The Sentinel US Pivotal Clinical Trial Design

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New York Presbyterian Hospital
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>Edwards Lifesciences, Medtronic, Direct Flow, Boston Scientific, Abbott, Claret Medical</td>
</tr>
<tr>
<td>Steering Committee</td>
<td>Edwards Lifesciences, Claret Medical</td>
</tr>
<tr>
<td>SAB (equity)</td>
<td>Thubrikar Aortic Valve, Inc, Dura Biotech, VS Medtech</td>
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</tbody>
</table>
Claret Sentinel™
Cerebral Protection System (CPS)

- Dual (proximal and distal) independent filter cerebral embolic protection device with embolic debris capture and removal
- 3rd generation device
- Universal size and shape
- Deflectable compound curve sheath facilitates cannulation of LCC
- Right transradial 6F sheath access using a standard 0.014” guidewire
- Filters are out of the way of TAVR delivery catheter and accessories during the procedure
<table>
<thead>
<tr>
<th>Study</th>
<th>Principal Investigator</th>
<th>Location</th>
<th># Patients</th>
<th>Trial Type</th>
<th>Procedure</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>First in Man</td>
<td>Prof. Christoph Naber</td>
<td>3 centers in Brazil &amp; Germany</td>
<td>40</td>
<td>Registry</td>
<td>TAVR (CoreValve &amp; Sapien)</td>
<td>EuroIntervention March 2012</td>
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<tr>
<td>MISTRAL-I</td>
<td>Dr. Nicolas van Mieghem</td>
<td>Rotterdam, Netherlands</td>
<td>40</td>
<td>Registry</td>
<td>TAVR (CoreValve &amp; Sapien)</td>
<td>Circulation October 2013</td>
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<tr>
<td>CLEAN-TAVI</td>
<td>Prof. Axel Linke</td>
<td>Leipzig University, Germany</td>
<td>100</td>
<td>Randomized</td>
<td>TAVR (CoreValve)</td>
<td>Manuscript in Review</td>
</tr>
<tr>
<td>MISTRAL-C</td>
<td>Dr. Nicolas van Mieghem</td>
<td>4 centers in Netherlands</td>
<td>74</td>
<td>Randomized</td>
<td>TAVR (Sapien 3)</td>
<td>EuroIntervention - In press</td>
</tr>
<tr>
<td>SENTINEL IDE*</td>
<td>Drs Susheel Kodali, Samir Kapadia, &amp; Prof. Axel Linke</td>
<td>16 centers in USA &amp; 3 in Germany</td>
<td>356</td>
<td>Randomized</td>
<td>TAVR (Sapien XT, Sapien 3, CoreValve, EvolutR)</td>
<td>Active Trial</td>
</tr>
<tr>
<td>SENTINEL-H</td>
<td>Prof. Christoph Naber</td>
<td>10 centers in Europe</td>
<td>220</td>
<td>Registry</td>
<td>TAVR (All-comers)</td>
<td>Presented at EuroPCR 2016</td>
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<tr>
<td>TEVAR – Essen</td>
<td>Prof. R Alexander Jánosi</td>
<td>West German Heart &amp; Vascular Center, Essen Germany</td>
<td>5</td>
<td>Pilot Study</td>
<td>TEVAR</td>
<td>Presented at LINC 2016</td>
</tr>
<tr>
<td>LAAO - Hamburg</td>
<td>Prof. Felix Meincke</td>
<td>AK St Georg, Hamburg Germany</td>
<td>5</td>
<td>Pilot Study</td>
<td>LAAO</td>
<td>Presented at TCT 2015</td>
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<tr>
<td>V-in-V</td>
<td>Dr Tobias Schmidt and Dr Christian Frerker</td>
<td>AK St Georg, Hamburg Germany</td>
<td>15</td>
<td>Registry</td>
<td>Aortic and Mitral V-in-V</td>
<td>British Medical Journal – May 2016</td>
</tr>
</tbody>
</table>
**Pivotal IDE study confirming the therapeutic importance of embolic debris capture and removal during TAVR**

**Objective:** Assess the safety and efficacy of the Claret Medical Sentinel Cerebral Protection System in reducing the volume and number of new ischemic lesions in the brain and their potential impact on neurocognitive function.

**Population:** Subjects with severe symptomatic calcified native aortic valve stenosis who meet the commercially-approved indications for TAVR with the Edwards Sapien THV/XT/S3 or Medtronic CoreValve/EvolutR.

N=356 subjects randomized 1:1:1 at sites in the U.S and Germany.

**Primary Investigators:**
- Samir Kapadia, MD, Cleveland Clinic
- Susheel Kodali, MD, Columbia University Medical Ctr
- Axel Linke, MD, Leipzig University, Germany

**Primary Efficacy Endpoint:** Reduction in median total new lesion volume as assessed by 3Tesla DW-MRI with baseline subtraction.

**Primary Safety Endpoint:** Occurrence of all MACCE at 30 days.

**Key Secondary Analyses** will include correlation of lesion number and volume to neurocognitive assessments, among other predictor analyses.
Protocol Defined Endpoints & Study Success Criteria

• **Primary Safety Endpoint (non-inferiority)**: MACCE at 30days defined as *All Death, All Stroke, and Acute Kidney Injury* derived from the Safety cohort (Safety Arm + Test Arm subjects) must be less than the pre-specified Performance Goal.

• **Primary Efficacy Endpoint (Superiority)**: Reduction in median total new lesion volume between the Imaging Arms (Test and Control Group) as assessed by DW-MRI.

Study Success Criteria

• **Efficacy Success Criteria**: To demonstrate a “treatment effect” of median total new lesion volume is ≥ 30% in favor of the Test Group having a lower median total new lesion volume as compared to the Control Group. This observed ratio difference is derived in order to demonstrate a *meaningful clinical treatment effect*. 
Key Inclusion and Exclusion Criteria

Inclusion:
• Severe symptomatic calcified native aortic valve stenosis who meet the commercially approved indications for TAVR
• Compatible left common carotid artery (6.5 – 10 mm) and brachiocephalic artery (9 – 15 mm) diameters without significant stenosis (> 70%) as determined by Multi-Slice Computed Tomography (MSCT) scan or equivalent imaging modality

Exclusion:
• Vasculature in the right extremity precluding 6Fr sheath radial or brachial access
• Inadequate circulation to the right extremity as evidenced by signs of artery occlusion (modified Allen’s test) or absence of radial/brachial pulse
• Hemodialysis shunt, graft, or arterio-venous fistula involving the upper extremity vasculature
• Aortic valve is a congenital unicuspid or bicuspid valve; or is non-calcified
• Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+)
• Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency
• Symptomatic or asymptomatic severe occlusive carotid disease requiring concomitant CEA/stenting

Exclusion cont.
• Subject has undergone carotid stenting or carotid endarterectomy within the previous 6 weeks
• Recent (within 6 months) CVA or a TIA
• Renal insufficiency (creatinine > 3.0 mg/dL or GFR < 30) and/or renal replacement therapy at the time of screening
• Life expectancy < 12 months due to non-cardiac co-morbid conditions
• Neurologic (Randomized subjects only)
  • Subject had active major psychiatric disease, severe visual, auditory, or learning impairment and who are unable to comprehend English and therefore unable to be consented for the study
• Subjects with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities
• Angiographic
  • Excessive tortuosity in the right radial/brachial/subclavian artery preventing Sentinel System access and insertion
• Subject whose brachiocephalic or left carotid artery reveals significant stenosis, calcification, ectasia, dissection, or aneurysm at the ostium or within 3 cm of the ostium
• Magnetic Resonance Imaging (Randomized subjects only)
  • Contraindications to MRI (subjects with any implantable temporary or permanent pacemaker or defibrillator, metal implants in field of view, metallic fragments, clips, or devices in the brain or eye before TAVR procedure)
• Planned implantation of a pacemaker or defibrillator implantation after TAVR
SENTINEL Study Leadership

Co-Principal Investigators:

Susheel Kodali, MD  Co-director, NYP Columbia Heart Valve Center and Director of Interventional Cardiology Fellowship Program, Columbia University Medical Center

Samir Kapadia, MD  Director, Sones Cardiac Catheterization Laboratory and Director of Interventional Cardiology Fellowship Program, Cleveland Clinic

Axel Linke, MD  Klinik fuer Innere Medizin und Kardiologie, Herzzentrum Leipzig

Clinical Steering Committee Chairman:

Marty Leon, MD  Director, Center for Interventional Vascular Therapy, Columbia University Medical Center

Study Medical Monitor:

Roxana Mehran, MD  Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials, Mount Sinai School of Medicine
SENTINEL Study Core Labs

Magnetic Resonance Imaging Core Lab:
Buffalo Neuroimaging Analysis Center – Buffalo, NY
Dr. Robert Zivadinov

Neurocognitive Core Lab:
Tananbaum Stroke Center, Neurological Institute, Columbia University Medical Center
Ronald Lazar, PhD

Histopathology Core Lab:
CVPath Institute
Dr. Renu Virmani

Sentinel CT Planning Center:
Cedars Sinai Medical Center
Dr. Hasan Jilaihawi
Follow-up Imaging - Unique Challenges

- Smaller lesions (micro-emboli) vs. conventional strokes (macro-emboli)
- Highly affected by usually negligible artifacts
- No well-established imaging or analysis protocols
- Longitudinal match-up is much more challenging than with usual stroke analysis
- Additional confounding factors
  - Pre-existing pathology in aged population
  - High risk-factor population
  - New-onset atrial fibrillation (NOAF) can cause secondary emboli
MRI methodology

- MRI quality crucial to reliable study results
- 3-Tesla MR scanner for optimal resolution across all study sites to increase resolution
- Diffusion-weighted (DW) and fluid-attenuated inversion recovery (FLAIR) MR sequences
  - To assess both acute (DW) and chronic (FLAIR) lesions
- Novel methodology with serial scan acquisition at baseline, 4-7 days and 30 days
  - $B_0$ mapping performed to eliminate over-estimation of existing lesions.
- Core lab analysis of all scans
  - Buffalo Neuroimaging Analysis Center, Buffalo, NY
  - Verification of MRI quality by use of dummy scans prior to site activation
SENTINEL Highly Specific/Sensitive Cognition Battery

<table>
<thead>
<tr>
<th>Neurocognitive Test</th>
<th>Laterality</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails A</td>
<td>Bi-hemispheral</td>
<td>Attention</td>
</tr>
<tr>
<td>Trails B</td>
<td>Bi-hemispheral</td>
<td>Executive function</td>
</tr>
<tr>
<td>Digit Span</td>
<td>Bi-hemispheral</td>
<td>Attention</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>Bi-hemispheral</td>
<td>Processing speed</td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>Left hemisphere</td>
<td>Processing speed</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td>Left hemisphere</td>
<td>Verbal memory</td>
</tr>
<tr>
<td>Rey Complex Figure (Copy)</td>
<td>Right hemisphere</td>
<td>Executive function</td>
</tr>
<tr>
<td>Brief Visual Memory Test</td>
<td>Right hemisphere</td>
<td>Visual memory</td>
</tr>
<tr>
<td>Mini Mental State Exam</td>
<td>-</td>
<td>Mental status</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>-</td>
<td>Depression</td>
</tr>
</tbody>
</table>

• NIH Stroke Scale is a limited assessment

• Cognition battery is a bilateral assessment evaluating 6 different domains

• MoCA and MMSE types of cognition tests are limited in full spectrum domain analysis and can result in false positive scores within narrow range of change from baseline.
SENTINEL data types for endpoint correlations

- **Histopathology and Histomorphometry**
  - Presence of debris in Filters
  - Type of debris in filters
  - Size of debris in filters
  - Stratified by valve type

- **Imaging**
  - Total lesion volume/group
  - Total number of lesions/group
  - **Incidence of cerebral infarction/group**
  - Cerebral territory mapping for protected vs all territories
  - Cerebral vascular mapping for protected vs all territories

- **Neurological & Cognitive**
  - Prevalence of large volume lesions and correlation to neurocognitive decline in all territories
  - Prevalence of large lesion density and correlation to neurocognitive decline in all territories
  - VARC 2 defined incidence of clinical strokes/group/territory
Final SENTINEL Enrollment Status (n=363)
**SENTINEL Patient Flow**

**Intent to Treat Population**

- **Imaging Control**
  - 119 Randomized
  - n/a No Sentinel
  - 1 No TAVR

- **Imaging Test**
  - 121 Randomized
  - 8 No Sentinel
  - 1 No TAVR

- **Safety**
  - 123 Randomized
  - 2 No Sentinel
  - 2 No TAVR

**Subjects Receiving both TAVR and Sentinel**

- 118
- 112
- 119

Note: 10 patients not receiving Sentinel include 6 due to insufficient vascular access, 1 due to LAA thrombus found at time of procedure, and 3 due to miscellaneous reasons.
## Baseline Aggregate Patient Demographics

### Key Demographics (Safety, Imaging Test and Control arms)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aggregate ITT Population (Safety, Imaging Test and Control Arms, n=363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>82.3 ± 8.31</td>
</tr>
<tr>
<td>Female (%)</td>
<td>52.1%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 6.26</td>
</tr>
<tr>
<td>STS PROM score – median (%)</td>
<td>6.7 ± 3.79</td>
</tr>
<tr>
<td>&lt;4%</td>
<td>22.7%</td>
</tr>
<tr>
<td>4-7%</td>
<td>41.7%</td>
</tr>
<tr>
<td>8-15%</td>
<td>31.5%</td>
</tr>
<tr>
<td>&gt;15%</td>
<td>4.1%</td>
</tr>
<tr>
<td>NYHA Class III or IV (%)</td>
<td>81.3%</td>
</tr>
</tbody>
</table>

Note: Continuous data presented as Mean ± SD (n); Min, Max. Categorical data presented using % (n/N).

ITT = Intention to treat population
# Baseline Patient Characteristics

Other comorbidities (Safety, Imaging Test and Control arms)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aggregate ITT Population (Safety, Imaging Test and Control Arms, n=363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Atrial Fibrillation</td>
<td>31.7%</td>
</tr>
<tr>
<td>History of Peripheral Vascular Disease</td>
<td>15.2%</td>
</tr>
<tr>
<td>History of Diabetes</td>
<td>35.0%</td>
</tr>
<tr>
<td>Previous Stroke with Permanent Deficit&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5.8%</td>
</tr>
<tr>
<td>Previous Transient Ischemic Attack (TIA)</td>
<td>7.4%</td>
</tr>
<tr>
<td>Porcelain Aorta</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Note: Continuous data presented as Mean ± SD (n); Min, Max. Categorical data presented using % (n/N).

ITT = Intention to treat population

<sup>1</sup> Defined as neurological deficit lasting more than 24 hours confirmed by imaging.
Baseline Patient Characteristics
Valve criteria (Safety, Imaging Test and Control arms)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aggregate ITT Population (Safety, Imaging Test and Control Arms) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve Area (cm²)</td>
<td>0.7 ± 0.18 (359)</td>
</tr>
<tr>
<td>Aortic valve area index (cm²/m²)</td>
<td>0.4 ± 0.10 (353)</td>
</tr>
<tr>
<td>Mean aortic valve gradient (mmHg)</td>
<td>42.3 ± 14.38 (357)</td>
</tr>
<tr>
<td>Peak aortic-jet velocity (m/sec)</td>
<td>4.1 ± 0.99 (294)</td>
</tr>
</tbody>
</table>

Note: Continuous data presented as Mean ± SD (n); Min, Max. Categorical data presented using % (n/N). ITT = Intention to treat population
Follow-up Compliance: MRI follow-up

119 Control Total

189/230 = 82.17% MITT
Follow-up Compliance: 30 Day Neurocog

184/230 = 80.00% MITT
Follow-up Compliance: 30-day safety

30 Day Safety

<table>
<thead>
<tr>
<th>YES</th>
<th>NO Imaging Arm</th>
<th>Test Group</th>
<th>Pt expired</th>
<th>YES</th>
<th>NO</th>
<th>No procedure</th>
<th>Safety Arm</th>
<th>Pt expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>7</td>
<td>9</td>
<td>1</td>
<td>110</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Count
- YES: 104
- NO Imaging Arm: 7
- Test Group: 9
- Pt expired: 1
- YES: 110
- NO: 6
- No procedure: 4
- Safety Arm: 3

Percentage
- YES: 86.0%
- NO Imaging Arm: 5.8%
- Test Group: 7.4%
- Pt expired: 0.8%
- YES: 89.4%
- NO: 4.9%
- No procedure: 3.3%
- Safety Arm: 2.4%

119 Control Total
121 Test Total

214/233=91.85% MITT
Conclusions

• SENTINEL is the largest randomized trial to date evaluating the role of cerebral embolic protection in TAVR
• The rigorous trial design allows the investigation of multiple hypothesis and correlation of imaging findings to clinical outcomes
  • Pre-procedure MRI, with 3T assessment and independent corelab calibration and blinded analysis
  • Specific and comprehensive neurocognition assays administered by certified neuropsychologists and managed and blindly analyzed by an independent corelab
  • Diligence in compliance and follow-up due to multiplicity of the assessments
  • Avoiding composite endpoints that mute the impact of individual components of safety and efficacy
• SENTINEL trial will help elucidate the role of cerebral protection in the high risk TAVR population and set the stage for the lower risk populations.

SENTINEL results to be released in Fall 2016