De Novo request for
Claret Medical Inc.’s Sentinel® Cerebral Protection System
Based on Data from the SENTINEL Study

FDA Review of DEN160043

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Office of Device Evaluation
Food and Drug Administration

February 23, 2017
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FDA Presentations

- CDR Sadaf Toor
  Introduction and Summary of SENTINEL Study Design

- Dr. Donna Buckley
  SENTINEL Clinical Results and Considerations

- Dr. Li Ming Dong
  SENTINEL Statistical Results and Considerations

- CDR Sadaf Toor
  Conclusions
Introduction Outline

• Device Description

• Proposed Indications for Use

• Regulatory History

• SENTINEL Study Design

• Discussion Points
Device Description

Ref: Figure 1: FDA Executive Summary
Indications for Use
(as proposed by the Sponsor)

“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 ischemic injury to the brain peri-procedurally. 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 in the left common carotid.”
Regulatory History

February 14, 2014 – FDA conditionally approved an Investigational Device Exemption (IDE) for the SENTINEL study (G130276)

- Edwards SapienXT valve only commercially available transcatheter aortic valve replacement (TAVR) device in the U.S.

October 2, 2014 – First SENTINEL patient enrolled

May 11, 2015 – Protocol modified to allow Medtronic CoreValve TAVR System

- Approximately 10% of randomized patients had been enrolled
Regulatory History (cont.)

July 27, 2015 – Protocol modified to allow the use of any FDA approved TAVR device

- Approximately 15% of the randomized patients had been enrolled

March 10, 2016 – Final SENTINEL patient enrolled

May 6, 2016 – FDA approved a Continued Access cohort of the SENTINEL study.

- Ultimately, not initiated by the sponsor

September 20, 2016 – FDA received De Novo request DEN160043

- Included the clinical study report of subjects enrolled in the SENTINEL study.
Scope of Meeting

The purpose of this Advisory Panel meeting is to obtain input on critical aspects of the supporting clinical data.

The Advisory Panel will not be asked to provide input on other regulatory aspects of the De Novo request.
SENTINEL Study Design

Objective:
• Assess the safety and effectiveness of the Sentinel System used for cerebral protection during TAVR compared to TAVR without cerebral protection.

Key study attributes:
• Prospective
• Single blind
• Multi-center
• Randomized
• Patients with severe symptomatic calcified native aortic valve stenosis indicated for TAVR
Primary Endpoints

**Safety**
- Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 Days.

MACCE = All Death, All Stroke, Acute Kidney Injury (class 3 at discharge or 72 hours post index procedure, whichever occurs first) as adjudicated by a Clinical Events Committee (CEC) using VARC-2 definitions.

**Effectiveness**
- Total new lesion volume in protected territories as assessed by DW-MRI at 2-7 days post-procedure.

Ref: Appendix V: FDA Executive Summary
Study Success Criteria

1. Primary safety endpoint: 30-Day MACCE rate for the Safety Cohort (Safety Arm and Test Arm) < Performance Goal of 18.3%.

2. Superiority with respect to the primary effectiveness endpoint (Primary Effectiveness Criterion #1): The Test Arm is superior to the Control Arm with respect to the median total new lesion volume in protected territories at Day 2-7 post-procedure.

3. Observed Clinical Treatment Effect (Primary Effectiveness Criterion #2): The ratio of the observed reduction in median total new lesion volume in the protected territories in the Test Arm compared to the median total new lesion volume in the protected territories in the Control Arm is ≥ 30%.
Primary Discussion Points

1. DW-MRI as a surrogate effectiveness endpoint
2. Primary and secondary effectiveness results
3. Debris capture
4. Neurocognitive outcomes
5. Indications for Use
6. Labeling considerations
7. Benefit-risk considerations
8. Post-market data
FDA Presentations

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  SENTINEL Clinical Results and Considerations

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  SENTINEL Statistical Results and Considerations

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  Conclusions
SENTINEL Clinical Results and Considerations

Donna Buckley, MD, MS

Division of Cardiovascular Devices
Office of Device Evaluation
SENTINEL Clinical Results and Considerations Outline

- Patient Accountability & Baseline/Procedural Characteristics
- Safety Results
- Effectiveness Results
SENTINEL Clinical Results and Considerations Outline

- Patient Accountability & Baseline/Procedural Characteristics
- Safety Results
- Effectiveness Results
Patient Enrollment and Accountability

Enrolled
N=428

Roll-In
N=65

Randomized
N=363

Safety Arm
N=123

Test Arm
N=121

Control Arm
N=119

SAFETY COHORT
(as randomized)

SENTINEL
No MR

SENTINEL
MR

Primary Safety Analysis: 30-Day MACCE Events < 18.3%

Ref: Figure 6: FDA Executive Summary
Patient Enrollment and Accountability

SAFETY COHORT (as randomized)

Enrolled N=428

Roll-In N=65

Randomized N=363

Safety Arm N=123

Test Arm N=121

Control Arm N=119

SENTINEL
No MR

SENTINEL
MR

VS

No SENTINEL
MR

Secondary Safety Analyses: 30 day MACCE comparing Test vs Control and (Test + Safety) vs Control

Ref: Figure 6: FDA Executive Summary
Patient Enrollment and Accountability

As Randomized

Safety Arm N=123
2 no TAVR
4 no f/u

Test Arm N= 121
1 no TAVR
2 no f/u
1 withdrawal

Control Arm N = 119
1 no TAVR
7 no f/u

Analyzed ITT Safety Data

ITT (Safety Analysis) N=117

> 95% of randomized patients were included in the ITT Safety Analysis

Ref: Figure 6: FDA Executive Summary
Primary Effectiveness Analysis: median new DW-MRI lesion volume at 2-7 days

- Effectiveness Criterion #1: (superiority) statistically lower for Test Arm vs Control Arm in protected territories
- Effectiveness Criterion #2: (observed treatment effect) 30% lower for Test vs Control in protected territories

Ref: Figure 6: FDA Executive Summary
Patient Enrollment and Accountability

Enrolled N=428

- Roll-In N=65
  - Safety Arm N=123
    - SENTINEL No MR
  - Randomized N=363
    - Test Arm N=121
    - Control Arm N=119

IMAGING COHORT

Secondary Effectiveness Analyses: primary analysis endpoints assessed for all territories

Ref: Figure 6: FDA Executive Summary
Patient Enrollment and Accountability

As Randomized

Safety Arm N=123

Test Arm N=121

Control Arm N=119

Analyzed ITT Effectiveness Data

11 no scan
10 pacemaker
6 device did not enter vasc
1 device removed pre-TAVR
1 no TAVR
1 withdrawal

9 no scan
8 pacemaker
2 scan rejected
1 no TAVR
1 died

ITT (Effectiveness Analysis) N=91

ITT (Effectiveness Analysis) N=98

> 20% of randomized patients were excluded from the ITT Effectiveness Analysis

Ref: Figure 6: FDA Executive Summary
Baseline & Procedural Characteristics

There were observed statistical differences in:

- Diastolic blood pressure
- STS score
- Stroke severity
- Procedure time
- Fluoroscopy time

No concerning trends in Baseline or Procedural Characteristics
SENTINEL Clinical Results and Considerations Outline

- Patient Accountability & Baseline/Procedural Characteristics
- Safety Results
- Effectiveness Results
Safety – Primary

30-day MACCE Events (Safety + Test) < 18.3% PG

<table>
<thead>
<tr>
<th>Population</th>
<th>Total Events</th>
<th>Patients w/ Events n/N, (%)</th>
<th>Performance Goal</th>
<th>Upper Limit of 95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT with imputation</td>
<td>N/A</td>
<td>18/244 (7.4%)</td>
<td></td>
<td>10.7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ITT</td>
<td>17</td>
<td>17/234 (7.3%)</td>
<td>18.3%</td>
<td>10.7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AT</td>
<td>17</td>
<td>17/225 (7.6%)</td>
<td></td>
<td>11.1%</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

The ITT Primary Safety Analysis demonstrated that the 30-day MACCE rate for the Safety Cohort was 7.3%. The 95% CI upper limit of this value is 10.7% which is below the PG of 18.3%.

Primary Safety Endpoint was Met.

Ref: Table 7: FDA Executive Summary
## Safety – Primary

### Composite Endpoint Components (ITT)

<table>
<thead>
<tr>
<th>Population</th>
<th>Total Events</th>
<th>Safety Cohort (Safety + Test Arms) N = 234</th>
<th>Control Arm N = 111</th>
<th>95% Confidence Interval for difference^4</th>
</tr>
</thead>
</table>
| Any MACCE           | 7.3% (17/234) [17]
                      | (4.3%, 11.4%)  | 9.9% (11/111) [12]
                      | (5.1%, 17.0%)  | [-9.8%, 4.5%]            |
| Death               | 1.3% (3/234) [3]
                      | (0.3%, 3.7%)   | 1.8% (2/111) [2]
                      | (0.2%, 6.4%)   | [-5.4%, 2.6%]            |
| Stroke              | 5.6% (13/231) [13]
                      | (3.0%, 9.4%)   | 9.1% (10/110) [10]
                      | (4.4%, 16.1%)  | [-10.3%, 3.3%]           |
| Disabling           | 0.9% (2/231) [2]
                      | (0.1%, 3.1%)   | 0.9% (1/109) [1]
                      | (0.0%, 5.0%)   | [-3%, 3%]                |
| Non-disabling       | 4.8% (11/231) [11]
                      | (2.4%, 8.4%)   | 8.2% (9/110) [9]
                      | (3.8%, 15.0%)  | [-10%, 3%]               |
| AKI (Class 3)       | 0.4% (1/231) [1]
                      | (0.0%, 2.4%)   | 0% (0.0%, 3.3%)         | [-1%, 2%]                  |

Ref: Tables 7 and 8: FDA Executive Summary
Safety: 30-day MACCE
Safety Cohort (Safety + Test Arms) vs. Control Arm (no Sentinel) (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Safety Cohort (Safety + Test Arms)</th>
<th>Control Arm</th>
<th>95% Confidence Interval for difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 234</td>
<td>N = 111</td>
<td></td>
</tr>
<tr>
<td>Any MACCE</td>
<td>7.3% (17/234) [17] [4.3%, 11.4%]</td>
<td>9.9% (11/111) [12] [5.1%, 17.0%]</td>
<td>[-9.8%, 4.5%]</td>
</tr>
<tr>
<td>Death</td>
<td>1.3% (3/234) [3] [0.3%, 3.7%]</td>
<td>1.8% (2/111) [2] [0.2%, 6.4%]</td>
<td>[-5.4%, 2.6%]</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.6% (13/231) [13] [3.0%, 9.4%]</td>
<td>9.1% (10/110) [10] [4.4%, 16.1%]</td>
<td>[-10.3%, 3.3%]</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.9% (2/231) [2] [0.1%, 3.1%]</td>
<td>0.9% (1/109) [1] [0.0%, 5.0%]</td>
<td>[-3%, 3%]</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>4.8% (11/231) [11] [2.4%, 8.4%]</td>
<td>8.2% (9/110) [9] [3.8%, 15.0%]</td>
<td>[-10%, 3%]</td>
</tr>
<tr>
<td>AKI (Class 3)</td>
<td>0.4% (1/231) [1] [0.0%, 2.4%]</td>
<td>0% (0.0%, 3.3%)</td>
<td>[-1%, 2%]</td>
</tr>
</tbody>
</table>

Ref: Table 8: FDA Executive Summary
# Safety: 30-day MACCE

**Imaging Cohort (ITT): Test (Sentinel) vs. Control (no Sentinel)**

<table>
<thead>
<tr>
<th></th>
<th>Test Arm</th>
<th>Control Arm</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any MACCE</strong></td>
<td>6.0% (7/117) [7] (2.4%,11.9%)</td>
<td>9.9% (11/111) [12] (5.1%,17.0%)</td>
<td>0.6157</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0.9% (1/117) [1] (0.0%,4.7%)</td>
<td>1.8% (2/111) [2] (0.2%,6.4%)</td>
<td>1.0000</td>
</tr>
<tr>
<td><strong>Stroke (all)</strong></td>
<td>4.3% (5/116) [5] (1.4%,9.8%)</td>
<td>9.1% (10/110) [10] (4.4%,16.1%)</td>
<td>0.4092</td>
</tr>
<tr>
<td><strong>Disabling Stroke</strong></td>
<td>0% (0.0%,3.1%)</td>
<td>0.9% (1/109) [1] (0.0%,5.0%)</td>
<td>0.2468</td>
</tr>
<tr>
<td><strong>Non-disabling Stroke</strong></td>
<td>4.3% (5/116) [5] (1.4%,9.8%)</td>
<td>8.2% (9/110) [9] (3.8%,15.0%)</td>
<td>0.7684</td>
</tr>
<tr>
<td><strong>AKI (Class 3)</strong></td>
<td>0.9% (1/116) [1] (0.0%,4.7%)</td>
<td>0% (0.0%,3.3%)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Ref: Table 11: FDA Executive Summary
## Safety: Major Vascular Complications

<table>
<thead>
<tr>
<th></th>
<th>Safety Cohort (Safety + Test Arms)</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the index procedure</td>
<td>6.1% (15/244) [15] (3.5%, 9.9%)</td>
<td>5.0% (6/119) [6] (1.9%, 10.7%)</td>
</tr>
<tr>
<td>Radial Artery</td>
<td>0% (0.0%, 1.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Brachial Artery</td>
<td>0% (0.0%, 1.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Within 30 days of the index procedure</td>
<td>2.5% (6/244) [6] (0.9%, 5.3%)</td>
<td>0.8% (1/119) [1] (0.0%, 4.6%)</td>
</tr>
<tr>
<td>Radial Artery</td>
<td>0% (0.0%, 1.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Brachial Artery</td>
<td>0.4% (1/244) [1] (0.0%, 2.3%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**One Sentinel Related Major Vascular Complication**

Ref: Table 12: FDA Executive Summary
# Safety: 30-Day SAE Rate

<table>
<thead>
<tr>
<th>Safety Cohort (Safety Arm + Test Arm)</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Events</strong></td>
<td><strong>Total Events</strong></td>
</tr>
<tr>
<td>ITT 170</td>
<td>89</td>
</tr>
<tr>
<td>AT 162</td>
<td>97</td>
</tr>
</tbody>
</table>

Similar overall 30-Day SAE rates in patients who received the Sentinel and those who did not receive the Sentinel

Ref: Table 13: FDA Executive Summary
Safety

The prespecified safety success criterion was met. No major concerns were noted regarding safety of the Sentinel device.
SENTINEL Clinical Results and Considerations Outline

• Patient Accountability & Baseline/Procedural Characteristics

• Safety Results

• Effectiveness Results
Effectiveness – Primary

median new DWMR lesion volume at 2-7 days

Success Criterion #1

<table>
<thead>
<tr>
<th>Population</th>
<th>Test Arm (mm³)</th>
<th>Control Arm (mm³)</th>
<th>Observed Treatment Difference (Test - Control)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT with Imputation²</td>
<td>109.1 (36.9, 379.7), n=121, 0 min, 5175.9 max</td>
<td>174 (39.6, 469.3), n=119, 0 min, 24300 max</td>
<td>-64.9</td>
<td>0.2354</td>
</tr>
<tr>
<td>ITT</td>
<td>102.8 (36.9, 423.2), n=91, 0 min, 5175.9 max</td>
<td>178 (34.3, 482.5), n=98, 0 min, 24300 max</td>
<td>-75.1</td>
<td>0.3345</td>
</tr>
<tr>
<td>PP</td>
<td>118.7 (50.1, 435.1), n=83, 0 min, 5175.9 max</td>
<td>181.9 (47.5, 482.5), n=89, 0 min, 24300 max</td>
<td>-63.3</td>
<td>0.5715</td>
</tr>
</tbody>
</table>

median, (25th percentile, 75th percentile), n, min, max

For the Imaging Cohort, there was a reduction of 75 mm³ in median new lesion volume in *protected territories* for patients who received the Sentinel device. The difference was not statistically significant (p=0.33).

**Primary Effectiveness Criterion #1 was not met.**

Ref: Table 9: FDA Executive Summary
Effectiveness – Primary

median new DWMR lesion volume at 2-7 days
Success Criterion #2

<table>
<thead>
<tr>
<th>Population</th>
<th>Test Arm (mm$^3$)</th>
<th>Control Arm (mm$^3$)</th>
<th>Target</th>
<th>Observed % Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>102.8 (36.9, 423.2), n=91, 0 min, 5175.9 max</td>
<td>178 (34.3, 482.5), n=98, 0 min, 24300 max</td>
<td>30%</td>
<td>42.2 (-3.2, 67.6)</td>
</tr>
<tr>
<td>PP</td>
<td>118.7 (50.1, 435.1), n=83, 0 min, 5175.9 max</td>
<td>181.9 (47.5, 482.5), n=89, 0 min, 24300 max</td>
<td>30%</td>
<td>34.8 (-8.1, 60.6)</td>
</tr>
</tbody>
</table>

median, (25th percentile, 75th percentile), n, min, max

For the Imaging Cohort, there was a reduction of 42.2% in median new lesion volume in protected territories for patients who received the Sentinel device. This is above the prespecified threshold of 30%.

Primary Effectiveness Criterion #2 was met.

Ref: Table 10: FDA Executive Summary
Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

<table>
<thead>
<tr>
<th>Population</th>
<th>Test Arm (mm³)</th>
<th>Control Arm (mm³)</th>
<th>Observed Treatment Difference (Test - Control) (mm³)</th>
<th>p-value</th>
<th>Test Arm (mm³)</th>
<th>Control Arm (mm³)</th>
<th>Observed Treatment Difference (Test - Control) (mm³)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT with Imputation</td>
<td>109.1 (36.9, 379.7), n=121, 0 min, 5175.9 max</td>
<td>174 (39.6, 469.3), n=119, 0 min, 24300 max</td>
<td>-64.9</td>
<td>0.2354</td>
<td>247.2 (97.6, 572.2), n=121, 0 min, 14179 max</td>
<td>311.1 (110.7, 848.4), n=119, 0 min, 24300 max</td>
<td>-63.9</td>
<td>0.5794</td>
</tr>
<tr>
<td>ITT</td>
<td>102.8 (36.9, 423.2), n=91, 0 min, 5175.9 max</td>
<td>178 (34.3, 482.5), n=98, 0 min, 24300 max</td>
<td>-75.1</td>
<td>0.3345</td>
<td>294 (69.2, 786.4), n=91, 0 min, 14179 max</td>
<td>309.8 (105.5, 859.6), n=98, 0 min, 24300 max</td>
<td>-15.8</td>
<td>0.8076</td>
</tr>
<tr>
<td>PP</td>
<td>118.7 (50.1, 435.1), n=83, 0 min, 5175.9 max</td>
<td>181.9 (47.5, 482.5), n=89, 0 min, 24300 max</td>
<td>-63.3</td>
<td>0.5715</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

median, (25th percentile, 75th percentile), n, min, max

There was 75.1 mm³ median lower lesion volume for protected territories for the Sentinel device which was reduced to a 15.8 mm³ difference when all territories were considered.

Ref: Table 9 and 14: FDA Executive Summary
Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

<table>
<thead>
<tr>
<th>Population</th>
<th>Protected Territories</th>
<th>All Territories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Arm (mm³)</td>
<td>Test Arm (mm³)</td>
</tr>
<tr>
<td></td>
<td>Control Arm (mm³)</td>
<td>Control Arm (mm³)</td>
</tr>
<tr>
<td>ITT with Imputation</td>
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Assessment of different analysis populations for All Territories yields inconsistent trends in results.

Ref: Table 9 and 14: FDA Executive Summary
Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

<table>
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<tr>
<th>Population</th>
<th>Protected Territories</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>Test Arm (mm³)</td>
<td>Control Arm (mm³)</td>
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<tr>
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median, (25th percentile, 75th percentile), n, min, max

Assessment of different analysis populations for All Territories yields inconsistent trends in results.

Ref: Table 9 and 14: FDA Executive Summary
### Effectiveness – Protected vs All Territories

**median new DWMR lesion volume at 2-7 days**

<table>
<thead>
<tr>
<th>Population</th>
<th>Test Arm (mm$^3$)</th>
<th>Control Arm (mm$^3$)</th>
<th>% Reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protected Territories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>102.8 (36.9, 423.2) n=91</td>
<td>178 (34.3, 482.5) n=98</td>
<td>42.2</td>
</tr>
<tr>
<td>PP</td>
<td>118.7 (50.1, 435.1) n=83</td>
<td>181.9 (47.5, 482.5) n=89</td>
<td>34.8</td>
</tr>
<tr>
<td><strong>All Territories</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>294 (69.2, 786.4) n=91</td>
<td>309.8 (105.5, 859.6) n=98</td>
<td>5.1</td>
</tr>
<tr>
<td>PP</td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*median, (25th percentile, 75th percentile), n, min, max

There was 42.2% reduction in median lesion volume for protected territories for the Sentinel device which was reduced to a 5.1% reduction when all territories were considered. Percent reduction was not tested for statistical significance.

Ref: Table 15: FDA Executive Summary
Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

<table>
<thead>
<tr>
<th>Population</th>
<th>Test Arm (mm³)</th>
<th>Control Arm (mm³)</th>
<th>% Reduction*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mm³)</td>
<td>(mm³)</td>
<td></td>
</tr>
<tr>
<td>Protected Territories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>102.8 (36.9, 423.2)</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0 min, 5175.9 max</td>
<td>0 min, 24300 max</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>118.7 (50.1, 435.1)</td>
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</tr>
<tr>
<td></td>
<td>n=91</td>
<td>n=98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 min, 14179 max</td>
<td>0 min, 24300 max</td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>(25th percentile, 75th percentile), n, min, max</td>
<td>(4)</td>
<td></td>
</tr>
</tbody>
</table>

Assessment of different analysis populations for All Territories yields inconsistent trends in results.

Ref: Table 15: FDA Executive Summary
Effectiveness – Neurocognitive
Change in Battery Composite Z-Score From Baseline (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Test Arm Mean ± SD, n</th>
<th>Control Arm Mean ± SD, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days</td>
<td>-0.09 ± 0.44, 93</td>
<td>-0.03 ± 0.37, 92</td>
</tr>
<tr>
<td>90 Days</td>
<td>0.18 ± 0.38, 77</td>
<td>0.18 ± 0.35, 76</td>
</tr>
</tbody>
</table>

No meaningful clinical trends between Test and Control Arms were noted with respect to changes in overall z-scores at both 30 days and 90 days follow-up.

Ref: Table 21: FDA Executive Summary
## Effectiveness – Neurocognitive

Change in Battery Composite Z-Score From Baseline (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Test Arm</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
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No meaningful clinical trends between Test and Control Arms were noted with respect to changes in overall z-scores at both 30 days and 90 days follow-up.

Ref: Table 21: FDA Executive Summary
Effectiveness – Neurocognitive
30-Day Change in Z-Score from Baseline (ITT)

Ref: Figure 7: FDA Executive Summary
Effectiveness – Additional Analyses

• Quality of Life
  ➢ No statistical/clinical differences between groups

• Valve Type Subanalysis
  ➢ Study not designed to assess differences between groups and data are inadequate to support inferences regarding performance of one valve type over another

Ref: Table 21: FDA Executive Summary
Effectiveness – Additional Analyses

• Debris Capture

- 99% of cases debris was captured – acute thrombus with tissue and foreign material was the most commonly removed debris.

- The distinction of embolic capture versus possible filter generated debris (e.g., arterial wall, acute thrombus) is unclear.

Ref: Table 21: FDA Executive Summary
Effectiveness

The SENTINEL study met one of the prespecified effectiveness study success criteria and did not meet the other. Primary analysis did not demonstrate statistical significance. A clinically meaningful reduction in cerebral ischemia is also difficult to interpret.
FDA Presentations

• CDR Sadaf Toor
  Introduction and Summary of SENTINEL Study Design

• Dr. Donna Buckley
  SENTINEL Clinical Results and Considerations

• Dr. Li Ming Dong
  SENTINEL Statistical Results and Considerations

• CDR Sadaf Toor
  Conclusions
SENTINEL Statistical Results and Considerations

Li Ming Dong, PhD

Division of Biostatistics
Office of Surveillance and Biometrics
SENTINEL Statistical Results and Considerations

- Analysis Populations
- Analyses of Primary Safety Endpoint
- Analyses of Primary Effectiveness
- MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia
Analysis Populations

Primary Safety Endpoint

- ITT with imputation
  - Multiple Imputation for missing 30-Day MACCE evaluations

- ITT
  - Completers of Safety Cohort (Safety Arm and Test Arm)

- AT (As-Treated)
  - Patients received Sentinel

Primary Effectiveness Endpoint

- ITT with imputation
  - Multiple imputation for missing MRI scans

- ITT
  - Completers of Imaging Cohort (Test Arm and Control Arm)

- PP (Per-Protocol)
  - ITT further excludes out-of-window MRI scans
SENTINEL Statistical Results and Considerations

• Analysis Populations

• Analyses of Primary Safety Endpoint

• Analyses of Primary Effectiveness

• MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia
Analysis of Primary Safety Endpoint

Safety Cohort

As Randomized
N=244
(ITT w. Imputation*)

10 missing

Analyzed ITT
N=234

9 no device

As Treated
N=225

Safety Arm
N=123

2 no TAVR
4 no/fu

ITT (Safety Analysis)
N=117

2 device not enter vascular

AT
N=115

Test Arm
N=121

1 no TAVR
2 no/fu
1 withdrawal

ITT (Safety Analysis)
N=117

6 device not enter vascular
1 device removed pre-TAVR

AT
N=110

* Through multiple imputation
## Primary Safety Results: MACCE at 30-Days

<table>
<thead>
<tr>
<th>Population</th>
<th>Total Events</th>
<th>Patients w/ Events n/N, (%)</th>
<th>Performance Goal</th>
<th>Upper Limit of 95% Confidence Interval</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT with imputation</td>
<td>N/A&lt;sup&gt;2&lt;/sup&gt;</td>
<td>18/244 (7.4%)</td>
<td></td>
<td>10.7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ITT</td>
<td>17</td>
<td>17/234 (7.3%)</td>
<td>18.3%</td>
<td>10.7%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AT</td>
<td>17</td>
<td>17/225 (7.6%)</td>
<td></td>
<td>11.1%</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

<sup>1</sup>Upper limit of 95% confidence interval and p-value based on exact one-sided test for alternative hypothesis: rate \( < PG \) with 0.05 alpha level

<sup>2</sup>Binary outcome based on imputation analysis, number of events does not apply

Ref: Table 7: FDA Executive Summary
Primary Safety: Sensitivity Analysis

Worse-case scenario: Assuming that all 10 subjects with missing 30-day MACCE data had a MACCE event, then

the MACCE rate would be 11.1% (27/244)

with upper 95% confidence bound 14.9% < PG of 18.3%.
Safety

The primary safety endpoint is met and missing data is unlikely to alter the conclusion.
SENTINEL Statistical Results and Considerations

- Analysis Populations
- Analyses of Primary Safety Endpoint
- Analyses of Primary Effectiveness
- MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia
Analysis of Primary Effectiveness Endpoint Imaging Cohort

As Randomized (ITT w. Imputation*)

Test Arm
N=121

- 11 no scan
- 10 pacemaker
- 1 device removed pre-TAVR
- 1 no TAVR
- 1 withdrawal
- 6 device not enter vascular

ITT (Effectiveness Analysis)
N=91

- 7 scan out of window
- 1 assignment error

PP
N=83

Control Arm
N=119

- 9 no scan
- 8 pacemaker
- 2 scan rejected
- 1 no TAVR
- 1 died

ITT (Effectiveness Analysis)
N=98

- 9 scan out of window
- 1 device removed pre-TAVR

PP
N=89

* Through multiple imputation

Missing: 51
- 30 Test
- 21 Control

Exclude: 18
- 8 Test
- 10 Control
Analysis of Primary Effectiveness Endpoint: Statistical Considerations

- Medians of the Test Arm and Control Arm were compared using Wilcoxon Rank Sum Test
  - Due to expected non-normal skewed distribution of lesion volumes

- Missing data
  - High rate of missing endpoint data for Imaging Cohort: 21% (51/240)
  - Missing rates per Arm: Test 25% (30/121)
    Control 18% (21/119)
# Analysis of Primary Effectiveness Endpoint

## Protected Territories

<table>
<thead>
<tr>
<th>Population</th>
<th>Test Arm (mm³)</th>
<th>Control Arm (mm³)</th>
<th>Observed Treatment Difference (Test - Control) (mm³)</th>
<th>p-value</th>
<th>Test Arm (mm³)</th>
<th>Control Arm (mm³)</th>
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<tbody>
<tr>
<td>ITT with Imputation</td>
<td>109.1 (36.9, 379.7), n=121, 0 min, 5175.9 max</td>
<td>174 (39.6, 469.3), n=119, 0 min, 24300 max</td>
<td>-64.9</td>
<td>0.2354</td>
<td>247.2 (97.6, 572.2), n=121, 0 min, 14179 max</td>
<td>311.1 (110.7, 848.4), n=119, 0 min, 24300 max</td>
<td>-63.9</td>
<td>0.5794</td>
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<td>102.8 (36.9, 423.2), n=91, 0 min, 5175.9 max</td>
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Note: Data presented as: median, (25th percentile, 75th percentile), n, min, max.
## Analysis of Primary Effectiveness Endpoint

### Protected Territories

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<th>Test Arm (mm³)</th>
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<th>p-value</th>
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<td></td>
</tr>
</tbody>
</table>

Note: Data presented as: median, (25th percentile, 75th percentile), n, min, max.
Analysis of Primary Effectiveness Endpoint

Total New Lesion Volume (Protected Territories)

- Test Arm
- Control Arm

Total New Lesion Volume (All Territories)

- Test Arm
- Control Arm
Analysis of Primary Effectiveness Endpoint

Total New Lesion Volume
(Protected Territories)

Total New Lesion Volume
(All Territories)
Lesion volume distributions showed a small, non-statistically significant shift towards lower lesion volumes in the protected territories for patients in the Test Arm compared with patients in the Control Arm.

When all territories are analyzed, there is no clear trend of lesion volume reduction.
SENTINEL Statistical Results and Considerations

- Analysis Populations
- Analyses of Primary Safety Endpoint
- Analyses of Primary Effectiveness
- MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia
2-7 day new lesion volume in *protected territories* by 30 day clinical stroke status (Imaging Cohort - ITT)

**New lesion volume**

Log (mm³)

- 75th percentile
- Median
- 25th percentile

<table>
<thead>
<tr>
<th></th>
<th>No Stroke</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n=170</td>
<td>n=14</td>
</tr>
</tbody>
</table>
2-7 day new lesion volume in *all territories* by 30 day clinical stroke status (Imaging Cohort - ITT)

New lesion volume
Log (mm$^3$)

No Stroke  
$n=170$

Stroke  
$n=14$

$\text{volume}=81\text{mm}^3$
Correlation of Day 2-7 DW-MRI New Lesion Volume in Protected Territories (log transformed) with Change in Neurocognitive Battery Composite Z-Score

<table>
<thead>
<tr>
<th></th>
<th>Test Arm</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 to 7 Days Post-TAVR</strong></td>
<td>-0.53 (49)</td>
<td>-0.25 (53)</td>
</tr>
<tr>
<td><strong>30 Day Follow-Up</strong></td>
<td>-0.21 (74)</td>
<td>-0.20 (72)</td>
</tr>
<tr>
<td>(23-45 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>90 Day Follow-Up</strong></td>
<td>-0.24 (54)</td>
<td>-0.10 (55)</td>
</tr>
<tr>
<td>(46-100 days)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Data presented as: $r$ (n)

Ref: Table 19: FDA Executive Summary
Correlation of Day 30 T2/FLAIR MRI Lesion Volume (log transformed) with Change in Neurocognitive Battery Composite Z-Score

<table>
<thead>
<tr>
<th></th>
<th>Test Arm</th>
<th>Control Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 Day Follow-Up</strong></td>
<td>-0.04</td>
<td>-0.16</td>
</tr>
<tr>
<td>(23-45 days)</td>
<td>(68)</td>
<td>(63)</td>
</tr>
<tr>
<td><strong>90 Day Follow-Up</strong></td>
<td>-0.06</td>
<td>-0.07</td>
</tr>
<tr>
<td>(46-100 days)</td>
<td>(50)</td>
<td>(47)</td>
</tr>
</tbody>
</table>

Note: Data presented as: $r$ (n)

Ref: Table 20: FDA Executive Summary
Summary: Lesion Volume Measurement as a Surrogate Effectiveness Endpoint

- DW-MRI based new lesion volume at Day 2-7 in protected territories: patients with clinical stroke tend to have somewhat higher lesion volume.

- DW-MRI based new lesion volume at Day 2-7 in all territories: similar trend.

- Weak correlation (-0.2) between Day 2-7 lesion volume and 30-day change in neurocognitive composite z-score.
FDA Presentations

- CDR Sadaf Toor
  Introduction and Summary of SENTINEL Study Design

- Dr. Donna Buckley
  SENTINEL Study Clinical Results and Considerations

- Dr. Li Ming Dong
  SENTINEL Study Statistical Conclusions and Considerations

- CDR Sadaf Toor
  Conclusions
Conclusions

• Safety:
  ➢ Prespecified safety success criterion was met
  ➢ No safety concerns with use of the device

• Effectiveness:
  ➢ Study design: Imaging + clinical evidence of reduced ischemic events
  ➢ Met criterion for prespecified observed treatment effect (>30% reduction)
  ➢ Did not demonstrate superiority with respect to the primary effectiveness endpoint
Conclusions (cont.)

• Although device traps debris, correlation with DW-MRI findings (protected vs. all territories) remains unclear

• Neurocognitive outcomes showed no clear clinical trend
Thank you