Sentinel®
Cerebral Protection System During TAVR

February 23, 2017
Claret Medical, Inc.
Circulatory System Devices Panel
Introduction

Thomas Engels
Vice President of Clinical Affairs
Claret Medical, Inc.
The Sentinel Cerebral Protection System

- Class 2 (proposed), temporary accessory device
- Placed prior to and removed after Transcatheter Aortic Valve Replacement (TAVR)
- TAVR associated with cerebrovascular events\(^1\)
- Embolic Protection Devices (EPD) have been used in carotid stenting for >15 years
- No alternative option available for embolic protection in TAVR
- Sentinel investigational in US
- Sentinel CE Marked 2013
  - >3,000 TAVR procedure

Proposed Sentinel System Indication

The Sentinel® Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce peri-procedural ischemic brain injury.

The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 mm – 10 mm for the left common carotid arteries.
Animation of the Sentinel System During TAVR
Safety and Effectiveness Outcomes

- Primary Safety
  - 30-Day MACCE vs. Performance Goal – Achieved

- Primary Effectiveness – Median New Lesion Volume (DW-MRI)
  - Observed treatment effect ≥ 30% – Achieved
  - Test vs. Control – Not achieved

- Other Relevant Study Outcomes
  - Sentinel system successfully delivered & retrieved in 94% of patients
  - Major Sentinel access-related complications were rare (N=1, 0.4%)
  - Embolic debris captured in 99% of patients
US Medical Device Classification

- **Class 1**
  - Lowest Risk
  - e.g. Surgical Gauze

- **Class 2**
  - Medium Risk
  - e.g. BAV

- **Class 3**
  - Highest risk
  - e.g. TAVR

- Medium risk, temporary accessory device
- *De Novo* pathway required due to lack of predicate cerebral protection device
- *De Novo* pathway risk/benefit balance on the basis of the totality of pre-market evidence and post market measures
Presentation Agenda

Background, Device Description, Trial Design, Safety and Effectiveness Data
Martin B. Leon, MD
Professor of Medicine,
Columbia University Medical Center

Histopathology
Renu Virmani, MD
President, CVPath Institute, Inc.
Clinical Professor, George Washington University

History of Neuroprotection
William A. Gray, MD
System Chief of the Division of Cardiovascular Disease,
Lankenau Medical Center, Main Line Health

Conclusion
Azin Parhizgar, PhD
President and Chief Executive Officer
Claret Medical, Inc.
# Additional Experts

## Interventional Cardiology
- **Samir Kapadia, MD**  
  Director, Cardiac Catheterization Laboratory  
  Cleveland Clinic

- **Susheel Kodali, MD**  
  Director, Structural Heart & Valve Center  
  Columbia University Medical Center

- **Axel Linke, MD**  
  Co-director, Department of Internal Medicine/Cardiology  
  University of Leipzig Heart Center

- **Roxana Mehran, MD**  
  Professor of Medicine, Cardiology  
  Mount Sinai, New York

## MRI Neuroimaging
- **Robert Zivadinov, MD, PhD**  
  Professor of Neurology  
  Director, Buffalo Neuroimaging Analysis Center

- **Michael Dwyer, PhD**  
  Director Of Technical Imaging  
  Buffalo Neuroimaging Analysis Center  
  Assistant Professor of Neurology  
  University of Buffalo

## Neurocognition
- **Ronald Lazar, PhD**  
  Professor of Neuropsychology  
  Columbia University Medical Center

## Neurology and Neurosurgery
- **Maxim Mokin, MD, PhD**  
  Director of Neuro Interventional Surgery  
  University of South Florida Health

- **Jesse Weinberger, MD**  
  Vascular Neurology Specialist  
  Mount Sinai Hospital

## Statistics
- **Roseann White, MA**  
  Director, Pragmatic Clinical Trial Statistics  
  Duke Clinical Research Institute
Background

Martin B. Leon, MD
Professor of Medicine
Columbia University Medical Center
Strokes are Considered a Major Complication after TAVR

PARTNER 1A RCT (SAPIEN TAVR vs. Surgery); 699 high-risk patients with severe AS;
Typical Examples of Heavily Calcified Aortic Valves

Radiograph of surgical specimen

Autopsy specimen
Technological refinement of transcatheter valves and adjunctive procedures, such as the use of embolic protection devices, will facilitate transcatheter replacement and may improve outcomes, but these new devices should be evaluated in controlled trials with randomization against current standard techniques.
In 2015, TAVR accounted for 32% of all Medicare AV replacements in the US.

Globally, TAVR is expected to grow approximately 4-fold in the next 10 years.

Courtesy of Dr M. Leon TVT 2016; Adapted from Credit Suisse TAVI Comment – January 2015
Strokes After TAVR

- Approximately 3% to 7% at 30 days in high surgical risk patients (CEC adjudicated FDA studies)
- Up to 85% of strokes occur within 1 week of TAVR
- Associated with increased 1-year mortality and reduced quality-of-life
- Frequency is highly dependent on stroke definitions (e.g. VARC-2*) and ascertainment methods (e.g. w/wo neurology assessments)

* VARC-2 = valve academic research consortium, standard definitions (JACC, 2012)
Strokes After TAVR

- 2621 patients from PARTNER (high and extreme risk); CEC adjudication
- Acute-phase (peri-procedural) stroke risk peaked at 2 days, with a low constant risk of 0.8% per year

Strokes After TAVR (Acute Phase)

Clinical neurologic events

- Strokes (disabling and non-disabling)
- Transient ischemic attacks (TIA)

Brain injury on neuro-imaging studies detected by DW-MRI

Neuronal injury without overt symptoms which may result in acute or chronic changes in neurocognitive function

1 Lansky AJ et al; JACC, Vol 69, No.6, 2017
Frequent early DW-MRI abnormalities (68%-100% of patients) after TAVR from 9 studies

Most patients have multiple infarcts which represent permanent ischemic brain damage

SENTINEL trial based on results from predicate trial (CLEAN-TAVI)
- Randomized, controlled study in 100 patients
- Single TAVR system
- Exact MRI methodology was used by the same core laboratory as is used in the current study
Sentinel Cerebral Protection System: Device Description and Case
Protected vs All Territories
Intra-cerebral Vasculature

Protected blood flow to the brain

RVA ~10%
RCCA ~40%
LCCA ~40%

Sentinel Placement

Unprotected blood flow to the brain

LVA ~10%

Protected and Unprotected Cerebral Vascular Territories

- **Protected**: 74% brain volume
- **Partially Protected**: 24% brain volume
- **Unprotected**: 2% brain volume
Sentinel Cerebral Protection System During TAVR

- Two independent filters capture & remove embolic material
- Polyurethane filter, pore size = 140 µm
- Standard R trans-radial sheath access (6F)
- One size accommodates most vessel sizes (brachiocephalic 9-15 mm and left common carotid [LCC] 6.5-10 mm)
- Deflectable compound-curve catheter facilitates cannulation of LCC
- Minimal profile in aortic arch (little interaction with other devices)
Sentinel Cerebral Protection System During TAVR – Case
SENTINEL Trial Overview
Patients with Severe Symptomatic Aortic Stenosis undergoing TAVR

Patients Randomized (1:1:1) (N=363)

- SAFETY ARM TAVR with Sentinel (N=123)
- TEST ARM TAVR with Sentinel (N=121)
- CONTROL ARM TAVR Only (N=119)

Histopathology & Morphometry

Clinical Follow-Up (Neurology Assessments in all patients)

Serial MRIs (Baseline, Day 2-7 & Day 30)

Serial Neurocognitive Assessment (Baseline, Day 30 & Day 90)
Key Inclusion Criteria

- Patients with symptomatic severe aortic stenosis eligible for treatment with a US commercially approved TAVR system
  - 4 different TAVR systems used (not stratified during randomization)

- Acceptable aortic arch anatomy and vessel diameters without significant stenosis
  - Brachiocephalic diameter 9 - 15 mm
  - Left common carotid diameter 6.5 - 10 mm
Key Exclusion Criteria

- Anatomic
  - Right extremity vasculature not suitable
  - Brachiocephalic, left carotid or aortic arch not suitable

- Clinical
  - CVA or TIA within 6 months
  - Neurological disease with persistent deficits
  - Carotid disease requiring treatment within 6 weeks
  - Contraindications to MRI
  - Renal insufficiency (CR >3.0 mg/dL or GFR <30 cc/min)
  - Severe LV dysfunction (EF <20%)
  - Balloon valvuloplasty (BAV) within 30 days
Multicenter Trial: 363 Patients at 19 Sites

5 Highest Enrolling Sites:
- Cedars-Sinai Medical Center (N=73)
- Leipzig Heart Center (N=66)
- University of Washington (N=15)
- University of Texas, Houston (N=12)
- University of Virginia (N=12)
Study Administration

**Co-Principal Investigators:**
Susheel Kodali, MD  
Columbia University Medical Center

Samir R. Kapadia, MD  
Cleveland Clinic

Axel Linke, MD  
Co-director, Department of Internal Medicine/Cardiology  
University of Leipzig Heart Center

**Clinical Steering Committee Chairman:**
Martin B. Leon, MD  
Columbia University Medical Center

**Study Medical Monitor:**
Roxana Mehran, MD  
Mount Sinai School of Medicine

**Clinical Events Committee:**
Cardiovascular Research Foundation  
Chair: Ozgen Dogan, MD  
Neurologists: Jesse Weinberger, MD  
Joshua Willey, MD

**Data Safety Monitoring Board:**
Cardiovascular Research Foundation  
Chair: Blase A. Carabello, MD

**Histopathology / Morphometry Core Laboratory:**
CV Path Institute  
Chair: Renu Virmani, MD

**MRI Core Laboratory:**
Buffalo Neuroimaging Analysis Center, University of Buffalo  
Chair: Robert Zivadinov, MD, PhD

**Neurocognitive Core Laboratory:**
Tananbaum Stroke Center, Neurological Institute  
Columbia University  
Chair: Ronald M. Lazar, PhD

**Sentinel CT Planning Center:**
Cedars-Sinai Medical Center  
Chair: Hasan Jilaihawi, MD

**Statistical Analysis**
Duke Clinical Research Institute  
Project Director: Roseann White, MA  
North American Science Associates, Inc (NAMSA)
Valve Type Distribution Over Time

Sapien XT (N=64) CoreValve (N=14) Evolut R (N=93) Sapien 3 (N=188)

# of Valves


8 18 29 5 9 13 60 46 25 1 3 1

82 53
Distribution of Valve Types Across Study Arms

No Significant Differences in Valve-type Distribution (p = 0.71)
SENTINEL Trial
Safety and Performance
**SEN TINEL Safety Populations**

Patients with Severe Symptomatic Aortic Stenosis Undergoing TAVR

Patients Randomized (1:1:1) (N=363)

- Safety Arm (N=123)
  - 2 No TAVR
  - 2 LTFU
  - 2 Withdrawal
- Test Arm (N=121)
  - 1 No TAVR
  - 1 LTFU
  - 2 Withdrawal
- Control Arm (N=119)
  - 1 No TAVR
  - 1 LTFU
  - 6 Withdrawal

Safety Cohort (N=363)

ITT (N=117)

- Safety Arm (N=117)
  - 2 No Sentinel
- Test Arm (N=117)
  - 7 No Sentinel
- Control Arm (N=111)
  - 1 No Sentinel

As-Treated (N=115)

- Safety Arm (N=115)
- Test Arm (N=110)
- Control Arm (N=111)
Primary Safety Endpoint

- Non hierarchical MACCE at 30 days
  - All-cause mortality
  - All strokes
  - Acute kidney injury (Stage 3) within 72 hours
- Historical MACCE performance goal
  - Weighted average of all FDA pivotal TAVR trials approved at time of SENTINEL trial initiation = 13.3%
  - Upper-bound of one-sided 95% CI for MACCE derived from Safety Cohort (Safety Arm + Test Arm subjects) must be <18.3% (13.3% + 5% non-inferiority margin)
- Device cohort (Safety + Test arm) also compared to concurrent randomized Control arm
# Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Sentinel Safety Arm (N=123)</th>
<th>Sentinel Imaging Arm (N=121)</th>
<th>Sentinel Control Arm (N=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, yrs)</td>
<td>82</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td>Female (%)</td>
<td>55</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>STS PROM Score (mean, %)</td>
<td>6.2</td>
<td>6.4</td>
<td>7.5</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Previous TIA (%)</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>h/o atrial fibrillation (%)</td>
<td>30</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Heavily calcified aorta (%)</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>h/o CAD (%)</td>
<td>54</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>h/o PVD (%)</td>
<td>16</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>NYHA III/IV (%)</td>
<td>83</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>$0.7 \pm 0.18$</td>
<td>$0.7 \pm 0.17$</td>
<td>$0.7 \pm 0.20$</td>
</tr>
<tr>
<td>Mean aortic valve gradient (mmHg)</td>
<td>$42 \pm 15$</td>
<td>$44 \pm 15$</td>
<td>$41 \pm 14$</td>
</tr>
</tbody>
</table>
# Sentinel Access and Device Success

## Reasons for No Sentinel (N=13, 5.6%)
- No TAVR: 3
- Inadequate vascular access: 6
- Late screen failure: 3
- Test patient treated as Control (protocol deviation): 1

<table>
<thead>
<tr>
<th>Sentinel Access</th>
<th>Sentinel (Safety + Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial</td>
<td>94.4%</td>
</tr>
<tr>
<td>Brachial</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Device Success</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Both Filters Deployed*</td>
<td>94.4%</td>
</tr>
<tr>
<td>≥ One Filter Deployed</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

*Acute delivery and retrieval success: Deployment and retrieval of the proximal and distal filters in accessible anatomies (not excessively tortuous or calcified)
## TAVR Procedural Factors in SENTINEL Study

<table>
<thead>
<tr>
<th></th>
<th>Sentinel (Safety + Test)</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR Procedure Time (Mean Minutes(^1))</td>
<td>87</td>
<td>74</td>
<td>0.013</td>
</tr>
<tr>
<td>TAVR Fluoroscopy Time (Mean Minutes(^2))</td>
<td>19</td>
<td>17</td>
<td>0.073</td>
</tr>
</tbody>
</table>

\(^1\) Time elapsed between first arterial access and removal of the last guide from the arterial access sheath

\(^2\) Time elapsed use of fluoroscopy during TAVR Procedure
Primary Safety Endpoint (30-Day MACCE)

Performance Goal (Including Non-Inferiority Margin)

18.3% (p < 0.001)  
18.3% (p < 0.001)  
18.3% (p < 0.001)

% of Patients with an Event

7.4%  N=18  Randomized (N=244)

7.3%  N=17  Analyzed ITT (N=234)

7.6%  N=17  As Treated (N=225)

Error bars represent upper bound of the one-sided 95% Upper CI
Imputation method based on the logistic regression method. Factors used in imputation algorithm: age, sex, BMI, history of diabetes, history of atrial fibrillation, previous stroke with permanent deficit, and geography
Safety Endpoint Evaluation (Without Non-Inferiority Margin)

% of Patients with an Event

Randomized (N=244) Analyzed ITT (N=234) As Treated (N=225)

7.4% 7.3% 7.6%

(p = 0.0025) (p = 0.0026) (p = 0.0048)

Calculated MACCE Rate

13.3%

Error bars represent upper bound of the one-sided 95% Upper CI
Imputation method based on the logistic regression method. Factors used in imputation algorithm: age, sex, BMI, history of diabetes, history of atrial fibrillation, previous stroke with permanent deficit, and geography
30-Day MACCE Sentinel vs. Concurrent Control (Analyzed ITT)

% of Patients with an Event

Sentinel (Safety + Test) (N=234)
- 7.3%
  - N=17

Control (N=111)
- 9.9%
  - N=11

Error bars represent upper bound of the one-sided 95% Upper CI
## 30-Day Clinical Safety Results (Analyzed ITT)

<table>
<thead>
<tr>
<th>Event</th>
<th>Sentinel (Safety + Test)</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=234</td>
<td>N=111</td>
<td></td>
</tr>
<tr>
<td>Any MACCE† patients</td>
<td>17 7.3%</td>
<td>11 9.9%</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (all-cause)</td>
<td>3 1.3%</td>
<td>2 1.8%</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>13 5.6%</td>
<td>10 9.1%</td>
<td>0.25</td>
</tr>
<tr>
<td>Disabling</td>
<td>2 0.9%</td>
<td>1 0.9%</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>11 4.8%</td>
<td>9 8.2%</td>
<td>0.22</td>
</tr>
<tr>
<td>AKI (Stage 3)</td>
<td>1 0.4%</td>
<td>0 0%</td>
<td>1.00</td>
</tr>
<tr>
<td>TIA</td>
<td>1 0.4%</td>
<td>0 0%</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Sentinel-related complications†</strong></td>
<td>1 0.4%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

†MACCE defined as Death (any cause), Stroke (any), Acute Kidney Injury (Stage 3).

Note: MACCE events adjudicated by independent Clinical Events Committee who were blinded to treatment arm.

1Late brachial artery pseudo-aneurysm treated with thrombin injection
Stroke Diagnosis ≤72 hours (Analyzed ITT)

**Days to Stroke**

- **Day 1**: Sentinel 1.3%, Control 4.5%
- **Day 2**: Sentinel 0.4%, Control 0.9%
- **Day 3**: Sentinel 1.3%, Control 2.7%
- **Total**: Sentinel 3.0%, Control 8.2%

*Fisher Exact Test, p=0.052, 63% Reduction*
Safety Summary

- Primary Safety Endpoint achieved
  - 30-day Sentinel MACCE vs. Performance Goal ($p < 0.001$)
- 30-Day MACCE
  - Sentinel 7.3% vs. Control 9.9%
- 30-Day stroke rate
  - Sentinel 5.6% vs. Control 9.1%
- Peri-procedural stroke rate ($\leq 72$ hours)
  - Sentinel 3.0% vs. Control 8.2%
- One (0.4%) Sentinel-related access site complication
Histopathology

Renu Virmani, MD
President, CVPath Institute Inc.
Clinical Professor
George Washington University
Histopathologic Analysis of Filters: Proximal and Distal

- 105 patients with 210 evaluable filters
- Filters processed and embedded in paraffin and sectioned
- Slides classified by thrombus and tissue type
  - Thrombus (acute and chronic)
  - Valve tissue
  - Calcium nodules
  - Arterial wall (intima or media including necrotic core)
  - Myocardium
  - Foreign material
Type of Tissue Identified

Acute + organizing thrombus

Arterial wall + thrombus

Valve tissue

Calcium nodules

Foreign material + thrombus

Myocardium + thrombus
Type of Morphometric Analysis Performed

- Automated analysis for particle size (HALO software)
- Five largest tissue samples measured manually in largest and smallest dimensions
- Morphology of tissue characterized
SENTINEL Histopathology: Total Embolic Material by Type

### Patients with Captured Debris (%)

- **ANY**: 99%
- **Acute Thrombus & Tissue/Foreign Material**: 98%
- **Arterial Wall**: 94%
- **Valve Tissue**: 50%
- **Calcification**: 50%
- **Foreign Material**: 35%
- **Myocardium**: 15%
- **Organizing Thrombus**: 7%
- **Acute Thrombus Alone**: 1%

**Tissue Type**
Morphometric Analysis: Embolic Material by Particle Size

Percent of Patients with at Least One Particle of Given Size

- ≥0.15 mm: 99%
- ≥0.5 mm: 91%
- ≥1 mm: 55%
- ≥2 mm: 14%

Automated measurement
Patient Quartile Analysis: 
Average Number of Particles ≥0.5 mm

1 in 4 Patients had 25 Particles ≥0.5 mm in Size

Average # of Particles Captured ≥0.5 mm:

- Q1: 0.9
- Q2: 3.7
- Q3: 8.9
- Q4: 25.1

Automated measurement
Morphometric Analysis: Embolic Material by Valve Type ≥ 0.5 and ≥ 1 Millimeter

% of Patients with a Particle ≥ 0.5 millimeter

- CoreValve (N=3): 100%
- Evolut R (N=24): 83%
- SAPIEN 3 (N=58): 72%
- SAPIEN XT (N=20): 76%

% of Patients with a Particle ≥ 1 millimeter

- CoreValve (N=3): 33%
- Evolut R (N=24): 58%
- SAPIEN 3 (N=58): 34%
- SAPIEN XT (N=20): 15%

Manual measurement
Filter through 40-micron mesh
- Processed, embedded in paraffin
- Sectioned at 4-6 microns
- Sections are stained, total of 5 sections per filter
- Assessed by light microscopy
Arterial Wall & Valve Tissue

Distal Filter

Arterial wall

Valve tissue

Proximal Filter

Arterial wall
Calcium Nodules

Distal Filter

Proximal Filter
Myocardium

Distal Filter

Proximal Filter
Foreign Material

Distal Filter

Proximal Filter
Largest Piece – Valve and Arterial Wall (5.4 mm)

Distal Filter
 Sentinel vs. TAVR Catheter Profile Comparison

- TAVR devices are larger, stiffer than Sentinel
- TAVR device features such as exposed metal frames or flared tubes or tips are prone to interacting with vessel wall

Profile in arch

- 16-20 F
- 6 F

Sentinel
Debris From TAVR

- TAVR traverses:
  - Iliac artery
  - Abdominal aorta
  - Thoracic aorta
  - Aortic arch
  - Ascending aorta

Tissue or foreign material combined with acute thrombus was found in 98%.
Debris captured from all valve types.
Acute thrombus alone observed in only 1% of patients.
Valve tissue and calcium nodules captured in 50% of patients.
Foreign material captured in 35% of patients.
1 in 4 Patients had 25 Particles ≥0.5 mm in size.
SENTINEL Trial Effectiveness

Martin B. Leon, MD
Professor of Medicine
Columbia University Medical Center
MRI Methodology and Acquisition Protocol

- Serial 3T scan acquisition at baseline, 2-7 days and 30 days on the same scanner
- All sites imaging core lab certified according to MRI technologist manual and approved by MRI physicist
- Sequences acquired:
  - Diffusion weighted (acute changes)
  - T2/FLAIR (chronic changes)
  - B0 Field Map
  - High-resolution 3D T1-weighted anatomical image
- Scans transferred, queried, accepted in real time
MRI Analysis of New DWI Lesion Volume and Number

- Blinded core lab analysis of all scans
- Serial co-registration and subtraction
- Artifact/distortion correction
- Per-lesion quantification and longitudinal tracking

Baseline DWI 2-7 days DWI Subtraction DWI
34.3mm³
52.7mm³ 34.3mm³
408.7mm³

Baseline FLAIR #1 Baseline FLAIR #2 Baseline FLAIR #3

DWI – diffusion weighted image
FLAIR – attenuated inversion recovery
Patients with Severe Symptomatic Aortic Stenosis undergoing TAVR

Patients Randomized (1:1:1) (N=363)

Imaging Cohort

Test Arm (N=121)
- 11 scan not done
- 10 pacemaker placed
- 6 Sentinel did not enter vasc.
- 1 Sentinel removed prior to TAVR
- 1 no TAVR
- 1 withdrawal

Control Arm (N=119)
- 9 scan not done
- 8 pacemaker placed
- 2 scan rejected
- 1 no TAVR
- 1 died

Paired Serial DW and FLAIR MRIs (Baseline, 2-7 days)

(N=91) (N=98)

Analyzed ITT
Primary Effectiveness Endpoint and Success Criteria

- Primary Effectiveness Endpoint
  - Median total new lesion volume in protected territories at Day 2-7 based on DW-MRI

- Study Success Criterion - Reduction in Median Total New Lesion Volume (Test vs. Control) in protected territories
  - Criterion #1: statistical superiority
  - Criterion #2: observed treatment effect ≥30%
Primary Effectiveness Endpoint: New Lesion Volume in Protected Territories

Randomized
p = 0.24†
37% Reduction

Median New Lesion Volume in Protected Territories (mm³)

Test (N=121) 109.1
Control (N=119) 174.0
IQR [37,380] [40,469]

Analyzed ITT
p = 0.33†
42% Reduction

Test (N=91) 102.8
Control (N=98) 178.0
IQR [37,423] [34,483]

Imputation method based on the predictive mean matching method.
Factors used in imputation algorithm based on blinded aggregate data: 850 Hounsfield Unit calcification score; BMI; Valve type; Procedural stroke; Pre/post dilatation; Mean aortic valve gradient

† Wilcoxon Test
# Median New Lesion Volume by Territory (Analyzed ITT)

<table>
<thead>
<tr>
<th>Territory</th>
<th>Median New Lesion Volume, mm$^3$ [IQR]</th>
<th>Test</th>
<th>Control</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protected</td>
<td></td>
<td>102.8</td>
<td>178.0</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[37,423]</td>
<td>[34,483]</td>
<td></td>
</tr>
<tr>
<td>Partially Protected</td>
<td></td>
<td>69.2</td>
<td>59.0</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0,269]</td>
<td>[0,229]</td>
<td></td>
</tr>
<tr>
<td>Unprotected</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[0,53]</td>
<td>[0,0]</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>294.0</td>
<td>309.8</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[69,786]</td>
<td>[100,886]</td>
<td></td>
</tr>
</tbody>
</table>

† Wilcoxon Test
Total Lesion Number and Volume for Patients with Stroke in All Territories

Lesion Volume $\text{mm}^3$

<table>
<thead>
<tr>
<th>Test (Sentinel)</th>
<th>Control (No protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N=5$</td>
<td>$N=9$</td>
</tr>
<tr>
<td>[min, max]</td>
<td>[min, max]</td>
</tr>
<tr>
<td>81, 487</td>
<td>134, 24300</td>
</tr>
</tbody>
</table>

Lesion Number

<table>
<thead>
<tr>
<th>Test (Sentinel)</th>
<th>Control (No Protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N=5$</td>
<td>$N=9$</td>
</tr>
<tr>
<td>[min, max]</td>
<td>[min, max]</td>
</tr>
<tr>
<td>1, 12</td>
<td>3, 50</td>
</tr>
</tbody>
</table>
In stroke patients, lesion size, number, and location are ALL important
Post Hoc Analysis of RCTs
Meta-Analysis of Effectiveness
Comparison of CLEAN-TAVI vs. SENTINEL Outcomes

- Test arm results consistent in both studies

<table>
<thead>
<tr>
<th>Protected Territories</th>
<th>Mean New Lesion Volume, mm³ (Coefficient of Variation)</th>
<th>Mean % Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Control</td>
</tr>
<tr>
<td>CLEAN-TAVI¹</td>
<td>474 (172%)</td>
<td>1030 (235%)</td>
</tr>
<tr>
<td>SENTINEL</td>
<td>413 (190%)</td>
<td>696 (363%)</td>
</tr>
</tbody>
</table>

- SENTINEL underpowered due to:
  - Observed lower new lesion volumes in the control arm
  - Higher variability in control vs design assumptions

¹ Raw mean calculated and used in the SENTINEL protocol
# Trials Available for Meta-Analysis of Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>CLEAN-TAVI</th>
<th>MISTRAL-C</th>
<th>SENTINEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Blind</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Randomized 1:1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Independent core lab analysis of DW-MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Study Sites</td>
<td>1 Site EU</td>
<td>4 Sites EU</td>
<td>19 Sites US &amp; Europe</td>
</tr>
<tr>
<td>Valve Type(s)</td>
<td>CoreValve</td>
<td>CoreValve SAPIEN 3 SAPIEN XT</td>
<td>CoreValve SAPIEN 3 SAPIEN XT Evolut R</td>
</tr>
<tr>
<td>Number of Patients with DW-MRI data</td>
<td>94</td>
<td>37</td>
<td>189</td>
</tr>
</tbody>
</table>
# Meta-Analysis of Effectiveness*

## Change in Mean New Lesion Volumes (Protected Territories)

<table>
<thead>
<tr>
<th>Study</th>
<th>% Change (95% CI) [Absolute Difference]</th>
<th>% Change Between Test and Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLEAN-TAVI</strong></td>
<td><strong>-52.7% (-73.8%, -15.0%)</strong> [-191]</td>
<td><strong>Favors Test</strong></td>
</tr>
<tr>
<td>(N=94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MISTRAL-C</strong></td>
<td><strong>-66.9% (-89.4%, 3.4%)</strong> [-45]</td>
<td><strong>Favors Test</strong></td>
</tr>
<tr>
<td>(N=36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SENTINEL</strong></td>
<td><strong>-18.9% (-53.0%, 40.2%)</strong> [-25]</td>
<td><strong>Favors Control</strong></td>
</tr>
<tr>
<td>(N=189)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td><strong>-37.5% (-57.6%, -8.0%)</strong> [-50]</td>
<td><strong>Favors Control</strong></td>
</tr>
<tr>
<td>(N=319)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient-level data used in analyses

---

*CO-74*
Meta-Analysis of Effectiveness*
Change in Mean New Lesion Volumes (All Territories)

<table>
<thead>
<tr>
<th>Study</th>
<th>% Change (95% CI) [Absolute Difference]</th>
<th>Favors Test</th>
<th>Favors Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEAN-TAVI (N=94)</td>
<td>-43.9% (-67.2%, -4.1%) [-304]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MISTRAL-C (N=36)</td>
<td>-58.6% (-88.3%, 46.2%) [-92]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENTINEL (N=189)</td>
<td>-1.4% (-40.9%, 64.5%) [-4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVERALL (N=319)</td>
<td>-24.4% (-47.7%, 9.3%) [-66]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient-level data used in analyses
Neurocognitive Sub-Study
## Methodology

<table>
<thead>
<tr>
<th>Domain</th>
<th>Neurocognitive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Digit Span</td>
</tr>
<tr>
<td></td>
<td>Trail Making Part A</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>Hopkins Verbal Learning Test</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>Brief Visual Memory Test</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Letter Number Sequencing</td>
</tr>
<tr>
<td></td>
<td>Trail Making Part B</td>
</tr>
<tr>
<td></td>
<td>Rey Complex Figure Test (Copy)</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>Digit Symbol</td>
</tr>
<tr>
<td></td>
<td>Controlled Oral Word Association</td>
</tr>
</tbody>
</table>

Corrected for the Covariates of Mental Status and Depression
Patients with Severe Symptomatic Aortic Stenosis undergoing TAVR

Patients Randomized (1:1:1) (N=363)

Imaging Cohort

Test Arm
(N=121)

Serial Neurocognition Evaluations (Baseline, 30 days)

(N=93)

Control Arm
(N=119)

(N=92)

Randomized

Analyzed ITT
## Primary Outcome: 
Z-score Change at 30 Days (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Sentinel Test (N=93)</th>
<th>Sentinel Control (N=92)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Z-Score</td>
<td>-0.09 ± 0.44</td>
<td>-0.03 ± 0.37</td>
<td>0.42</td>
</tr>
<tr>
<td>Components of Z-Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>0.14 ± 0.51</td>
<td>0.03 ± 0.55</td>
<td>0.18</td>
</tr>
<tr>
<td>Executive Function</td>
<td>0.25 ± 0.86</td>
<td>0.14 ± 0.86</td>
<td>0.47</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>0.12 ± 0.39</td>
<td>0.14 ± 0.43</td>
<td>0.55</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>-0.32 ± 0.8</td>
<td>-0.28 ± 0.85</td>
<td>0.46</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>-0.36 ± 0.79</td>
<td>-0.46 ± 0.91</td>
<td>0.43</td>
</tr>
</tbody>
</table>

*Data presented as Mean ± SD, model adjusted for education and baseline Geriatric Depression Score and baseline Mini Mental State Score.
Primary Effectiveness – Median New Lesion Volume (Protected Territories)
  - Observed treatment effect $\geq 30\%$ – Achieved
  - Test vs. Control – not achieved

Meta analysis (3 RCTs) provides additional evidence of effectiveness
SENTINEL Results in the Context of Neuroprotection History

William A. Gray, MD
System Chief of the Division of Cardiovascular Disease
Main Line Health
Accessory Devices: Catheter-based Filters Used in Carotid Artery Stenting Are Similar to Sentinel

Common Features:
- Pores ~100-140μm
- Atraumatic wire frames for centering and sealing
- Deployed over a 0.014” wire from a collapsed state
SENTINEL: First RCT in Filter Embolic Protection

- Evaluation metrics are not established
  - Low incidence of clinical endpoints (e.g., stroke) limits their utility
  - DW-MRI surrogate is therefore valuable, but still being refined (timing, effect of pre-existing abnormalities, etc.)
  - DW-MRI lesions – relevancy of volume vs number vs location not established
- Expected treatment effect of DW-MRI surrogate not established or clinically validated
Filters Used in Sentinel and Carotid Artery Stenting Are Safe

- Vascular trauma from filter embolic protection in CAS is rare
- Similarly there was no filter-related vascular trauma reported in SENTINEL
  - Finding is consistent with parallels in filter construction
- Dwell times are short
Both CAS and TAVR EPD Capture Significant Amounts of Liberated Debris
Types of embolic material collected by filters:

- Foam cells
- Smooth muscle cells
- Cholesterol
- Collagen/elastin
- Platelet/fibrin

57% of samples contained embolic material
## Analysis of Particles Collected Per Filter in ARChER and in SENTINEL

<table>
<thead>
<tr>
<th>Filter Type</th>
<th>French Size</th>
<th>Debris Captured %</th>
<th>≥20 Particles Per Patient %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RX Accunet</td>
<td>6 Fr</td>
<td>57%¹</td>
<td>24%¹</td>
</tr>
<tr>
<td>Sentinel</td>
<td>6 Fr</td>
<td>99%</td>
<td>53%</td>
</tr>
</tbody>
</table>

EPD with Both CAS and TAVR Demonstrate Similar Stroke Reduction

The Impact of Device Approval

- Carotid artery stent coupled with EPD approval in US in 2004
- Approval led to significant increase in use of protected carotid artery stenting
  - 5,000 to 75,000
  - 50% decrease in overall complication rates after device approval
- Improvements likely secondary to
  - Widespread EPD availability
  - Refinements in patient selection and technique
Summary: 5 Perspectives

- SENTINEL is the first pivotal multicenter US IDE study to isolate EPD neuroprotective procedural and outcomes.
- SENTINEL safety profile is consistent with prior carotid artery (CAS) EPD studies.
- Similar to carotid EPD, SENTINEL filter collection resulted in a high percentage of debris capture.
- Incorporation of Sentinel into TAVR resulted in stroke reduction similar to that seen after adoption of carotid stenting embolic protection.
- Further outcome improvements possible once TAVR EPD is broadly available.
Concluding Remarks

Azin Parhizgar, PhD
President and Chief Executive Officer
Claret Medical, Inc.
Company Perspective

- Claret focused on developing best cerebral protection device to protect from acute embolic ischemic injury or stroke
- 4-year commercial history outside US
- SENTINEL: first US/EU, multicenter, randomized, controlled EPD trial
- Provides safety in a rapidly evolving TAVR field
Effectiveness Endpoint Success Criteria: ITT
New Lesion Volume in Protected Territories

Test (N=121)

Control (N=119)

IQR [37,423] [34,483]

42% Reduction

102.8

178.0

Analyzed ITT
Sentinel Debris Type
Patient Quartile Analysis: Average Number of Particles ≥0.5 mm

1 in 4 Patients had 25 Particles ≥0.5 mm in Size

Average # of Particles Captured ≥0.5 mm

<table>
<thead>
<tr>
<th>Patient Quartile</th>
<th>Average # of Particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>0.9</td>
</tr>
<tr>
<td>Q2</td>
<td>3.7</td>
</tr>
<tr>
<td>Q3</td>
<td>8.9</td>
</tr>
<tr>
<td>Q4</td>
<td>25.1</td>
</tr>
</tbody>
</table>

Patient Quartiles
Primary Safety Endpoint Met (30-Day MACCE)

Performance Goal (Including Non-Inferiority Margin)

Calculated MACCE Rate

% of Patients with an Event

Randomized (N=244) 7.4% N=18
Analyzed ITT (N=234) 7.3% N=17
As Treated (N=225) 7.6% N=17
**Stroke Diagnosis ≤72 hours (ITT)**

<table>
<thead>
<tr>
<th>Days to Stroke</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1.3%</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.4%</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.9%</td>
</tr>
<tr>
<td>Total*</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

- Sentinel: 2.7%
- Control: 3.0%

**63% Reduction**

*p=0.052*

*Fisher Exact Test*
Summary

- Sentinel
  - is safe, with minimal complications, injury or disruption of the TAVR workflow
  - performs as intended
  - reduced the peri-procedural stroke rate compared to control (3% vs 8.2%)
  - yields an observed treatment of effect of 42%
  - captures a wide spectrum of emboli destined for the brain in 99% of the patients
Post-approval Training Program

- Committed to comprehensive training
- Sentinel safety and technical success demonstrated that IDE training was effective
- Elements of training program to mimic IDE study:
  - Comprehensive didactic training
  - Hands on learning with anatomical model
  - Proctor up to 5 cases at each site
Post-Market Surveillance Recommendations

- Close collaboration with FDA in formulating an effective PMS program to ensure a safe commercial roll out
- Program to include:
  - Post-market registry
    - Collect additional data in a real-world setting
  - A registry or TVT module
Sentinel®
Cerebral Protection System During TAVR

February 23, 2017
Claret Medical, Inc.
Circulatory System Devices Panel