Sentinel® Cerebral Protection System During TAVR

February 23, 2017
Claret Medical, Inc.
Circulatory System Devices Panel
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
- 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
  - Test vs. Control – Not achieved
  - Observed treatment effect ≥ 30% – Achieved

- Other Relevant Study Outcomes
  - Embolic debris captured in 99% of filters
  - Sentinel system successfully delivered & retrieved in 94% of patients
  - Vascular complications were rare
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 (clinical, pre-clinical) 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, Philadelphia, PA

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

Statistics

Roseann White, MA
Director, Pragmatic Clinical Trial Statistics
Duke Clinical Research Institute

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
Background

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

The NEW ENGLAND JOURNAL of MEDICINE

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

PARTNER 1A RCT (SAPIEN TAVR vs. Surgery); 699 high-risk patients with severe AS; N Engl J Med 2011;364:2191-2202
Strokes are Considered a Major Complication after TAVR

But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith and colleagues report a 5.5% risk of stroke or transient ischemic attack within 30 days after transcatheter replacement...

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

Necropsy radiograph

Surgical 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)
2621 patients from PARTNER (high and extreme risk); CEC adjudication

- Instantaneous stroke risk peaked at 2 days, with a low constant risk of 0.8% per year
Strokes After TAVR (Acute Phase)

Neurological Events (#/100 patient months)

Weeks After TAVR

TF TAVR  ± 1 Standard Error
TA TAVR  ± 1 Standard Error

Spectrum of Brain Injury Caused by Embolic Material

- 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\(^1\) which may result in acute or chronic changes in neurocognitive function

\(^1\) Lansky AJ et al; Neuro ARC, JACC, 2017 (in press)
Brain Injury on Neuro-imaging (DW-MRI) after TAVR

- 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
- Large population-based studies demonstrate associations with cognitive decline, clinical stroke, and mortality
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%

Unprotected blood flow to the brain

- LVA ~10%

Sentinel Placement

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
SENTINEL Trial Design 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)

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
**Study Administration**

**Co-Principal Investigators:**
- Susheel Kodali, MD  
  Columbia University Medical Center
- Samir R. Kapadia, MD  
  Cleveland Clinic
- Axel Linke, MD  
  Klinik fuer Innere Medizin und Kardiologie  
  Herzzentrum Leipzig

**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)

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Sapien XT</th>
<th>CoreValve</th>
<th>Evolut R</th>
<th>Sapien 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4 2014</td>
<td>8</td>
<td>18</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>Q1 2015</td>
<td>18</td>
<td>2</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>Q2 2015</td>
<td>29</td>
<td>4</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>Q3 2015</td>
<td>9</td>
<td>13</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Q4 2015</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Q1 2016</td>
<td>3</td>
<td>1</td>
<td>72</td>
<td>82</td>
</tr>
</tbody>
</table>
Histopathology

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

- 105 patients with evaluable filters
- Filtered material washed and tissue samples evaluated by light microscopy
- 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
- Five largest tissue samples measured manually in largest and smallest dimensions
- Tissue particles segregated and counted by morphologic type (thrombus excluded)
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
Acute & Organizing Thrombus

Distal Filter

Proximal Filter
Arterial Wall & Valve Tissue

Distal Filter

Valve tissue

Arterial wall

Proximal Filter

Valve tissue

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
Morphometric Analysis: Embolic Material by Particle Size

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

Percent of Patients with at Least One Particle of Given Size

Automated measurement
Manual measurement

Morphometric Analysis: Embolic Material by Valve Type $\geq 0.5$ and $\geq 1$ Millimeter

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>% of Patients With a Particle $\geq 0.5$ millimeter</th>
<th>% of Patients With a Particle $\geq 1$ millimeter</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoreValve (N=3)</td>
<td>100%</td>
<td>33%</td>
</tr>
<tr>
<td>Evolut R (N=24)</td>
<td>83%</td>
<td>58%</td>
</tr>
<tr>
<td>SAPIEN 3 (N=58)</td>
<td>72%</td>
<td>34%</td>
</tr>
<tr>
<td>SAPIEN XT (N=20)</td>
<td>76%</td>
<td>15%</td>
</tr>
</tbody>
</table>

0%  25%  50%  75%  100%
Sentinel vs. TAVR Catheter Profile Comparison

- Sentinel much smaller profile
- Sentinel much less stiff
- Each TAVR system presents features such as exposed metal frames or flared tubes or tips which are prone to interacting with the vessel wall

<table>
<thead>
<tr>
<th>Profile in arch</th>
<th>Profile at Insertion</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 Fr</td>
<td>Sentinel</td>
<td>Evolut R</td>
</tr>
<tr>
<td>14-16 Fr</td>
<td>S3</td>
<td></td>
</tr>
<tr>
<td>6 Fr</td>
<td>Sentinel</td>
<td></td>
</tr>
</tbody>
</table>
Histopathology Summary

- Debris captured in >99% of patients
- Debris capture across all valve types
- Foreign material (catheter particulate and coatings) captured in 35% of patients
- Valve tissue and calcium nodules captured in 50% of patients
- Particles ≥0.5 mm captured in more than 70% of patients regardless of valve type
SENTINEL Trial
Safety and Performance
SENTINEL Safety Populations

Patients with Severe Symptomatic Aortic Stenosis Undergoing TAVR

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

Safety Cohort

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

As-Treated Safety Cohort

ITT With Imputation

ITT (N=117)
- 2 No Sentinel

As-Treated (N=115)

As-Treated With Imputation (N=111)

As-Treated With Imputation (N=110)
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>Imaging (N=121)</th>
<th>Control (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 (cm$^2$)</td>
<td>0.7 ± 0.18</td>
<td>0.7 ± 0.17</td>
<td>0.7 ± 0.20</td>
</tr>
<tr>
<td>Mean aortic valve gradient (mmHg)</td>
<td>42 ± 15</td>
<td>44 ± 15</td>
<td>41 ± 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

## Sentinel Access

<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>

## Device Success

<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)

% of Patients with an Event

Performance Goal (Including Non-Inferiority Margin)

(\textit{p} < 0.001)  
(\textit{p} < 0.001)  
(\textit{p} < 0.001)

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Rate</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT With Imputation (N=244)</td>
<td>7.4%</td>
<td>18</td>
</tr>
<tr>
<td>ITT (N=234)</td>
<td>7.3%</td>
<td>17</td>
</tr>
<tr>
<td>As Treated (N=225)</td>
<td>7.6%</td>
<td>17</td>
</tr>
</tbody>
</table>

Error bars represent upper bound of the 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

- ITT With Imputation (N=244): 7.4% (p = 0.0025)
- ITT (N=234): 7.3% (p = 0.0026)
- As Treated (N=225): 7.6% (p = 0.0048)

Calculated MACCE Rate

Error bars represent upper bound of the 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 (ITT)

% of Patients with an Event

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Patients with an Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel (Safety + Test) (N=234)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Control (N=111)</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Event</th>
<th>SENTINEL (Safety + Test)</th>
<th>Control (N=111)</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>Events</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>Stroke</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>Sentinel-related complications</td>
<td>1 (0.4%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Sentinel-related complications*: Late brachial artery pseudo-aneurysm treated with thrombin injection

*MACCE defined as Death (any cause), Stroke (any), Acute Kidney Injury (Stage 3). MACCE rate is based on patients. Note: MACCE events adjudicated by independent Clinical Events Committee who were blinded to treatment arm.
Stroke Diagnosis ≤72 hours (ITT)

% of Patients

<table>
<thead>
<tr>
<th>Days to Stroke</th>
<th>Sentinel</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.4%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.9%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Day 3</td>
<td>1.3%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Total*</td>
<td></td>
<td>3.0%</td>
</tr>
</tbody>
</table>

*p=0.052, Fisher Exact Test
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 (≤72 hours)
  - Sentinel 3.0% vs. Control 8.2%
- One (0.4%) Sentinel-related access site complication
SENTINEL Trial Effectiveness
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

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

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

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, 2-7days)

ITT With Imputation

ITT

(N=91)  
(N=98)
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

ITT With Imputation

**p = 0.24**†
37% Reduction

<table>
<thead>
<tr>
<th></th>
<th>Median New Lesion Volume in Protected Territories (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td>109.1 [37,380]</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>174.0 [40,469]</td>
</tr>
</tbody>
</table>

ITT

**p = 0.33**†
42% Reduction

<table>
<thead>
<tr>
<th></th>
<th>Median New Lesion Volume in Protected Territories (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td>102.8 [37,423]</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>178.0 [34,483]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Territory</th>
<th>Median New Lesion Volume, mm³ [IQR]</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Control</td>
</tr>
<tr>
<td>Protected</td>
<td>102.8 [37,423]</td>
<td>178.0 [34,483]</td>
</tr>
<tr>
<td>Partially Protected</td>
<td>69.2 [0,269]</td>
<td>59.0 [0,229]</td>
</tr>
<tr>
<td>Unprotected</td>
<td>0 [0,53]</td>
<td>0 [0,0]</td>
</tr>
<tr>
<td>All</td>
<td>294.0 [69,786]</td>
<td>309.8 [100,886]</td>
</tr>
</tbody>
</table>

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

Lesion Volume and Number Smaller With Sentinel

Test (Sentinel) N=5 [81,487]
Test (No protection) N=9 [134,24,300]

Control (No protection) N=9 [3,50]
In Stroke Patients, Lesion Size, Number, and Location are ALL Important

All three of these Control arm patients had strokes

3D renderings of 2-7d DW-MRI scans from 3 control stroke patients
Post Hoc Analysis of RCTs
Meta-Analysis of Effectiveness

SENTINEL underpowered due to observed lower median new lesion volume and higher variability in the Control arm than study sample size assumptions
## 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>Single Site Germany</td>
<td>Multi-center Europe</td>
<td>Multi-center US &amp; Europe</td>
</tr>
<tr>
<td>Valve Type(s)</td>
<td>CoreValve</td>
<td>SAPIEN 3, SAPIEN XT, CoreValve, Evolut R</td>
<td>SAPIEN 3, SAPIEN XT, CoreValve, 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></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>-52.7% (-73.8%, -15.0%) [-191]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mistral C (N=36)</td>
<td>-66.9% (-89.4%, 3.4%) [-45]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENTINEL (N=189)</td>
<td>-18.9% (-53.0%, 40.2%) [-25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVERALL (N=319)</td>
<td>-37.5% (-57.6%, -8.0%) [-50]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient-level data used in analyses*
Meta-Analysis of Effectiveness*
Change in Mean New Lesion Volumes (All Territories)

<table>
<thead>
<tr>
<th>Group</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)

Control Arm
(N=119)

Serial Neurocognition Evaluations (Baseline, 30 days)

(N=93)  (N=92)
Primary Outcome: Z-score Change at 30 Days (ITT)

<table>
<thead>
<tr>
<th></th>
<th>SENTINEL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (N=93)</td>
</tr>
<tr>
<td>Composite Z-Score</td>
<td>-0.09 ± 0.44</td>
</tr>
</tbody>
</table>

Components of Z-Score

<table>
<thead>
<tr>
<th></th>
<th>SENTINEL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (N=93)</td>
</tr>
<tr>
<td>Attention</td>
<td>0.14 ± 0.51</td>
</tr>
<tr>
<td>Executive Function</td>
<td>0.25 ± 0.86</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>0.12 ± 0.39</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>-0.32 ± 0.8</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>-0.36 ± 0.79</td>
</tr>
</tbody>
</table>

*Data presented as Mean ± SD, model adjusted for education and baseline Geriatric Depression Score and baseline Mini Mental State Score.
SENTINEL Trial Effectiveness Summary

- Primary Effectiveness – Median New Lesion Volume (Protected Territories)
  - Observed treatment effect ≥ 30% – Achieved
  - Test vs. Control – did not achieve statistical significance
- 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
- Deployed over a 0.014” wire from a collapsed state

- Cordis Angioguard
- Guidant Accunet
- BSC/EPI EZ
- Abbott Vascular/Mednova
- eV3/Microvena Spider
- Claret Sentinel
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 very 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
Both Sentinel and Carotid Artery Stent Filter Embolic Protection are Safe

- Vascular trauma from filter embolic protection in CAS is rare
- Similarly there was no filter-related vascular trauma reported in SENTINEL
  - This finding is consistent with the parallels in filter construction
- Dwell times are short
Both CAS and TAVR EPD Capture Significant Amounts of Liberated Debris
57% Debris Collected in CAS EPD: ARCHerR Study

- Total study = 581 patients
- Types of embolic material collected by filters
  - Foam cells
  - Smooth muscle cells
  - Cholesterol
  - Collagen/elastin
  - Platelet/fibrin

57% of samples contained embolic material
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
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 improvements in patient selection and technique
- SENTINEL is just the beginning of the EPD experience in TAVR
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.
- SENTINEL filter collection resulted in higher percentage of debris capture in patients (99% vs. 57%) compared to CAS EPD data with wider spectrum of debris type.
- SENTINEL stroke reduction similar to that seen after CAS EPD adoption.
- 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 best in class cerebral protection device
  - Protects brain from acute embolic ischemic injury or stroke
- 4 year safety and performance record outside US
- Pivotal IDE trial
  - Largest randomized controlled trial of its kind
  - Surrogate endpoint
  - Complex combination of multiple serial neuroimaging, neurological and cognitive evaluations
  - High risk TAVR population
- Sentinel is a periprocedural accessory device to a rapidly evolving therapy
Sentinel Debris Type

- 6.4 mm
- 2.8 mm
- 6.9 mm
- 4.5 mm
Sentinel Debris Size in Filters
Primary Safety Endpoint Met (30-Day MACCE)

Performance Goal (Including Non-Inferiority Margin) = 18.3%

Calculated MACCE Rate

- ITT With Imputation (N=244): 7.4%
- ITT (N=234): 7.3%
- As Treated (N=225): 7.6%

% of Patients with an Event
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>

*p=0.052, Fisher Exact Test
Primary Effectiveness Endpoint: New Lesion Volume in Protected Territories

- Test (N=121)
  - Median: 109.1
  - IQR: [37,423]

- Control (N=119)
  - Median: 174.0
  - IQR: [34,483]

37% Reduction
Summary

- Sentinel, as a temporary accessory device to TAVR:
  - performs as intended
  - is safe, with minimal complications, injury or disruption of the TAVR workflow
  - reduced the peri-procedural stroke rate compared to control (3% vs 8.2%)
  - captures a wide spectrum of emboli destined for the brain in 99% of the patients
  - yields an observed treatment of effect of 37%
Post-approval Training Program

- Sentinel safety and technical success demonstrated that IDE training is sufficient
- Elements of training program to mimic IDE study:
  - Comprehensive didactic training
  - Hands on learning with anatomical model
  - Clinical specialist to 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:
  - Proctored training
  - Post-market registry
    - Collect additional data in a real-world setting
    - App based, or
    - TVT module
Sentinel®
Cerebral Protection System During TAVR

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