today
- Medtronic CoreValve
- Edwards Sapien

Tomorrow
- Next Gen. Medtronic CoreValve
- Boston Sci. Lotus™
- Medtronic Engager
- Saint Jude Portico™
- Edwards Sapien XT
- Direct Flow
- JenaValve
- Symetis ACCURATE
CoreValve Innovation

Focused Efforts on:
• Expansion of patient access
• Further improvement of ease of use
• Continue to advance patient and procedural outcome
CoreValve Evolut Innovation Pipeline

- CoreValve Evolut
  - 23 mm
  - Delivery System

- Next Gen
  - Delivery System

- CoreValve Evolut Recaptureable
  - 23 mm
  - Also compatible with CoreValve 26/29/31 mm

- CoreValve Evolut Recaptureable
  - 26/29/31 mm

Also compatible with AccuTrak Delivery System

18 mm to 29 mm Annulus Size Range to Avoid Patient Prosthesis Mismatch
Recapturable after Valve Deployment

Retrievable, Repositionable, Resheathable

• More control for final valve deployment → Should contribute to reduced PVL and conduction disturbance

• Repositionable system with 18 Fr delivery across full valve size range
…Expect CE Mark Trials on Two New Valve Platforms in 2012

Edwards SAPIEN 3 Valve

Edwards CENTERA Valve

Balloon Expandable

Self Expanding

Commercial Device*  IDE Trial Enrolling

SAPIEN THV  SAPIEN XT THV

U.S. Offering

O.U.S. Commercial Offering

SAPIEN XT THV

OUS Offering

* The Edwards SAPIEN XT valve, the Edwards SAPIEN valve with the Ascendra delivery system, the Edwards SAPIEN 3 valve and the Edwards CENTERA valve are investigational devices and are not available for commercial sale in the U.S.
SAPIEN 3 Advances

Ultra Low-Profile Balloon Expandable Platform

- Designed to further **reduce PV leaks**
- Lower profile valve delivered through a **14 Fr eSheath**
- Discrete valve that anchors in the **annulus**
- Treated bovine pericardial tissue **leaflets**
- Dramatically reduced profile for the **transapical approach**
CENTERA is Edwards’ First Self-Expanding Transcatheter Valve

**Ultra Low-Profile Self Expanding Platform**

- **Motorized delivery system** for stable deployment and single operator use
- **Repositionable**
- Delivered through a 14 Fr eSheath
- Discrete valve that anchors in the annulus
- Treated bovine pericardial tissue leaflets
- Transfemoral and subclavian approach

*First-in-Man Experience Completed*
The Lotus™ Valve System
Product Details and Design Goals

**Device Delivery:**
- Nitinol valve frame
- No balloon inflation or rapid pacing of heart for insertion
- Introducer sheath same outer diameter as commercially available 18F sheaths

**Device Positioning:**
- Self-centering
- Controlled positioning for accurate placement
- Fully retrievable (before release)
- Valve begins functioning early in deployment process

**Device Implant:**
- Bovine pericardium tri-leaflet aortic valve
- Adaptive™ Seal conforms to irregular surfaces of native anatomy to minimize perivalvular leaks

The Lotus Valve System is an investigational device, not available for sale.
Sadra Lotus™ Valve Concept

- Braided nitinol stent structure
- Radial expansion as it shortens
  - Enables a more flexible delivery system
  - Enables device repositioning or retrieval
  - Provides significant radial strength
The Lotus™ Valve System

Components and Function

Nitinol Frame
designed for retrieval and repositioning

Locking Mechanism

Bovine Pericardium
Long-Term Proven material

Adaptive Seal
Designed to conform to irregular anatomical surfaces, and to minimize perivalvular leaks
# REPRISE Clinical Program

## REPRISE I Feasibility

**Objective**

To assess the acute safety and performance of the Lotus™ Valve System for transcatheater aortic valve replacement (TAVR) in symptomatic patients with calcified stenotic aortic valves who are considered high risk for surgical valve replacement.

**Primary Endpoint**

Clinical procedural success: Device Success without inhospital MACCE thru discharge or 7d post-procedure

**Valve size**

23 mm

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### REPRISE I Study Sites in Australia

- Principal Investigator: Prof. Ian Meredith
- Prof. Ian Meredith, Monash Heart Center
- Prof. Rob Whitbourn, St. Vincent Hospital
- Prof. Stephen Worthley, Royal Adelaide Hospital

The Lotus Valve System is an investigational device, not available for sale. See glossary.
# REPRISE Clinical Program

**Objectives**
To evaluate the safety and performance of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with severe calcific aortic stenosis who are considered high risk for surgical valve replacement.

| Primary Endpoint | Device Performance Endpoint: Mean aortic valve pressure gradient at 30d  
Safety Endpoint: All-cause mortality at 30d |
|------------------|--------------------------------------------------------------------------------|
| Valve size       | 23 and 27 mm  
N                 | 120 patients in Australia, France, Germany, UK |

**Principal Investigator**: Prof. Ian Meredith

- Prof. Ian Meredith, Monash Heart Center
- Prof. Rob Whitbourn, St. Vincent Hospital
- Prof. Stephen Worthley, Royal Adelaide Hospital
- Prof. Thierry Lefevre, Institut Jacques Cartier
- Dr. Didier Tchetche, Clinique Pasteur
- Prof. Gilles Rioufol, Univ. De Lyon
- Prof. Didier Carrie, CHU de Rangueil
- Dr. Simon Redwood, St. Thomas Hospital
- Dr. Ganesh Manoharan, Royal Victoria, Belfast
- Dr. Daniel Blackman, Spire Leeds Hospital
- Dr. David Hildick-Smith, Royal Sussex
- Prof. Peter Boekstegers, Helios Klinikum, Siegburg
- Prof. Rudiger Lange, German Heart Center, Munich
- Prof. Friedrich Mohr, Herzzentrum, Leipzig

The Lotus Valve System is an investigational device, not available for sale. See glossary.
## Primary Endpoint - Discharge/7 Days

**REPRISE I (N=11)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>Clinical Procedural Success (per patient)</td>
<td>9/11</td>
</tr>
<tr>
<td>Device Success</td>
<td>10/11</td>
</tr>
<tr>
<td>Successful access, delivery, deployment, valve positioning, delivery system retrieval</td>
<td>11/11</td>
</tr>
<tr>
<td>Intended valve performance&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10/11</td>
</tr>
<tr>
<td>One valve implanted</td>
<td>11/11</td>
</tr>
<tr>
<td>No MACCE through discharge or 7 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10/11</td>
</tr>
</tbody>
</table>

*Presented by Ian Meredith, MBBS, PhD. at EuroPCR 2012*

<sup>a</sup> AVA > 1.0 cm² plus either a mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate/severe prosthetic valve aortic regurgitation

<sup>b</sup> Major adverse cardiovascular or cerebrovascular events including all-cause mortality, peri-procedural MI ≤ 72 hours, major stroke, urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction

Values are n/N
Aortic Regurgitation
Discharge Transthoracic Echocardiography

No Moderate / Severe AR by Independent Adjudication

N = 11
Presented by Ian Meredith, MBBS, PhD. at EuroPCR 2012
Mean Aortic Gradient by Patient

REPRISE I (N=11)

Presented by Ian Meredith, MBBS. PhD at EuroPCR 2012
VARC=Valve Academic Research Consortium; J Am Coll Cardiol 2011, 57:253
Aortic Valve Area by Patient
REPRISE I (N=11)

Presented by Ian Meredith, MBBS, PhD, at EuroPCR 2012
“Discharge” is defined as discharge or 7 days post-procedure, whichever comes first
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
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<tr>
<td>In-hospital MACCE</td>
<td>1/11</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0/11</td>
</tr>
<tr>
<td>Peri-procedural MI (≤72 hours)</td>
<td>0/11</td>
</tr>
<tr>
<td>Major stroke&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1/11</td>
</tr>
<tr>
<td>Urgent/emergent conversion to surgery or repeat procedure for valve-related dysfunction</td>
<td>0/11</td>
</tr>
</tbody>
</table>

Presented by Ian Meredith, MBBS, PhD, at EuroPCR 2012

<sup>a</sup> Preliminary adjudication is major stroke; final adjudication per VARC will occur at 90 days

“Discharge” is defined as discharge or 7 days post-procedure, whichever comes first. MACCE = major adverse cardiovascular and cerebrovascular events; MI = myocardial infarction
Symetis ACURATE TF™ and TA™ Bioprosthesis

- Porcine pericardium
- Self-expanding nitinol stent
- Stent covered inside and out with double porcine pericardium skirt
ACURATE™ Highlights

• Trans Apical:
  - FIM (n=40) 6M results @ EACTS 2011
  - Pilot (n=50) 30D results @ TCT 2011
  - FIM (n=40) 1Y results @ AHA 2011
  - Pivotal (n=150) enrollment start Q4 2011
  - SAVI post-market registry (n=250) with commercial implants
  - Received CE Certification in November 2011 for commercial use

• Trans Femoral:
  - FIM (n=20) enrollment start Q1 2012 (Brazil/Germany/France)
  - Pilot (n=50) enrollment start Q3 2012
ACURATE TF™ 3-Step Implant

Initial Alignment

1. Upper Crown & Gentle Push

2. Stabilization Arches

3. Full Release
ACURATE TA™ Bioprosthesis

- Treats native annuli from 21mm to 27mm
- Repositionable, self-aligning
- Composed of:
  - Biologic porcine tissue valve for long term durability
  - Self-expandable nitinol stent = form fit
  - PET skirt for ↓ PV leak
First Human Use (FHU)

- 3 patients treated in Sao Paulo by Dr. Alex Abizaid
- Feasibility proven – 3 successful implants
- 3 patients discharged home and well at 5 months
- No reported MACCE to date and follow-up ongoing
- Easy catheter tracking and implantation (tactile feedback)
- No procedure difficulties
- Demonstrates good hemodynamics, low leak
- Green light to start TF FIM!
FHU 001

- Good initial positioning
- Easy upper crown positioning
- Controlled deployment
- Minimal leak
- Low gradient
- First patient, first success
## ACURATE TF™ FHU Outcomes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Assessment</th>
<th>Screening TTE</th>
<th>30D</th>
</tr>
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<tbody>
<tr>
<td><strong>Patient 001</strong>&lt;br&gt;Male, 78 y/o&lt;br&gt;STS Score: &lt;6&lt;br&gt;NYHA Class III&lt;br&gt;AAn: 24.0 cm²</td>
<td>Mean Gradient</td>
<td>57 mmHg</td>
<td>7.8 mmHg</td>
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<tr>
<td></td>
<td>AVA/EOA</td>
<td>0.7 cm²</td>
<td>1.9 cm²</td>
</tr>
<tr>
<td></td>
<td>Peak jet</td>
<td>4.9 m/s</td>
<td>2.1 m/s</td>
</tr>
<tr>
<td></td>
<td>PVL / IVL</td>
<td>n/a</td>
<td>+1 / 0</td>
</tr>
<tr>
<td><strong>Patient 002</strong>&lt;br&gt;Female, 72 y/o&lt;br&gt;STS Score: &lt;6&lt;br&gt;NYHA Class III&lt;br&gt;AAn: 22.5 cm²</td>
<td>Mean Gradient</td>
<td>48 mmHg</td>
<td>11.1 mmHg</td>
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<tr>
<td></td>
<td>AVA/EOA</td>
<td>0.8 cm²</td>
<td>1.8 cm²</td>
</tr>
<tr>
<td></td>
<td>Peak jet</td>
<td>4.3 m/s</td>
<td>2.2 m/s</td>
</tr>
<tr>
<td></td>
<td>PVL / IVL</td>
<td>n/a</td>
<td>0 / 0</td>
</tr>
<tr>
<td><strong>Patient 003</strong>&lt;br&gt;Female, 92 y/o&lt;br&gt;STS Score: ≥6&lt;br&gt;NYHA Class III&lt;br&gt;AAn: 22.4 cm²</td>
<td>Mean Gradient</td>
<td>65 mmHg</td>
<td>9.6 mmHg</td>
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<tr>
<td></td>
<td>AVA/EOA</td>
<td>0.4 cm²</td>
<td>1.9 cm²</td>
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<tr>
<td></td>
<td>Peak jet</td>
<td>5.2 m/s</td>
<td>2.4 m/s</td>
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<tr>
<td></td>
<td>PVL / IVL</td>
<td>n/a</td>
<td>+1 / 0</td>
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## TF FIM Design

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<th>Prospective, multicenter, non-randomized, open</th>
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<tr>
<td>Purpose</td>
<td>Feasibility</td>
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<tr>
<td>Enrollment Number</td>
<td>20 patients</td>
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<tr>
<td>Follow-up Visits</td>
<td>Post-procedure, 7 &amp; 30D and 12M</td>
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<tr>
<td>TeleCheck</td>
<td>6M and 2, 3, 4 &amp; 5Y</td>
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<td>Clinical Sites</td>
<td>(1) BR, (3) DE, (1) FR</td>
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<tr>
<td>Study Start</td>
<td>FPI in MAY 2012</td>
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<tr>
<td>Primary Endpoint</td>
<td>ACM @ 30D</td>
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<tr>
<td>Secondary Endpoints</td>
<td>1. MACCE @ 30D and 12M</td>
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<tr>
<td></td>
<td>2. NYHA Class @ 30D and 12M</td>
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<tr>
<td></td>
<td>3. Procedural success post-implant</td>
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<td>4. Device success @ 30D and 12M</td>
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## TF FIM Enrollment

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<th>SITE</th>
<th>MAY</th>
<th>JUN</th>
<th>Total</th>
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<tr>
<td>Bad</td>
<td>2</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Nauheim</td>
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<td></td>
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<td>Hamburg</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Bonn</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Sao Paulo</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>9</strong></td>
<td><strong>10</strong></td>
<td><strong>20</strong></td>
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ACURATE TF™ Take Away

- Successful FHU in Brazil (n=3)
- Currently enrolling in TF FIM trial (n=20)
- 9 patients implanted in Brazil and Germany to date
- TF Pilot (n=50) in Q4
- TF FIM + TF Pilot = TF 70
- TF 70 = CE Mark in 2013
FIM Gradient

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30D</th>
<th>6-Month</th>
<th>12-Month</th>
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<tbody>
<tr>
<td><strong>Mean Grad</strong></td>
<td>51.9</td>
<td>12.3</td>
<td>11.9</td>
<td>11.3</td>
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FIM EOA

<table>
<thead>
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<th>Baseline</th>
<th>30D</th>
<th>6-Month</th>
<th>12-Month</th>
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<tr>
<td>EOA</td>
<td>0.6</td>
<td>1.4</td>
<td>1.5</td>
<td>1.4</td>
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</table>
FIM PV Leak

12M FU: 96.7% of patients $\leq +1$ PVL
Only 1 patient $\geq +2$ PVL
12M FU: 90% of patients with improvement from baseline
Direct Flow Medical

2 sizes matching valvuloplasty balloons

22F Design

18F Design
Conformable cuff design and precise positioning maximizes sealing to prevent PV leaks
Direct Flow Valve

Designed for Patient Safety
• “Surgical” valve design
• Repositionable & Removable
• Minimizes PV Leaks and AI
• Deliverability/Profile
• Immediately competent
• Durability

Unique design allows assessment of patient outcomes prior to final device deployment
2 Year Imaging Follow Up
Bijuklic et al, Circulation Cardiovasc Interv, Nov 2011

Investigational device not for sale in or outside the United States
2 Year Data *(EU Feasibility Trial)*

**NYHA Functional Class**

- Baseline
- 30 D
- 180 D
- 365 D
- 730 D

All Patients
NYHA Class I or II

- Class I
- Class II
- Class III
- Class IV

Investigational device not for sale in or outside the United States
2 Year Data (EU Feasibility Trial)

Aortic Insufficiency

* As measured by TTE

Investigational device not for sale in or outside the United States
2 Year Data *(EU Feasibility Trial)*

**Kaplan Meier Curve - Survival**

- 30 D: 0.91
- 180 D: 0.86
- 365 D: 0.76
- 2 Year: 0.71

2 Year Survival 71%

Investigational device not for sale in or outside the United States
St Jude Medical (Portico Transcatheter Heart Valve)

St. Jude Medical TAVI System:
Next Generation Design Features

Unique self expanding stent design provides the ability to...
- Re-sheath*
- Reposition
- Retrieve*
...the valve at implant site

Bovine and porcine pericardial valve with Anti-calcification technology**

Open stent cell design allows access to coronaries and low crimp profile

Tissue cuff designed to minimize PV leak

Low placement of leaflets/cuff within the stent frame allows for minimal protrusion into the LVOT

Anti-calcification technology is used on SJM Epic™ and Trifecta™ surgical aortic valves

* Until fully deployed
** There is no clinical data currently available that evaluates the long-term impact of anti-calcification tissue treatment in humans
*** Trifecta is an investigational device in the US and is not commercially available.

First Human Implant June 7th, 2011
St. Jude Medical TAVI System: Next Generation Design Features

- **Nitinol** self expanding stent
- Open stent cell allows access to coronaries and low crimp profile
- **Bovine and porcine** pericardial valve (Linx™ anticalcification technology*)
- Low placement of leaflets/cuff within stent frame allows for minimal protrusion into the LVOT

*There is no clinical data currently available that evaluates the long-term impact of anticalcification tissue treatment in humans.
St Jude Medical TAVI System

Program Status

- Pre-IDE meetings in 2010
- First-in-man study
- European trial
- U.S. IDE submission
- CE Mark
Jena Valve

- Self-expanding nitinol stent with flexible stent posts
- Porcine root valve
- Sizes 23, 25, 27
- 32F introducer sheath for transapical access
Paravalvular Regurgitation

<table>
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<tr>
<th></th>
<th>Post procedure</th>
<th>3 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td>None</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Trace</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minimal (Grade 1)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate (Grade 2)</td>
<td>2</td>
<td>0</td>
<td>0</td>
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30 d safety outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>FIM pts (N=10)</th>
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<tbody>
<tr>
<td>All cause death (30 d)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Emergent cardiac surgery</td>
<td>1</td>
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<tr>
<td>Onset of AV block</td>
<td>0</td>
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Heart Leaflet Technology