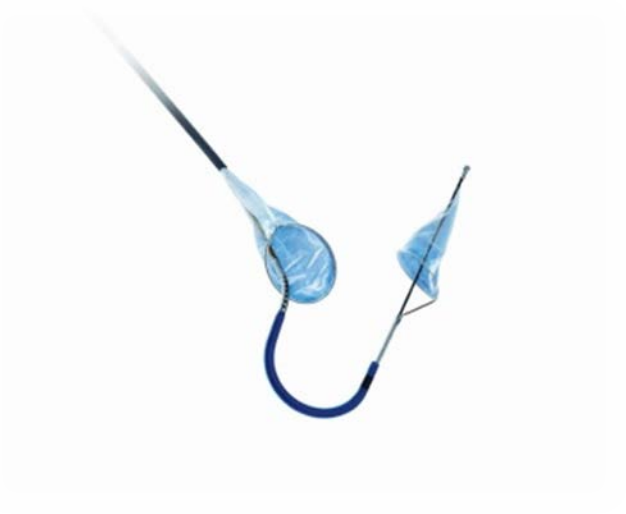
Sentinel® Cerebral Protection System

Cerebral Protection in Transcatheter Aortic Valve Replacement



Sponsor's Executive Summary

24 JAN 2016

Sponsored by Claret Medical, Inc.

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List of Abbreviations

3T	3 Tesla
AE	Adverse Event
AICD	Automated Internal Cardiac Defibrillator
AKI	Acute Kidney Injury
BAV	Balloon valvuloplasty
BAV	Balloon Valvuloplasty
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CEA	Carotid Endarterectomy
CEC	Clinical Events Committee
CR	Serum Creatinine
CT	Computed Tomography
CVA	Cerebrovascular Accident
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
DW-MRI	Diffusion-Weighted Magnetic Resonance Imaging
EDC	Electronic Data Capture System
EPD	Embolic Protection Device
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HU	Hounsfield Unit
IFU	Instructions for Use
IQR	Interquartile Range
IRB	Institutional Review Board
ITT	Intent to Treat
LCC	Left Common Carotid
LTFU	Lost to Follow-Up

LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiovascular and Cerebral Event
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MSCT	Multi-Slice Computed Tomography
NAMSA	North American Science Associates, Inc.
NIHSS	National Institutes of Health Stroke Scale
NTB	Neurocognitive Test Battery
NYHA	New York Heart Association
OUS	Outside United States
PPM	Permanent Pacemaker
PROM	Predicted Risk of Mortality Score
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement
SF-12	12-Item Short Form Health Survey
SOP	Standard Operating Procedures
STS	Society of Thoracic Surgeons
T2/FLAIR	T2-Weighted-Fluid-Attenuated Inversion Recovery
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Effects
VARC	Valve Academic Research Consortium
VCI	Vascular Cognitive Impairment

1. Synopsis

1.1. Introduction

Embolic ischemic strokes can occur in patients undergoing surgical and interventional cardiovascular procedures, including transcatheter aortic valve replacement (TAVR). The origin of these embolic cerebrovascular events is variable and can include dislodged cholesterol particles, atherosclerotic plaque material, thrombus, valve and arterial wall tissue, calcified valve material, and sheared interventional catheter coating material. In addition to overt stroke, procedure-related emboli can cause silent ischemic brain lesions or microinfarcts, potentially leading to cognitive decline and/or increased risk of future clinical stroke and mortality.[1]

Embolic protection devices (EPD), used for prevention of cerebral embolization in carotid stenting procedures for nearly two decades, have a proven safety profile and have demonstrated clinically meaningful reduction in neurological events).[2] The use of EPD in TAVR is a developing field which recognizes the likelihood that mechanical manipulation of interventional devices in the vasculature as well as aortic valve and aortic annulus may result in stroke and new ischemic lesions by dislodging pre-existing atherosclerotic and other debris and sending it into the cerebral blood flow. TAVR procedures require extensive mechanical manipulation of catheters and TAVR devices (placement of a large bore delivery catheter in the aortic arch, balloon valvuloplasty, valve positioning and re-positioning, valve expansion, post-dilatation, corrective catheter manipulation, use of guidewires and diagnostic catheters, etc.) and thus afford many opportunities for debris dislodgement and embolization.

The incidence of clinically apparent stroke after TAVR varies between 2% and 10%, depending on the assessor (i.e. cardiologist or neurologist), timing of assessment, definitions used (VARC-1[3] vs VARC-2[4]), and rigor of reporting.[5] The SENTINEL study, the pivotal trial at the focus of this Advisory Committee meeting, revealed a higher total stroke rate of 9.1% in the TAVR control arm (no cerebral protection) than seen in contemporary studies sponsored by valve device manufacturers.[6,7] Claret Medical (Sponsor) believes this finding to be primarily due to the rigor of the SENTINEL protocol: all patients underwent neurological assessment pre- and post-procedure by neurologists or certified neurological examiners; VARC-2 definitions were utilized; two independent stroke neurologists adjudicated all the cerebral events, and all strokes (disabling and non-disabling) were reported.

To address concerns related to the creation of new ischemic lesions during TAVR, Claret Medical has developed the Sentinel® Cerebral Protection System (Sentinel System), an EPD that utilizes fine mesh filters to capture and remove embolic material that may enter the cerebral circulation. The Sentinel System is designed to protect the parts of the brain supplied by the left and right common carotid and

[1] Smith, E., et al. "Cerebral Microinfarcts: The Invisible Lesions." Lancet Neurol. 2012; 11(3): 272–282.
[2] Matsuma, JS, et al. "Results of carotid artery stenting with distal embolic protection with improved systems: Protected Carotid Artery Stenting in Patients at High Risk of Carotid Endarterectomy (PROTECT) trial." J Vasc Surg. 2012 Apr; 55(4):968-976.
[3] Leon MB, et al. "Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium." J Am Coll Cardiol. 2011;57:253-69
[4] Kappetein AP, et al. "Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2)." Eur J Cardiothorac Surg. 2012 Nov;42(5):S45-60
[5] Leon MB, et al. "Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery." N Engl J Med, 2010; 363:1597-1607.
[6] Leon, M. et al. "Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients." The New England Journal of Medicine, 2016; 374: 1609-1620
[7] Adams, D. et al. "Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis." The New England Journal of Medicine, 2014; 370: 1790-1798

right vertebral arteries. The Sentinel System is an accessory device composed of two filters which are placed prior to the TAVR procedure. The first filter (proximal filter) is placed in the aortic arch takeoff section of the Brachiocephalic artery and the second filter (distal filter) is placed in the proximal part of the left Common Carotid artery. The Sentinel System is removed following completion of valve replacement (see **Section 3.3** for more details)

Placement of the Sentinel System filters approximately 90% of the blood flow to the brain and fully protects approximately 74% of brain tissue (reference the green area in the figure below). An additional 24% of brain tissue is partially protected via blood flow through the Circle of Willis (reference the yellow area in the figure below). Only 2% of brain tissue supplied by the Left Posterior Inferior Cerebellar Artery (PICA) is completely unprotected by the Sentinel System (reference the red area in the figure below).

For the purpose of discussion later in this document, the term “Protected Territories” refers to the green area while the term “All Territories” encompasses all areas of the brain (green, yellow, and red).

Claret Medical is requesting marketing clearance for the Sentinel System via the *de novo* regulatory pathway[8]. The *de novo* pathway was selected in cooperation with the Food and Drug Administration (FDA) since the risk profile of the device did not warrant a Class III designation and there were no Class II devices previously cleared via the 510(k) process which Claret Medical could use to establish substantial equivalence. Claret Medical proposes the following indication for the Sentinel System:

[8] FDA guidance. *De Novo* Classification Process (Evaluation of Automatic Class III Designation, 14 Aug 2014 (Draft)

The Sentinel 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.

1.2. Global Clinical Evidence

Claret Medical has significant and consistent European clinical experience with use of Claret EPD during TAVR, as reported in the CLEAN-TAVI, MISTRAL-C, and SENTINEL-H trials.

CLEAN-TAVI was an investigator-initiated, single center, single blind, 1:1 randomized, 100 high risk severe Aortic Stenosis (AS) patient clinical study that utilized only one operator and one transcatheter valve (Medtronic CoreValve). The study documented statistically significant reductions in both the number and volume of new DW-MRI lesions measured at 2 and 7 days post-procedure, across both protected regions and the entire brain (p-values range from <0.001 to 0.02) in patients who received the Sentinel System versus standard of care (no cerebral protection). A 39% reduction in new lesion volume was observed between the Test and Control at Day 2 and a 51% reduction in new lesion volume was observed at Day 7. The study concluded that cerebral protection devices might reduce brain injury as evaluated by diffusion-weighted magnetic resonance imaging (DW-MRI). CLEAN-TAVI was used as the basis of the design and statistical assumptions for the pivotal SENTINEL study.

MISTRAL-C was an investigator-initiated, multi-center, single blind, 1:1 randomized, 65 high risk severe AS patient clinical trial that utilized several valves and observed results similar to those of CLEAN-TAVI: a 52% reduction in new DW-MRI lesion volume in the entire brain between the Test and Control Arms (p = 0.17). Control patients experienced a greater amount of neurocognitive deterioration as indicated by the Mini-Mental State Examination (MMSE). In those patients who received a Sentinel System, tissue-derived debris was captured in 100% of patients and thrombotic material was captured in 87%. MISTRAL-C concluded that filter-based EPD capture debris en route to the brain in all TAVR patients and that the use of embolic protection may lead to fewer and overall smaller brain lesions as assessed by MRI.

The SENTINEL-H Post-Market Registry[9] was a prospective, multi-center, international “real world” registry that enrolled a total of 217 patients from six centers in Germany, Norway, Luxembourg and Switzerland and analyzed the embolic debris captured by the Sentinel System in a real-world clinical setting. The results from the SENTINEL-H study closely mirrored those observed in MISTRAL-C, with debris captured in 99% of patients and the majority of debris consisting of aortic wall and aortic valve tissue.

1.3. SENTINEL Pivotal Study

The SENTINEL study was a multi-center, blind, three arm, 1:1:1 randomized controlled trial of 363 high risk severe AS patients at 17 sites in the United States and 2 sites in Germany[10]. Patients were randomized to one of two Sentinel System arms or a Control arm. Investigational sites were allowed to use any commercially available TAVR device, and this led to a total of four valves being used during study enrollment (the balloon-expandable Edwards SAPIEN XT and SAPIEN 3 valves and the self-expanding Medtronic CoreValve and CoreValve Evolut R valves).

[9] Data on file at Claret Medical, Inc.
[10] Please refer to Appendix E for additional study oversight information.

1.3.1. Safety

The primary safety endpoint was met. The 30-day MACCE rate (7.3%) for patients in whom the Sentinel System was used was significantly non-inferior to the pre-specified historical performance goal of 13.3% with a non-inferiority margin of 5% (performance goal = 18.3 %, p <.0001). The observed rate of MACCE in the Safety Cohort was lower than the observed rate in the concurrent Control Arm of the trial (7.3% vs 9.9%) but the difference was not significant (p = 0.40). The Sentinel System introduced minimal risk to patients as evidenced by the high rate of device deployment and retrieval success (94.4%) and only one (0.4%) case of vascular injury at the access site.

SENTINEL was not powered to show a difference in strokes between the Test and Control Arms. Strokes were observed in 5.6% of Sentinel patients and 9.1% of Control patients. In patients with strokes, the size and number of DW-MRI lesions was reduced by use of the Sentinel System. The study demonstrated the safety of the Sentinel System in a high risk TAVR population with a broad range of co-morbidities.

1.3.2. Effectiveness – Debris Capture

The Sentinel System captured and removed debris in 99% of patients. These results mirrored those observed in MISTRAL-C and SENTINEL-H and further demonstrated that debris is released in virtually all TAVR procedures regardless of valve type. The debris captured included acute/organized thrombus, calcification, valve tissue, arterial wall tissue, TAVR catheter hydrogel coating material, and myocardial tissue. The study's morphometric analysis showed a broad range of debris sizes with some particle dimensions up to 5 mm, and that large debris ($\geq$ 0.5 mm) was captured in 70% of patients regardless of valve type.

1.3.3. Effectiveness – Superiority

The primary effectiveness endpoint (median total new lesion volume in protected territories, hereafter referred to as new lesion volume) trended in favor of Sentinel but was not statistically significant. The results showed new lesion volume of 109.1 mm^3 in the Test Arm and 174 mm^3 in the Control Arm (p=0.24). Although there was a 42% reduction in new lesion volume in patients who received the Sentinel System, the confidence intervals were broad (95% confidence intervals: -3.2%, 67.6%).

The Sponsor believes that statistical significance was not reached primarily due to reduced power of the study resulting from the limited dataset (i.e. CLEAN-TAVI, a single center trial using one TAVR valve type) used to design the study. Additionally, the three factors below likely contributed to the study missing its endpoint:

- The study found that baseline T2-Weighted-Fluid-Attenuated Inversion Recovery (T2/FLAIR-MRI) lesion burden was the most significant predictor of post-TAVR new lesion formation. However, the study did not control for patients' pre-existing baseline brain lesion volume which introduced significant variance.
- Choice of the surrogate endpoint of DW-MRI neuro imaging inherently introduced a degree of variance due to the nature of the DW-MR signal (rapid decay over time), and inter/intra site and patient variability of the imaging acquisition windows that could not be controlled for in obtaining the peak signal.
- New valve types were introduced sequentially into the trial as they became commercially available in the United States therefore adjusting the randomization scheme to include valve as well as treatment was not possible. This led to an unbalanced distribution (52% SAPIEN 3,

26% Evolut R, 18% SAPIEN XT, 4% CoreValve). Inclusion of multiple valve types introduced a second layer of variability into the data that was not accounted for in the study design and power calculation assumptions.

The Neurocognition results were not shown to be different between the Test and Control Arms. The SENTINEL study demonstrated a correlation between neurocognition and new lesion volume and frequency. The study showed a strong association and a correlation between an increase in new lesion volume and deterioration in neurocognitive function, both in areas of the brain protected by the Sentinel System and in all territories of the brain ($r = -0.25$, $p = 0.002$ and $r = -0.27$, $p = 0.001$, respectively). This association and correlation was also observed in new lesion number (frequency) in protected territories and all territories of the brain ($r = -0.31$, $p = 0.0001$ and $r = -0.30$, $p = 0.0002$, respectively). The sponsor believes that neurocognition was not shown to be different between the Test and Control Arms due to the study not being sufficiently powered to evaluate this endpoint and the patient's markedly reduced level of cognition at baseline (below average for their age, i.e., floor effect) due to their pre-existing baseline lesion volume.

1.4. Post Hoc Analyses

To examine the reasons for failure to meet the primary surrogate effectiveness endpoint, Claret Medical completed two non-pre-specified post hoc analyses: 1) a patient level meta-analysis of three EPD RCT studies, and 2) a multi variable analysis.

(b)(4) [redacted]

1.4.2. Multivariable Analysis

The multivariable analysis identified a significant predictor of future embolic events not previously identified in embolic protection studies or TAVR literature, despite its known characterization in other neurological disciplines, such as multiple sclerosis.[11] Baseline brain lesion volume burden detected by FLAIR/T2 MRI imaging sequence is specific to each patient's medical history and represents a quantitative measure of prior cerebrovascular events experienced by the patient over their lifetime.

The majority (65%) of variance observed in the SENTINEL post procedure DW-MRI data was attributed to pre-existing baseline lesion volume. Treatment arm assignment was the largest contributor of non-patient specific variables at 14% while the valve type contribution was less impactful at 6%.

1.5. Conclusion

The totality of the data from the SENTINEL trial demonstrates that:

[11] Filippi, M. "Role of magnetic resonance imaging in the diagnosis and monitoring of multiple sclerosis: Consensus report of the White Matter Study Group." Journal of Magnetic Resonance Imaging, 2002: Vol 15, Issue 5: 499-504

1) Use of the Sentinel System as an accessory device to TAVR is safe: the primary safety endpoint of MACCE at 30 days was met and numerically lower than the contemporary control, the device does not introduce undue new risk to the patients by demonstrating a low vascular access injury rate of 0.4%, and the device success rate was 94.4%.
2) Sentinel captures a broad spectrum of debris in 99% of TAVR patients. Debris >0.5 mm in diameter was captured in >70% of patients and was prevented from entering cerebral circulation. Capturing and removing the debris during TAVR with the Sentinel System, may enhance the safety of the TAVR procedures.
3) The primary surrogate effectiveness endpoint did not reach statistical significance, despite a 42% reduction in new lesion volume between test and control.
4) The results of Neurocognition were not shown to be different between the Test and Control Arms; however, new embolic brain lesions were associated with neurocognitive dysfunction in patients as assessed 30 days post procedure.
5) (b)(4) [redacted]
6) A post hoc multivariable analysis shed light on the nature and extent of variance observed in the study.

2. Unmet Need

TAVR-associated stroke and ischemic lesions are a still a significant health risk. The STS/ACC TVT Registry (>53,000 TAVR patients in the United States) shows no significant decline in 30-day stroke rate from 2012 (2.6%) to 2015 (2.2%).[12,13] The TVT Registry has also demonstrated that stroke risk is independent of increased physician TAVR experience. This finding is corroborated by a multinational registry of over 1,900 subjects in eight international centers.[14] The TVT registry provides only site reported strokes and does not require assessment by a certified neurologist, and thus likely underestimates the true stroke rate. As the TAVR population expands to younger patients, the long-term impact of a stroke increases, a great concern for both physicians and patients.

TAVR-related stroke or new ischemic lesions may result from a variety of patient/disease related causes such as severity of atherosclerosis, age, gender, hyperlipidemia, history of atrial fibrillation, and/or procedural related sources including mechanical manipulation of instruments or interventional devices, access routes and annulus sizing during the procedure. These mechanical manipulations are due, but not limited to, the placement of a relatively large bore delivery catheter in the aortic arch, balloon valvuloplasty, valve positioning, valve re-positioning, valve expansion, and corrective catheter manipulation as well as use of guidewires and guiding or diagnostic catheters required for proper positioning of the TAVR device.

The Sentinel System is an accessory device that is placed prior to the TAVR procedure and removed following completion of valve replacement. In the Edwards Lifesciences SAPIEN PARTNER Cohort A trial, 50% of strokes occurred in the first 24 hours, 96% in the first 9 days, and 100% in the first 28 days.[15] Similarly, in the SENTINEL trial 62% of the strokes occurred within the first 72 hours and 100% in the first 7 days. Given that a large proportion of the strokes occurred peri-procedurally, the use of an EPD to capture and remove procedural embolic debris may have helped reduce the clinical stroke rate as well as ischemic lesion burden to the brain. Embolic filter-based technology has an established basis of clinical safety and effectiveness in carotid stenting, suggesting the potential value of EPD use during the similarly debris-liberating TAVR procedure.

New cerebral lesions detected with MRI are reported in 48% of patients after valve surgery and between 67% and 100% after TAVR[16] (see **Table 1**).

[12] Holmes D, et al. “Annual Outcomes with Transcatheter Valve Therapy.” The Annals of Thoracic Surgery, 2016; Volume 101, Issue 2: 789-800
[13] Eltchaninoff H, et al. “Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry.” Eur Heart J, 2011; 32:191-197.
[14] Wassef A. et al, The effect of procedural volume and experience on clinical outcomes after transcatheter aortic valve replacement: Results from the international multicenter TAVR registry. Poster presented at: American College of Cardiology Scientific Session; April 2016; Chicago, IL.
[15] Miller, DC et al. “Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial.” J Thorac Cardiovasc Surg., 2012; 143(4):832-843.
[16] Kahlert P, et al. “Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study.” Circulation, 2010; 121:870-878

Table 1: New Cerebral Lesions in TAVR Patients

Study	Percentage of TAVI Patients with New Cerebral Lesions on DW-MRI
Rodes-Cabau, 2011	68%
Ghanem, 2010	73%
Arnold, 2010	68%
Kahlert, 2010	84%
Astarci, 2011	69%
DEFLECT III Control Arm, 2015	89%
Bijuklic, 2015	67%
CLEAN-TAVI, Control Arm, 2014	98%
PROTAVI-C, 2014	100%
NeuroTAVR, 2015	94%
MISTRAL-C, 2016	100%
SENTINEL, 2016	94%

While most of these lesions do not result in clinically apparent symptoms, subtle neurological and neurocognitive symptoms may go undetected and ischemic lesions may lead to long-term neurocognitive decline. Several studies have linked the presence of apparently sub-clinical micro-emboli after heart surgery to eventual neurocognitive decline.[17] Vascular cognitive impairment (VCI) may also result from multiple, initially subclinical, cerebral embolizations. Population based studies demonstrated that these ischemic lesions increase the risk of future strokes three to fourfold.[18]

Risks related to these ischemic lesions are likely similar across all patients with severe aortic stenosis, regardless of surgical risk score (which is more related to other health factors) since by definition they have severely stenotic valves. Data published in 2016 has shown the TAVR and SAVR in-hospital stroke rates are similar across the surgical risk spectrum (EuroScore)[19], see **Figure 2** below. This data represents over 20,000 patients treated in 2013 in Germany and shows there are no statistically significant differences in stroke rates for any comparisons except low-risk patients treated trans-apically.

[17] Clark RE, et al. "Microemboli during coronary artery bypass grafting. Genesis and effect on outcome." J Thorac Cardiovasc Surg, 1995; 109:249-257; discussion 257-248.
[18] Vermeer, Sarah E, et al. "Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population." Journal of the American Stroke Association, 2003; 34:1126-1129
[19] Möllmann H, et al. Clin Res Cardiol 2016

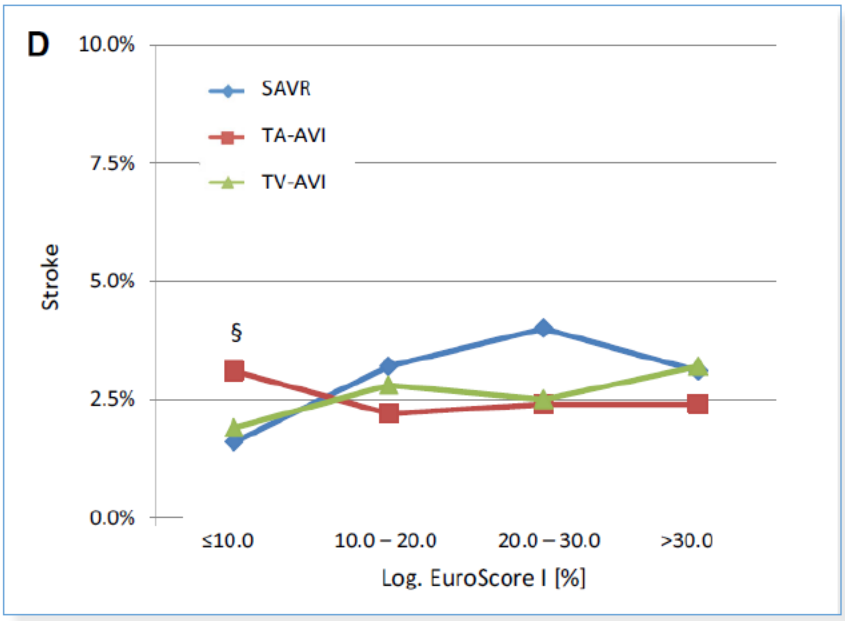


Figure 2: Stroke Rate Compared to EuroScore

A meta-analysis of seven European registries[20] of almost 10,000 patients with EuroScores varying from 16% to 33% demonstrated the patient risk profile assessed by the average EuroScore was not associated with the incidence of stroke (p=0.74). Similarly, the PARTNER II trial[21] showed intermediate risk patients treated with the SAPIEN 3 device had a stroke rate of 2.6% (n=1076), vs. High-risk S3HR stroke rate of 1.5% (n=583), see Figure 3.

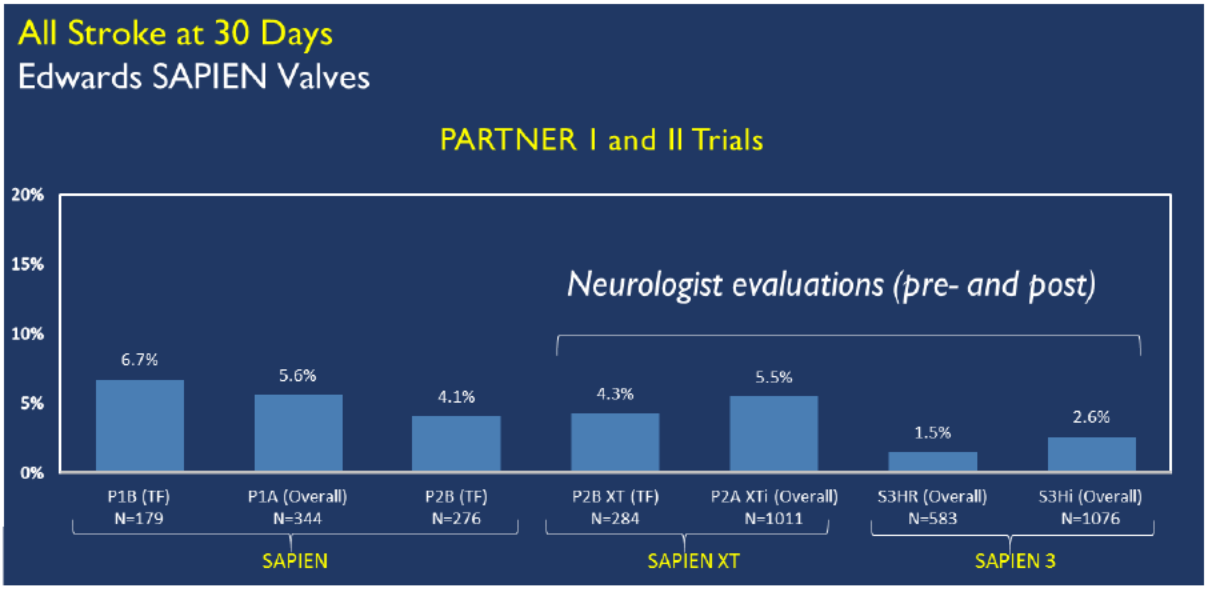


Figure 3: PARTNER II Stroke Results

[20] Zeinah, M, et al. Annals of Cardiovascular and Thoracic Academy (ACTA) 2015; December 18: 1-11.
[21] Leon, M. et al. "Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients." The New England Journal of Medicine, 2016; 374: 1609-1620

Lower surgical risk, and younger, patients likely have longer life expectancies over which to benefit from reduced neurological injury (stroke and cognitive decline). The MISTRAL-C study captured debris in 100% of low-intermediate risk STS score patients and CLEAN-TAVI captured debris in all intermediate risk patients that constituted more than 60% of the treated population. These data underscore the need for cerebral embolic protection across the TAVR risk spectrum.

3. Device Information & Summary

3.1. Indications for Use – Proposed

The Sentinel Cerebral Protection System (Sentinel 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.

3.2. Target Population

The Sentinel System is targeted for use in patients receiving treatment for severe aortic valve stenosis in accordance with the approved indication for the applicable transcatheter aortic valve.

3.3. Device Overview

The Sentinel System (**Figure 4**) is a 6 French, 95 cm working length, single use, temporary, percutaneously-delivered embolic protection catheter inserted into the right radial or brachial artery. The system is designed to capture and remove embolic material (thrombus/debris) that may enter protected arteries during TAVR.

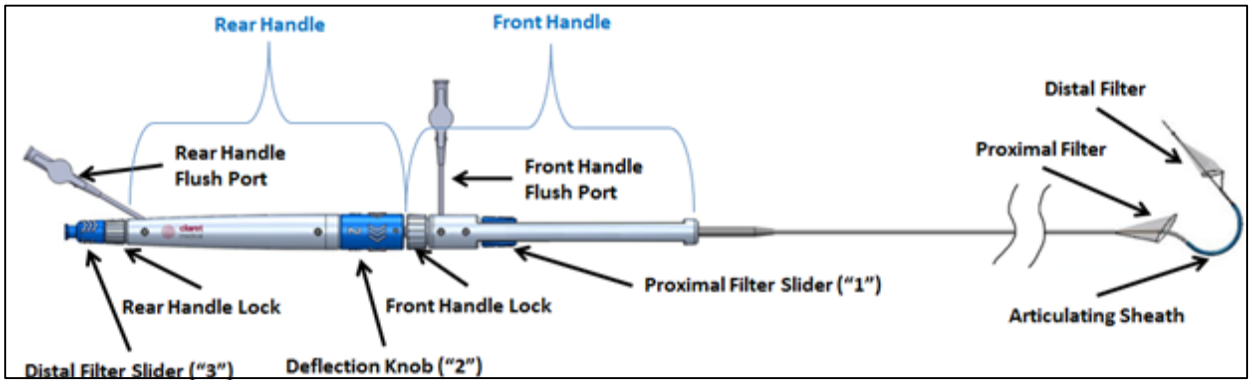


Figure 4: Sentinel Cerebral Protection System

The Sentinel System employs two embolic filters, one delivered to the brachiocephalic artery (Proximal Filter), and one to the left common carotid artery (Distal Filter). The nominal diameters are 15 mm (Proximal Filter) and 10 mm (Distal Filter). A fluoroscopic image of a deployed Sentinel System and diagram of protected arteries are shown in **Figure 5** illustrating the placement of the (1) Proximal Filter, (2) Articulating Sheath, and (3) Distal Filter.

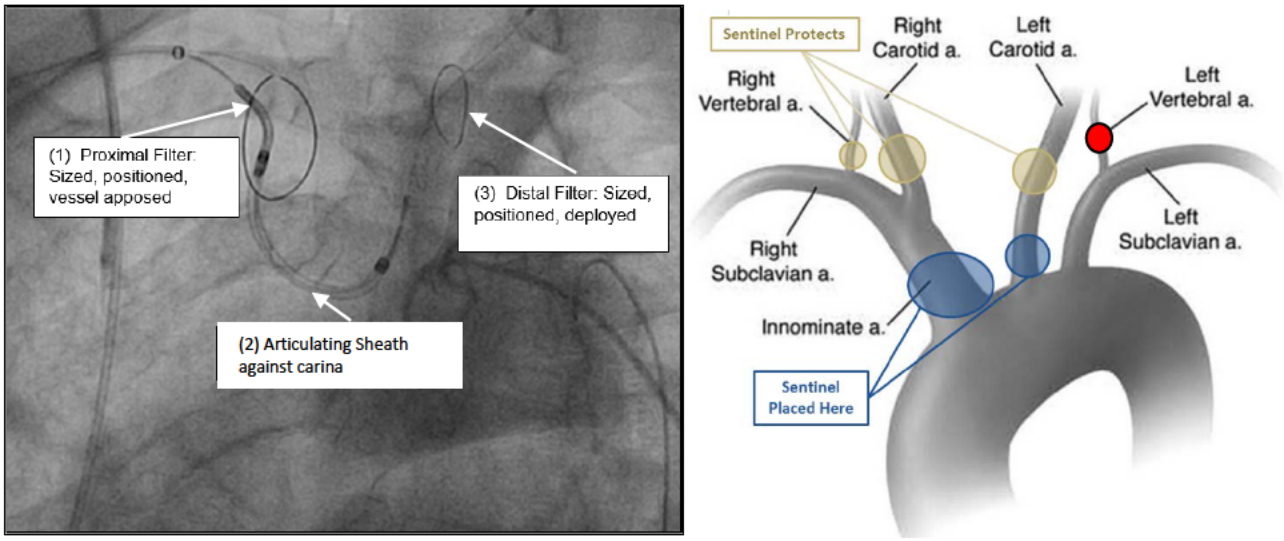


Figure 5: Deployed Catheter System (Angiographic Image and Representation)

At the completion of the TAVR procedure, the Proximal and Distal Filters are re-sheathed and removed from the patient, along with any captured embolic debris.

4. Regulatory History

4.1. CE Mark

The Sentinel System received CE Mark in Europe in December 2013 and is commercially available in select European Union geographies. Over 3,000 Sentinel Systems have been used worldwide to date, with the data from some of these patients included in the CLEAN-TAVI, MISTRAL-C, and SENTINEL-H post-market studies.

4.2. United States Regulatory History

The Sentinel System is proposed as a Class II (moderate to high risk) non-exempt device that will be regulated under general and special controls via the *de novo* regulatory pathway. The *de novo* process provides a pathway to Class II classification for devices for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device. The *de novo* pathway was selected in cooperation with the Food and Drug Administration (FDA) as the risk profile of the device did not warrant a Class III designation and there were no Class II devices previously cleared via the 510(k) process which Claret Medical could use to establish substantial equivalence.

5. Global Clinical Evidence

5.1. Summary

- Three (3) OUS post-market studies (n = 299) demonstrate the safety and effectiveness of the Sentinel System.
- Procedural success was demonstrated in 97% of real-world patients.
- Embolic debris was captured and removed in 99% of patients.
- CLEAN-TAVI was a single center, single blind, investigator initiated study of 100 patients that demonstrated statistically significant reductions in both the number of new lesions and new lesion volume, for both potentially protected brain regions as well as the entire brain, at 2 and 7 days after TAVI.
- MISTRAL-C was a multi-center, single blind, investigator initiated study of 65 patients that demonstrated use of the Sentinel System reduced both the total number and the total volume of lesions. Control group patients experienced a statistically significant greater amount of neurocognitive deterioration than Sentinel patients.
- SENTINEL-H Post-Market Registry analyzed the embolic debris captured by the Sentinel System in a real-world international clinical setting in 217 patients and demonstrated that debris was captured in 99% of registry patients.

5.2. CLEAN-TAVI

The Claret Embolic Protection and TAVI (CLEAN-TAVI) study was a single-center, single blind investigator-initiated clinical trial conducted in 2014 at the University of Leipzig Heart Center in Germany. The objective of the study was to determine the effect of an EPD (Claret Montage Dual Filter System, precursor to the Sentinel System) on the number and volume of cerebral lesions in high risk severe aortic stenosis (AS) patients undergoing transcatheter aortic valve implantation (TAVI). The primary endpoint was the numerical reduction in positive post-procedure DW-MRI brain lesions, relative to baseline, at 2 days following TAVI in potentially protected territories. Additional, secondary endpoints included results of serial neurological and neurocognitive assessments.

The study was randomized 1:1 and enrolled 100 high risk patients with severe aortic stenosis. Patients and follow-up assessors were blinded to treatment assignment. Patients were randomly assigned to undergo TAVI with an EPD (filter group) or without a cerebral protection device (control group). All patients received treatment with the Medtronic CoreValve only. Prior to the TAVI procedure, all patients received 3 Tesla diffusion-weighted magnetic resonance imaging (DW-MRI) and neurological and neurocognitive assessments to establish baseline values. Follow-up DW-MRI, neurological, and neurocognitive assessments were performed at 2 days and 7 days after TAVI. All MRI scans were blindly analyzed at an independent MRI Core laboratory.

EPD delivery success (both filters deployed) was achieved in 46 of 50 patients (92%), total or partial device success (at least one filter deployed) in 48 of 50 (96%), and total procedural success (both filters deployed and in place during TAVI procedure) in 45 patients (90%).

Overall, the study documented statistically significant reductions between filter and control groups in both the number of new lesions and new lesion volume, for both potentially protected brain regions and the entire brain (p-values ranging from 0.02 to <0.001). At the 2 and 7 follow-up assessments, 10 patients had neurological symptoms indicative of stroke, 5 in the filter group and 5 in the control

group. Strokes were classified according to the VARC-2 definitions and were determined to all be minor and non-disabling. No transient ischemic attacks were identified.

The study concluded that for patients with severe aortic stenosis undergoing TAVI, the use of the Claret Montage Dual Filter System significantly reduced the number and volume of ischemic cerebral lesions in protected regions at 2 and 7 days after TAVI, reference figure below.

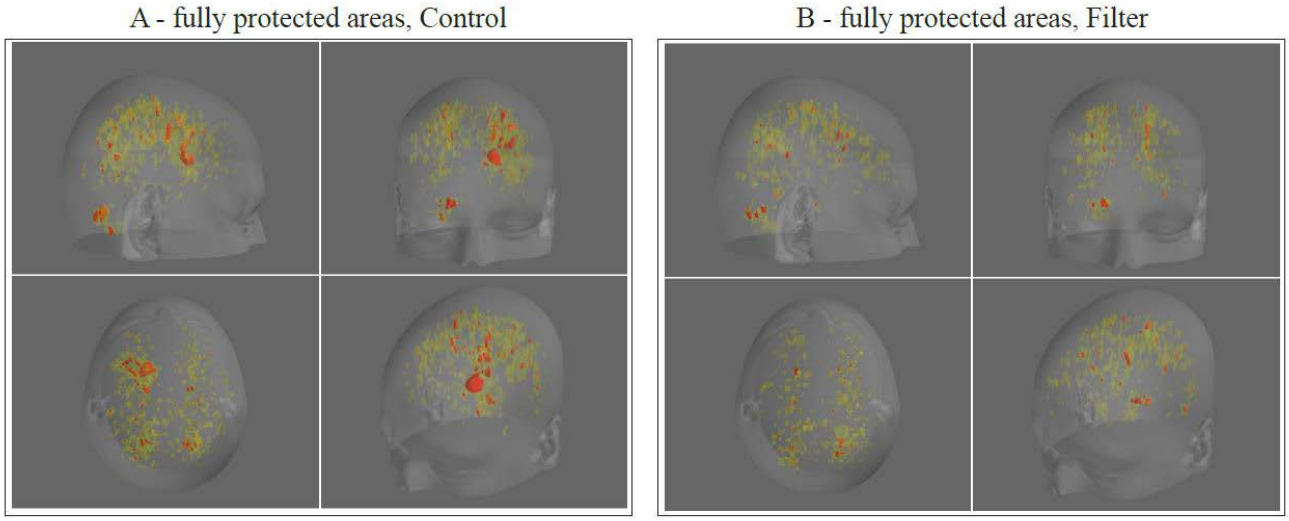


Figure 6: Comparison of Protected and Unprotected Patients – CLEAN-TAVI

5.3. MISTRAL-C

The MRI Investigation in TAVI with Claret (MISTRAL-C) study was a multi-center, single blind, investigator-initiated randomized trial conducted from 2013-2015 in four centers in the Netherlands. The objective of the study was to determine if the use of the Sentinel System during TAVI could affect the early incidence of new brain lesions, as assessed by DW-MRI, and neurocognitive performance.

Sixty-five high risk severe AS patients were randomly assigned in a 1:1 fashion to undergo TAVI with the Sentinel System (filter group) or without (control group). For inclusion in the study, patients were required to be at high risk for surgical aortic valve replacement (SAVR), and selected for transfemoral TAVI by Heart Team consensus. In addition, aortic arch anatomy had to be compatible with the sizing requirements for the Sentinel System. Key exclusion criteria were the presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline and a history of prior stroke with sequelae and dementia.

All patients received 3 Tesla DW-MRI and neurological examinations one day prior to TAVI, and between 5-7 days following the procedure. All MRI scans were blindly analyzed at an independent MRI Core laboratory.

Stroke was classified using the Valve Academic Research Consortium 2 (VARC-2) definitions. Neurocognitive evaluation was conducted using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). Debris captured in the device filters underwent histopathogical examination.

Patients in the study received one of four valve types: Medtronic CoreValve (25%), Edwards SAPIEN XT (15%), Edwards SAPIEN 3 (54%), or St. Jude Portico (1%). The Sentinel device was successfully

deployed in all but two patients, one of which was a screening failure, and there were no associated device related injuries. There were two disabling strokes (7%) in the control group, zero (0%) in the in filter group, and zero (0%) non-disabling strokes in either group. Use of the Sentinel System reduced the total number and total volume of new lesions but the reduction was not statistically significant. DW-MRI findings demonstrated 78% of patients had new brain lesions at a median of five days after TAVI. Over a quarter of patients undergoing TAVI with the Sentinel System had no new brain lesions in all brain territories, while half had no new lesions in the protected territories.

The study found that control group patients experienced a statistically significantly greater amount of neurocognitive deterioration, as tested by the MMSE, than filter group patients (p = 0.017), reference the figure below. Histopathological results revealed that debris, primarily consisting of thrombotic and tissue derived material, was captured in all filter group patients.

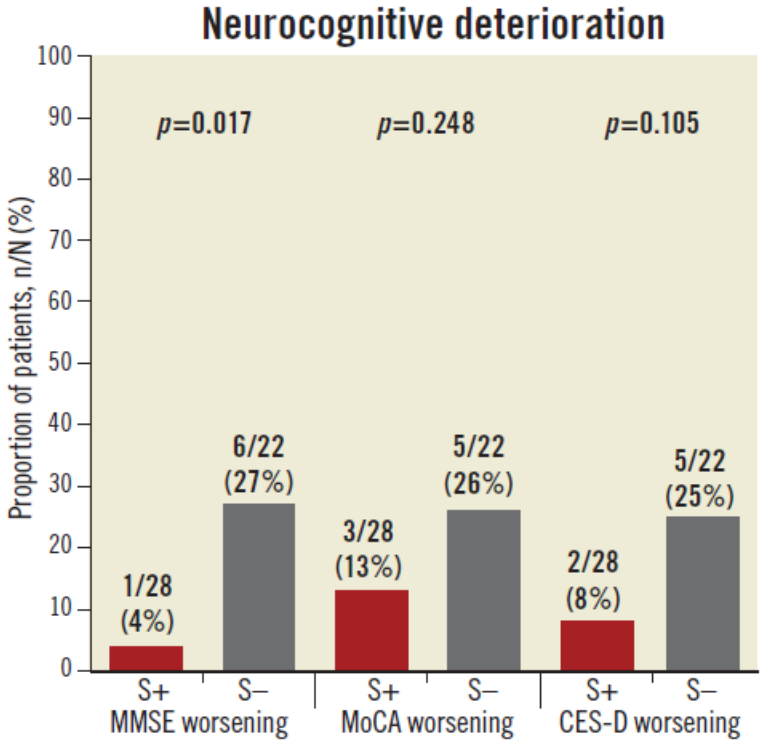


Figure 7: Neurocognitive Findings in MISTRAL-C

The study concluded that the Sentinel System captured debris en route to the brain in all TAVR patients and that the use of embolic protection could lead to fewer and overall smaller brain lesions as assessed by DW-MRI.

5.4. SENTINEL-H

The Claret Medical SENTINEL-H Post-Market Registry was a prospective, multi-center, international registry that enrolled patients at six centers in Germany, Norway, Luxembourg and Switzerland. The objective of the study was to analyze the embolic debris captured by the Sentinel System in a real-world international clinical setting. A total of 217 patients with severe symptomatic calcified native aortic valve stenosis, selected for TAVR by heart team consensus and treated with CE-Marked TAVR devices, were enrolled in the registry. Basic patient information, including EuroScore, and procedural

information (device interference, procedural success, time to placement, contrast usage, etc.) were collected for each patient.

Patients in the study received a valve from one of the following manufacturers: Edwards (45%), Direct Flow (20%), Boston Scientific (17%), Medtronic (12%), St. Jude (5%), Symetis (<1%), or Jena Valve (<1%). The Sentinel System was successfully deployed 97% of patients, and there were no cases of dislocation of the Sentinel System by TAVR delivery catheters. The median (± SD) time to place the Sentinel System was 4 ± 6 minutes.

A total of 420 filters (211 proximal, 209 distal) from 212 patients were assessed for debris by an independent histopathology core lab and debris was captured in 99% of patients. Acute thrombus associated with tissue or foreign material was the most common debris type, see **Figure 8**.

The high rates of successful deployment and debris capture regardless of valve type suggest a strong clinical value for embolic protection during TAVR.

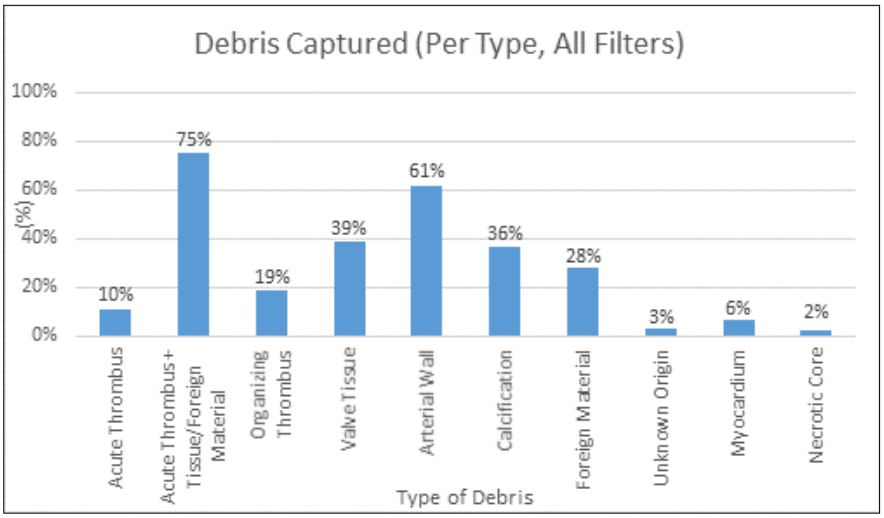


Figure 8: SENTINEL-H Captured Debris

6. SENTINEL Study Design

6.1. Objective

To assess the safety and efficacy of the Claret Medical Sentinel Cerebral Protection System used for cerebral protection during TAVR compared to TAVR without cerebral protection.

6.2. Study Hypothesis

The Sentinel System is a safe and effective method for capturing and removing embolic material (thrombus/debris) during endovascular procedures in order to reduce the ischemic burden in the cerebral anterior circulation.

6.3. Design

The SENTINEL study is a prospective, blind, multi-center, randomized study using the Sentinel System in patients with high risk severe aortic valve stenosis indicated for TAVR. Patients as well as the Sponsor, all core laboratories, Study Operations Committee, and the Clinical Events Committee (CEC) were blinded to study arm assignment. A total of 363 patients at 17 centers in the United States and 2 centers in Germany (see **Appendix A** for a full site listing) were randomized across 3 arms (Safety, Test, and Control) in a 1:1:1 fashion according to the study overview shown in **Figure 9**. A description of the evaluations performed for patients in each arm is provided in **Table 2**. A more in-depth breakdown of required study assessments is available in **Appendix B**.

Table 2: Evaluations Performed by Arm

	Safety Arm	Test Arm	Control Arm
Safety Follow-Up ▪ Discharge ▪ Day 30 ▪ Day 90	**Yes**	**Yes**	**Yes**
Neurological Assessment ▪ Baseline ▪ Discharge ▪ Day 30 ▪ Day 90 if stroke ≤ 30 days	**Yes**	**Yes**	**Yes**
MRI Assessment ▪ Baseline ▪ Day 2-7 ▪ Day 30	**No**	**Yes**	**Yes**
Neurocognitive Assessment ▪ Baseline ▪ Day 2-7 ▪ Day 30 ▪ Day 90	**No**	**Yes**	**Yes**
Quality of Life Assessment ▪ Baseline ▪ Day 30 ▪ Day 90	**No**	**Yes**	**Yes**

Histopathological Assessment of Captured Debris	No	Yes	N/A

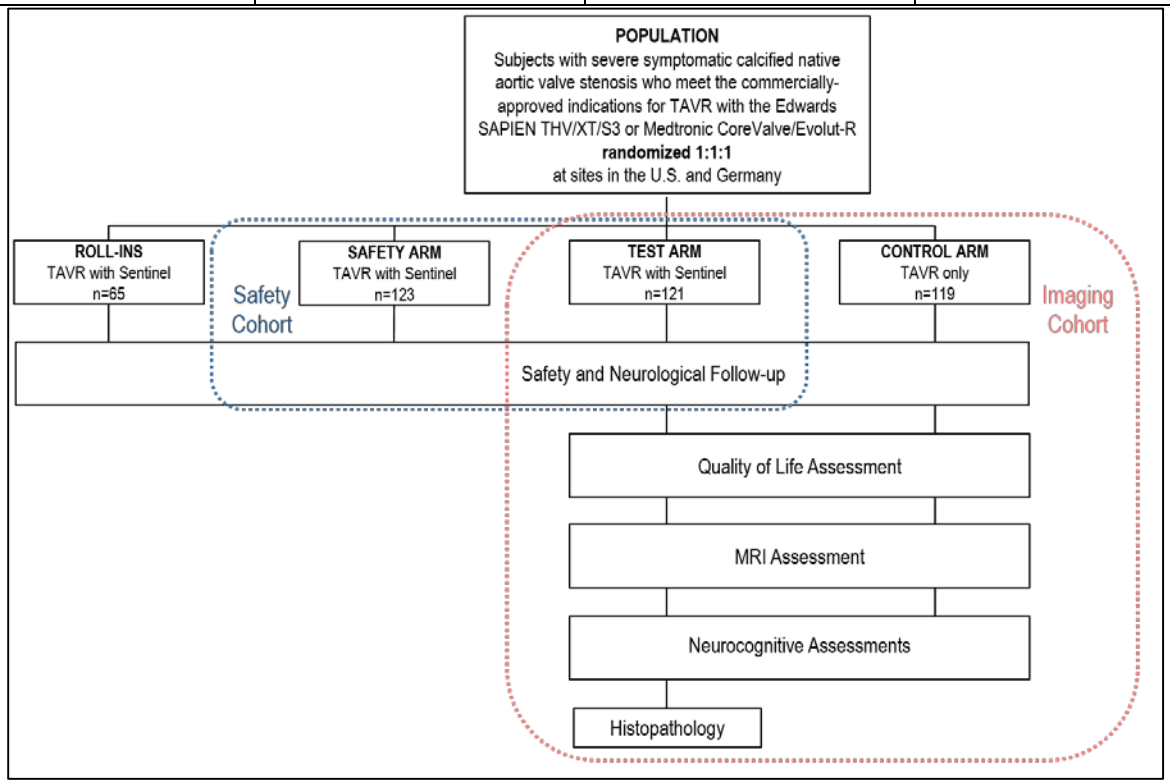


Figure 9: SENTINEL Study Overview

All MRI evaluations were performed using 3 Tesla MRI systems on patients participating in the Test and Control Arms. These evaluations consisted of two different sequences, diffusion-weighted (DW) and Fluid Attenuated Inversion Recovery (T2/FLAIR), both performed at baseline, 2-7 day, and 30-days post-procedure. DW-MRI was specified for identification of new (2-7 day) cerebral lesions due to its sensitivity to small and early infarcts. T2/FLAIR MRI was specified for identifying chronic baseline lesions and persistent long-term (30 day) new lesions (reference **Figure 10** below and **Appendix P** for additional MRI acquisition and analysis information).

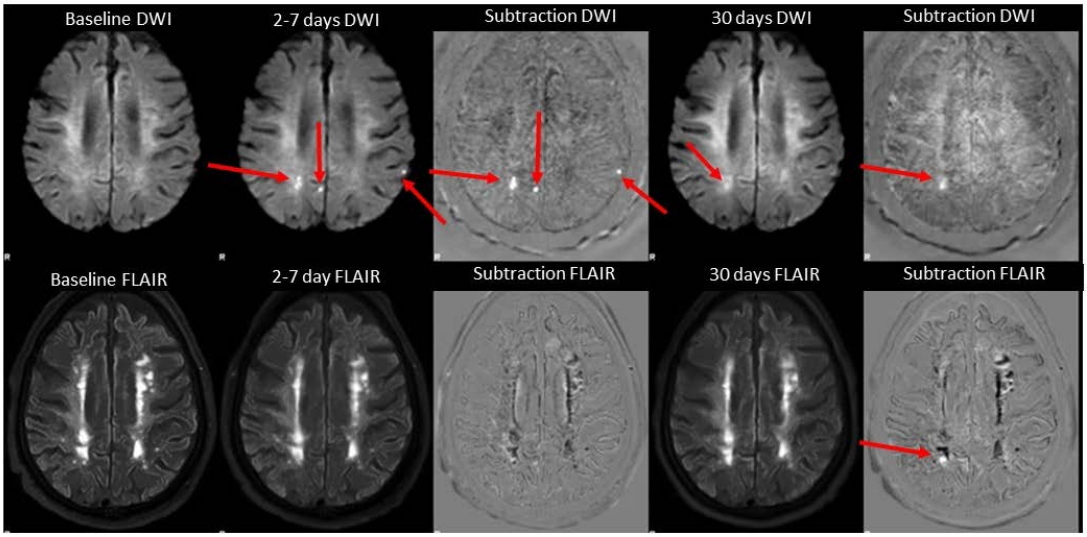


Figure 10: MRI Analysis Images

6.4. Inclusion/Exclusion Criteria

6.4.1. Key Inclusion Criteria:

- Severe symptomatic aortic stenosis eligible for treatment with a US commercially approved TAVR system
- Left common carotid artery (6.5 – 10 mm) and brachiocephalic artery (9 – 15 mm) diameters without significant stenosis

6.4.2. Key Exclusion Criteria:

- **Anatomic**
  - Right extremity vasculature not suitable
  - Brachiocephalic, left carotid or aortic arch not suitable
- **Clinical**
  - Cerebrovascular Accident (CVA) or Transient Ischemic Attack (TIA) within 6M
  - Neurological disease with persistent deficits
  - Carotid disease requiring treatment within 6 weeks
  - Contraindications to MRI
  - Renal insufficiency (CR > 3.0 or GFR < 30) or Renal Replacement Therapy
  - Severe left ventricular dysfunction (EF < 20%)
  - Balloon valvuloplasty (BAV) within 30 days

A complete list of inclusion/exclusion criteria can be found in **Appendix C**.

6.5. Study Endpoints & Statistical Methods

6.5.1. Primary Safety Endpoint (non-inferiority)

The primary safety endpoint for the study is to evaluate the rate of Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days compared to a historical performance goal. MACCE events were adjudicated using VARC-2 definitions by a Clinical Events Committee (CEC) blinded to

treatment arm and composed of two cardiologists, a vascular neurologist, a stroke neurologist, and a nephrologist.

- MACCE was defined as all death, all stroke, and acute kidney injury (AKI) class 3 within 72 hours of discharge, whichever occurs first.

Safety Endpoint Derivation

The point estimate for the historical performance goal for the safety endpoint in the TAVR population was derived from published FDA documents as well as the published literature.

(b)(4)

[redacted]

(b)(4) [redacted]

Safety Hypothesis
Using the pre-specified threshold for evaluating the study results, the null and alternative hypotheses were:

Ho: $p \geq 18.3\%$
Ha: $p < 18.3\%$

where p equals the 30-day primary endpoint event rate defined as death, stroke, or acute kidney injury (AKI Class 3).

Using a hypothesized event rate of 12%, a type I error of 5% and a type II error of 20%, the upper bound of the exact one-sided 95% confidence interval for the primary endpoint event rate must have been less than the pre-specified threshold of 18.3% for the null hypothesis to be rejected in favor of the alternative. A 5% loss to follow-up was also factored into sample size calculations; therefore, a minimum of 224 patients were required to sufficiently power the study.

6.5.2. Primary Efficacy Endpoint

The efficacy endpoint was set as a combination of observational and statistical superiority surrogate endpoints.

- *Observational Study Success Criteria:*
  Demonstration of an observed ratio of the median total new lesion volumes of ≥30% in favor of the Test Arm having a lower median total new lesion volume in the *protected* territories as compared to the Control Arm.
- *Primary Superiority Endpoint:*
  Reduction in median total new lesion volume in *protected* territories between the Test and Control Arms as assessed by DW-MRI at Day 2-7 post-procedure. Total new lesion volume was defined as the sum of all diffusion-positive new cerebral lesions in post-procedural DW-MRI relative to the pre-TAVR baseline DW-MRI scans. *Protected* territories were defined as brain territories uniquely perfused by the vessels protected by the Sentinel System, namely the left and right carotid arteries, and the right vertebral artery.

Efficacy Endpoint Derivation
The Observational Study Success criteria was established through collaboration between Claret Medical and the FDA. A 30% treatment effect is generally considered to be clinically meaningful even though many studies show a lower effect. The goal of a 30% treatment effect was established to provide viable evidence to allow the clinical community to move forward while the scientific understanding of cerebral embolic protection evolves.

Primary superiority efficacy success is predicated on detecting a significant difference ($p < 0.05$) in median total new lesion volume in favor of the Test Arm in the protected territories in comparison to the Control Arm. A new DWI lesion is one present on a post-treatment scan that was not present on the pretreatment scan. (b)(4) [redacted]

(b)(4)

[redacted]

Efficacy Hypothesis

The null and alternative hypotheses for determining if there was a significant difference were:

$$H_0: \mu_{test} = \mu_{control}$$
$$H_A: \mu_{test} \neq \mu_{control}$$

where,

μ test = Test Arm day 2-7 DW-MRI median total new lesion volume (protected territories)

μ control = Control Arm day 2-7 DW-MRI median total new lesion volume based (protected territories)

Data imputation was based on the Markov Chain Monte Carlo (MCMC) algorithm specifying missing at random (MAR). This imputation offered a model-based solution where missing values were treated as unknown parameters. The missing values were sampled sequentially in a MCMC simulation.

Based on these simulations, the posterior distributions of the incomplete data were obtained given the observed data for prediction purposes. This approach took into account the uncertainty about the missing values, estimating the posterior marginal distributions of the parameters of interest conditioned on observed (and partially observed) data.

(b)(4)

[redacted]

The imputed dataset was used to test the efficacy endpoint hypothesis. The null hypothesis was to be rejected and the primary efficacy endpoint of superiority considered met if the p-value from the Wilcoxon test was less than 0.05 and the median lesion volume in the Test Arm was less than the Control Arm. The median total new lesion volume was presented by Arm, along with the inter-quartile range (IQR) and range. The differences between Test and Control were evaluated on the imputed dataset using the Hodges-Lehmann estimate of location shift, and a 95% confidence interval about the shift.

6.5.3. Key Secondary Endpoints

- In-hospital MACCE [all study arms] through discharge
- MACCE at 30 days [all study arms]
- Occurrence of major vascular complications [all study arms] at index and 30 days
- Occurrence of other Serious Adverse Events [all study arms] at 30 days
- Sentinel System acute delivery and retrieval success [Safety and Test Arms]

Additional secondary endpoint analyses may be found in **Appendix F** and **Appendix G**.

6.5.4. Post-Hoc Meta-Analysis and Multivariable Modeling

(b)(4) [redacted]

Univariate and multivariable analyses were performed to help identify sources of variance in the study.

6.6. Methods

6.6.1. Screening and enrollment

Patients with severe aortic stenosis who met all anatomical screening and study inclusion criteria, and none of the exclusion criteria, were eligible to enroll in the study. Patients in the Test and Safety Arms (Safety Cohort) received the Sentinel System during TAVR, and patients in the Control Arm underwent TAVR without the Sentinel System.

As a part of the screening process, eligible patients underwent a computed tomography (CT) angiogram (as per standard of care) which was evaluated by an independent CT core laboratory to determine anatomical suitability for the Sentinel System. Patients determined ineligible per the CT evaluation were screen-failed from the study. Patients determined to be anatomically eligible proceeded to randomization after meeting all inclusion/exclusion criteria and baseline study assessments. Patients were considered enrolled in the study after signing the informed consent and meeting all the clinical, imaging and neurocognitive baseline requirements as specified by their randomized study arm assignment. (See **Figure 11** for scheme)

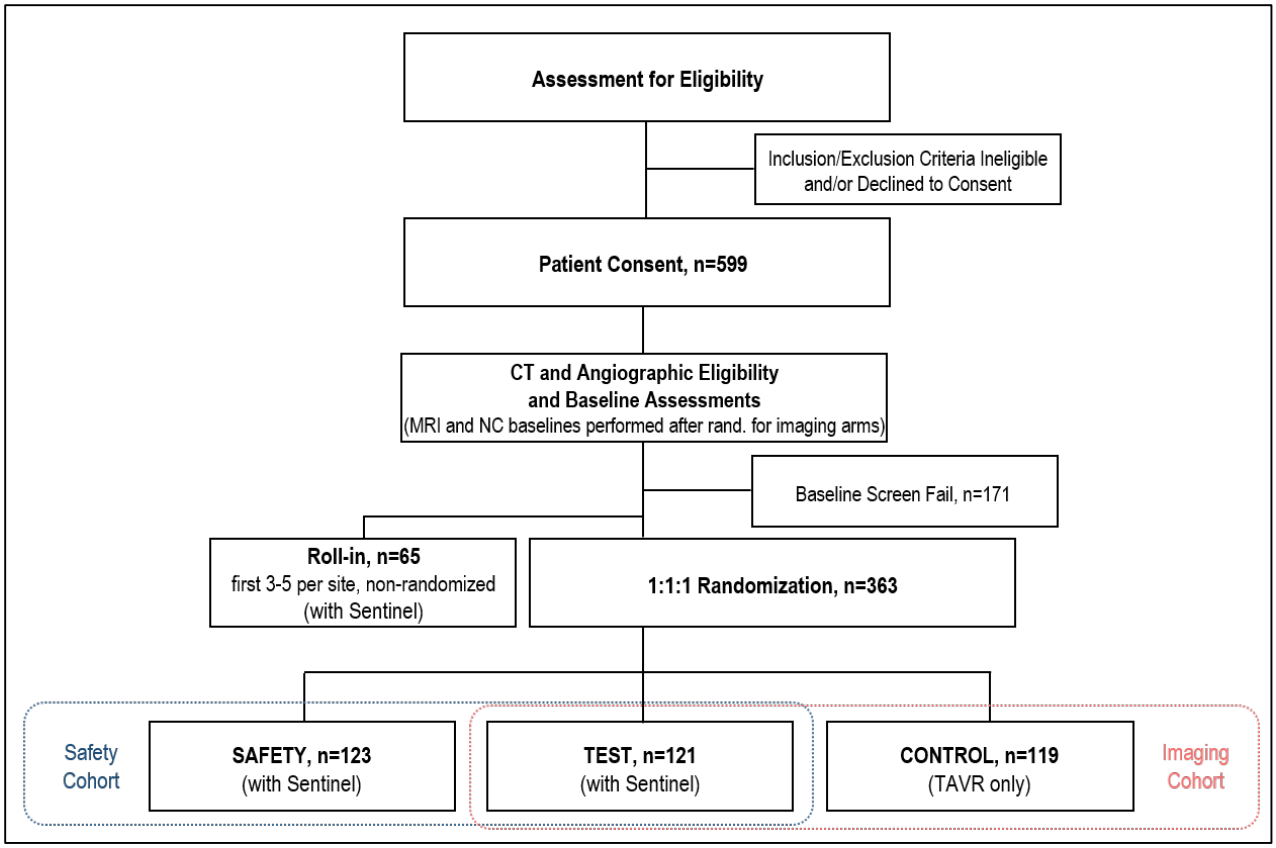


Figure 11: SENTINEL Enrollment Scheme

Prior to randomizing patients into one of the study arms, sites were allowed to treat up to five (5) Roll-In patients with the Sentinel System as part of their device training program. There were no significant differences with regards to patient safety between Roll-In and Test patients; however, procedure time was slightly longer in the Roll-In group due to training. Results for Roll-In patients can be found in **Appendix D**.

6.6.2. Study Specific Evaluations

Patients in the Imaging Cohort (Test and Control Arms) underwent standardized 3 Tesla MRI scanning of the brain in a serial fashion at baseline, 2-7 and 30 days post procedure. Site radiology units were trained and all scanners were certified by the independent academic MRI core laboratory. All scans were performed according to a strictly controlled qualification and validation algorithm

Histopathology and histomorphometry evaluations were performed by an independent pathology core laboratory on debris retrieved from Sentinel System filters from Test Arm patients only.

Imaging Cohort patients were administered a neurocognitive test battery by site examiners trained and qualified by the independent neurocognition core laboratory at baseline, 2-7, 30 and 90 days post procedure. The battery was designed to evaluate the following domains: Attention, Executive Function, Processing Speed, Working Memory, Verbal Memory, Visual Memory, Mental Status, and Depression. A z-score for each domain was calculated based on the normative means and standard deviations for each neurocognitive test. These norms were stratified by age at time of visit.

Imaging Cohort patients were administered the 12-Item Short Form Health Survey (SF-12) to assess Quality of Life.

All patients underwent neurological testing by a site neurologist or certified examiner. Both the Modified Rankin Scale (mRS) and the National Institute of Health Stroke Scale (NIHSS) were utilized.

6.6.3. Analyses

The primary safety analysis was based on the ITT population derived from the combination of the Safety and Test Arms (Safety Cohort). The primary safety endpoint included imputation for missing clinical outcomes data using the Markov Chain Monte Carlo (MCMC) algorithm offered an alternative model-based solution where missing values were treated as unknown parameters. The imputation model included the following parameters based on an analysis of the blinded, aggregate SENTINEL data:

- (b)(4)

A tipping point analysis was also performed in order to determine how many additional patients would be needed for the MACCE rate to exceed the performance goal.

The primary superiority efficacy endpoint analysis, set as a combination of statistical superiority and observational clinical treatment effect based on previous observations from first-in-man studies. Data imputation was based on the MCMC algorithm specifying missing at random (MAR). An imputation using the MCMC algorithm offered an alternative model-based solution where missing values were treated as unknown parameters. The imputation model included the following parameters identified to correlate with lesion volume based on aggregate, blinded analysis of data:

- (b)(4)

To further assess potential effects of missing data, a sensitivity analysis was performed where missing data was imputed using the highest and lowest volumes observed in the 2-7 Day DW-MRI scans. This analysis evaluated the best and worst case scenarios for missing data:

Best case: Test Arm subjects with missing data had their 2-7 Day total new lesion volume imputed with the lowest value observed among all randomized imaging subjects with data available. Control Arm subjects with missing data had their 2-7 Day total new lesion volume imputed with the highest value observed among all randomized imaging subjects with data available.

Worst case: Test Arm subjects with missing data had their 2-7 Day total new lesion volume imputed with the highest value observed among all randomized imaging subjects with data available. Control Arm subjects with missing data had their 2-7 Day total new lesion volume imputed with the lowest value observed among all randomized imaging subjects with data available.

6.6.4. Safety and Blinding

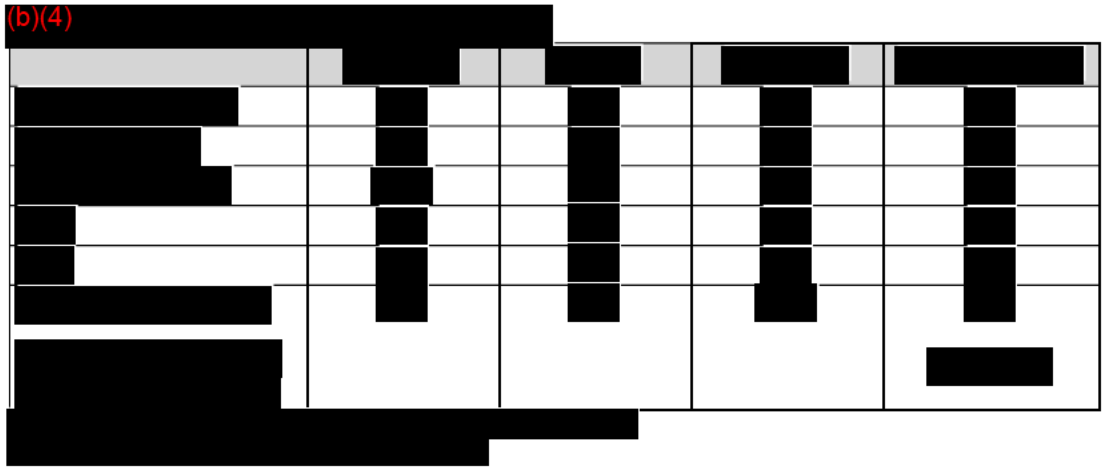
An independent Clinical Events Committee (CEC) was used to adjudicate pre-specified clinical events, and a Data Safety Monitoring Board (DSMB) was used for safety surveillance as well as an independent Medical Monitor. Patients, all core laboratories, and the CEC were blinded to study arm assignment. Additional study oversight information is provided in **Appendix E**.

6.7. Patient Withdrawal, Exit, and Loss to Follow-Up

Patients were exited from the study upon completing the final protocol required 90-day follow-up visit. In some cases, patients prematurely exited or withdrew from the study for, including but not limited to, the following reasons:

- Not eligible for treatment (including patients who may have signed Informed Consent and been randomized).
- Patient death.
- Voluntary withdrawal – the patient voluntarily chose not to participate further in the study.
- Lost to follow-up (LTFU) – the patient was more than 14 days late to a study visit and three documented attempts to contact the patient were unsuccessful. A patient who missed a study visit but attended a subsequent visit was no longer considered lost to follow-up. A missed visit was considered a protocol deviation and the deviation was documented and reported.
- Physician decision – In the physician's opinion, it was not in the best interest of the patient to continue study participation.
- Patient was determined to be ineligible during the procedure per the angiographic inclusion criteria or experienced a clinical event that put the patient at risk.

The tables below summarize patients who exited the study at 30 days (primary safety endpoint) and at 90 days (study completion). Note: Some subjects received a 30-day follow-up visit prior to study exit and are reflected in the overall safety follow-up rates.



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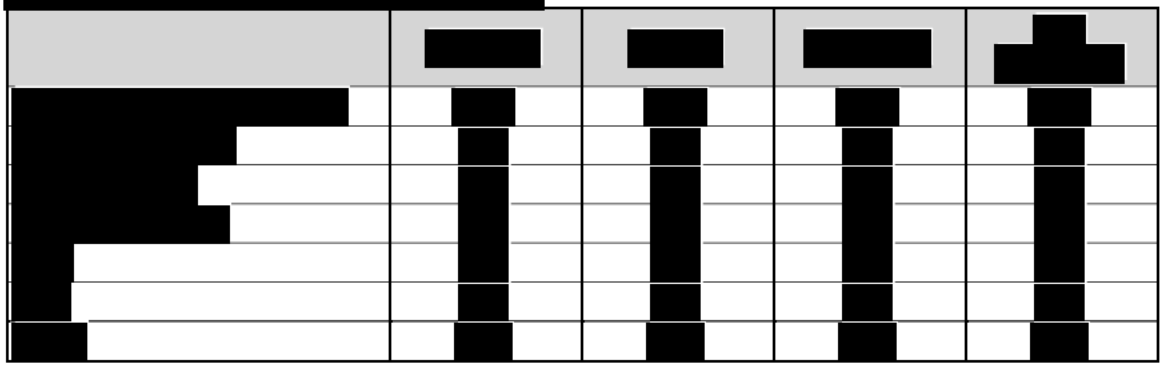


6.8. Study Analysis Populations

Statistical analyses were conducted on the following study populations as appropriate:

6.8.1. Intent to Treat with Imputation (ITT with Imputation)

Primary Safety and Efficacy Endpoints

Patients enrolled and randomized to a treatment arm, with imputation for patients that had missing data for clinical and/or MRI follow-up assessments. Patients were analyzed based on assigned treatment rather than treatment received.

6.8.2. Intent to Treat (ITT)

All Safety and Efficacy Endpoints

Patients enrolled and randomized to a treatment arm; including all available follow-up data regardless of completion within protocol defined follow-up windows. Efficacy and neurocognitive analyses required paired baseline and follow-up assessment data. Patients were analyzed based on assigned treatment rather than treatment received.

6.8.3. As Treated

All Safety Endpoints

Patients placed into an analysis population based on the treatment received, regardless of treatment assigned, e.g. a patient randomized to the treatment arm, but who did not receive the Sentinel System, was analyzed as a control patient in the "As Treated" analysis. This analysis population was used only for safety analyses.

6.8.4. Per Protocol

All Efficacy Endpoints

Patients in whom the investigational study procedure was attempted, as prescribed by their treatment arm, *and* whose follow-up assessments were in the pre-specified windows.

- MRI: Baseline (within 14 days prior to TAVR); 2-7 days; 30 day (+/-7 days)
- Neurocognitive Test Battery: Baseline (within 14 days prior to TAVR); 30 day (23-45 days); 90 day (+/- 10 days)

Per protocol (PP) analyses required paired baseline and follow-up assessment data.

Patient flows for all analysis populations are illustrated in **Figure 12, Figure 13,** and **Figure 14** below.

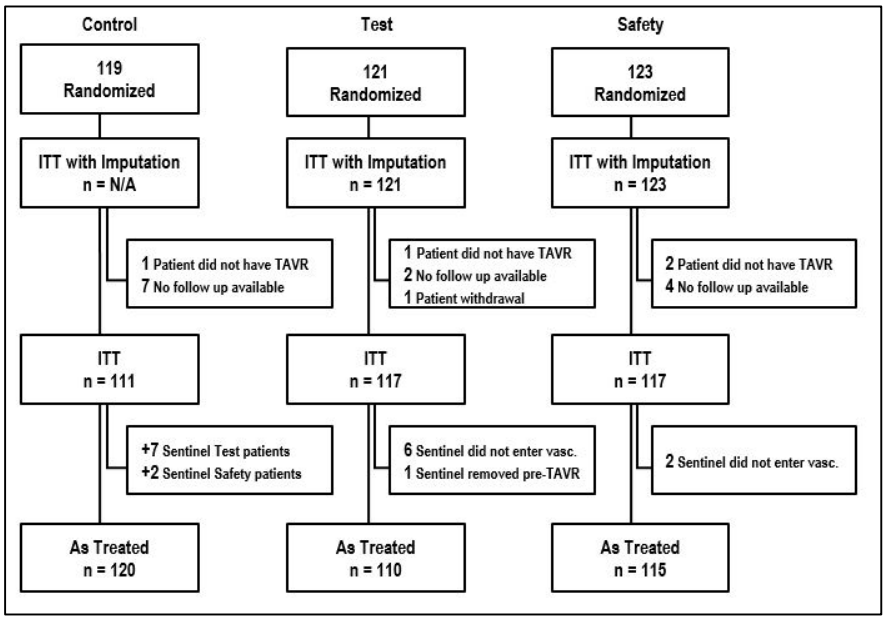


Figure 12: Study Flow for Safety Analyses

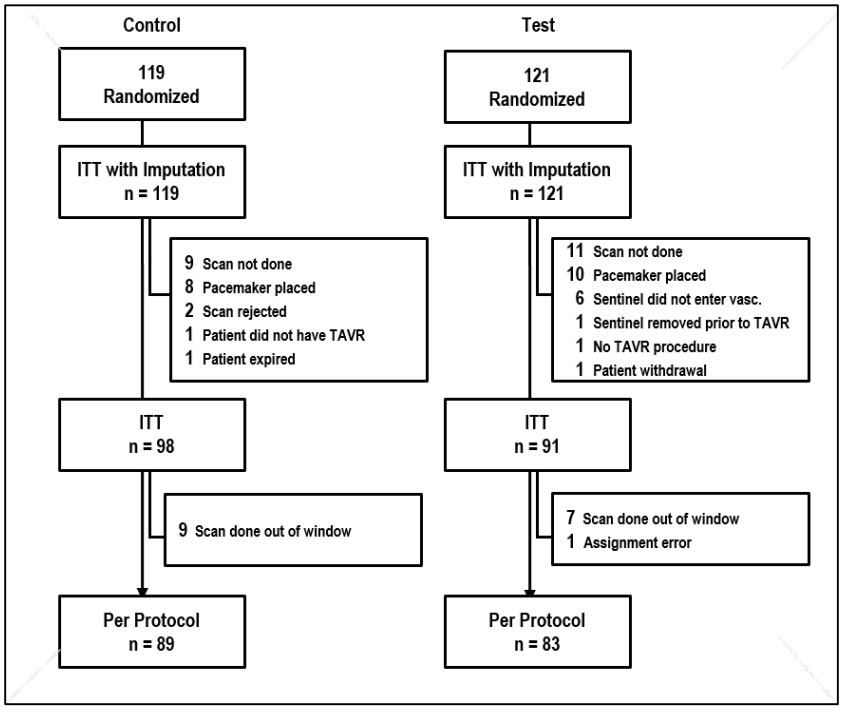


Figure 13: Study Flow for Efficacy Analyses

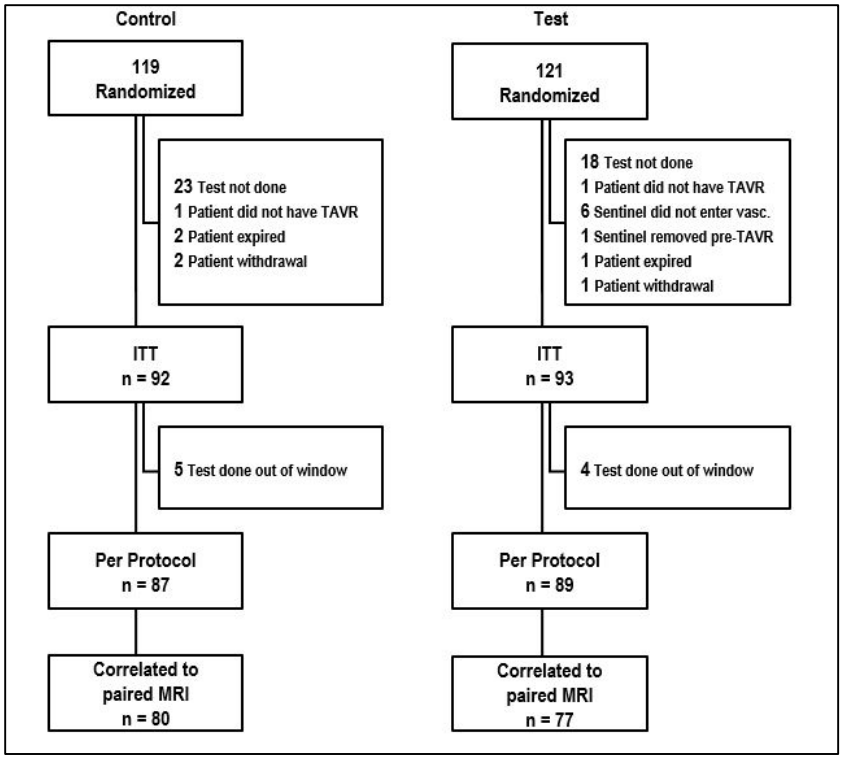


Figure 14: Study Flow for Neurocognitive Analyses

7. SENTINEL Study Results

The data presented below are based on the ITT population unless otherwise stated. Imputation was only pre-specified for primary safety and efficacy analyses per the SENTINEL protocol and statistical analysis plan, but may be provided in other analyses for informational purposes.

For safety, the ITT population consisted of all patients with clinical follow-up, for efficacy the ITT population consisted of all patients with baseline and all available matched follow-up MR imaging.

Poolability information is provided in **Appendix L**.

7.1. Demographics

Overall, baseline characteristics of the study arms were balanced (**Table 6**) though statistically significant differences between arms were observed in relation to diastolic blood pressure, STS score, and stroke severity. A second table comparing baseline characteristics of patients that received MRI follow-up relative to those that missed the MRI assessment is provided in **Table 7** where only BMI and valve criteria was found to be statistically different. Expanded demographics tables with descriptive statistics are available in **Appendix H**.

Table 6: Abbreviated Baseline Demographics and Medical History

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Demographics					
Age (years)	81.5 ± 8.98	82.0 ± 7.95	83.4 ± 7.90	82.3 ± 8.31	0.18
Male	44.7%	47.9%	51.3%	47.9%	0.61
Physical Exam					
BMI (kg/m²)	27.2 ± 5.76	28.8 ± 7.48	27.4 ± 5.25	27.8 ± 6.26	0.34
Systolic Blood Pressure (mmHg)	140.5 ± 19.82	137.3 ± 21.89	135.1 ± 19.56	137.7 ± 20.52	0.12
Diastolic Blood Pressure (mmHg)	70.4 ± 12.66	68.3 ± 12.86	66.3 ± 12.08	68.3 ± 12.61	0.04
STS Predicted Risk of Mortality Score (PROM)	6.2 ± 3.17	6.4 ± 3.28	7.5 ± 4.66	6.7 ± 3.79	0.01
STS PROM Score (Categorized)					
<4	18.0%	13.2%	10.1%	13.8%	0.19
4-7	54.1%	56.2%	53.8%	54.7%	
8-15	25.4%	28.9%	28.6%	27.6%	
>15	2.5%	1.7%	7.6%	3.9%	
Medical History					
History of Atrial Fibrillation	30.1%	34.7%	30.3%	31.7%	0.69
History of Peripheral Vascular Disease	16.3%	14.0%	15.1%	15.2%	0.90
History of Coronary Artery Disease	53.7%	50.4%	55.5%	53.2%	0.73
Diabetes Type II	26.8%	38.8%	37.8%	34.4%	0.09
History of Stroke					
Previous Transient Ischemic Attack (TIA)	8.1%	7.4%	6.7%	7.4%	0.97
Previous Stroke with Permanent Deficit[2]	8.1%	4.1%	5.0%	5.8%	0.44

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Stroke Severity					
Major	3.3%	4.1%	0.8%	2.8%	0.04
Minor	4.9%	0%	4.2%	3.0%	
Valve Criteria					
Aortic valve area index (cm^2/m^2)	0.4 ± 0.09	0.4 ± 0.10	0.4 ± 0.10	0.4 ± 0.10	0.41
Mean aortic valve gradient (mmHg)	41.8 ± 14.65	44.2 ± 14.81	40.9 ± 13.56	42.3 ± 14.38	0.18
Baseline Neurological Status					
mRS Score	1.0 ± 1.27	0.8 ± 1.13	1.0 ± 1.11	0.9 ± 1.17	0.53
T2/FLAIR MRI Lesion Volume (mm^3)	N/A	7377.5	7916.7	7847.9	0.43
NYHA					
I	3.3%	3.4%	3.4%	3.4%	0.97
II	15.0%	11.8%	13.8%	13.5%	
III	56.7%	58.8%	53.4%	56.3%	
IV	25.0%	26.1%	29.3%	26.8%	

Note: Continuous data presented as Mean ± SD. Categorical data presented using %.
[1] 1 p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.
[2] Defined as neurological deficit lasting more than 24 hours confirmed by imaging.

Table 7: Abbreviated Baseline Demographics & Medical History, Observed vs Missing MRI

	Observed MRI (N=189)	Missing MRI (N=51)	Total (N=240)	p-value[1]
Demographics				
Age (years)	82.9 ± 7.62	82.0 ± 9.05	82.7 ± 7.94	0.46
Male (%)	47.6%	56.9%	49.6%	0.27
Physical Exam				
BMI (kg/m^2)	27.6 ± 5.57	29.8 ± 9.00	28.1 ± 6.49	0.03
Systolic Blood Pressure (mmHg)	137.2 ± 20.29	132.5 ± 22.19	136.2 ± 20.75	0.15
Diastolic Blood Pressure (mmHg)	67.6 ± 12.64	66.3 ± 12.00	67.3 ± 12.49	0.50
STS PROM Score	6.8 ± 3.94	7.4 ± 4.46	6.9 ± 4.06	0.39
STS PROM Score (Categorized)				
<4	12.2%	9.8%	11.7%	0.55
4-7	56.1%	51.0%	55.0%	
8-15	28.0%	31.4%	28.8%	
>15	3.7%	7.8%	4.6%	
Medical History				
History of Atrial Fibrillation	33.3%	29.4%	32.5%	0.74
History of Peripheral Vascular Disease	14.8%	13.7%	14.6%	1.00
History of Coronary Artery Disease	53.4%	51.0%	52.9%	0.76
Diabetes Type II	37.6%	41.2%	38.3%	0.63
History of Stroke				
Previous Transient Ischemic Attack (TIA)	7.4%	5.9%	7.1%	1.00
Previous Stroke with Permanent Deficit[2]	3.2%	9.8%	4.6%	0.06
Stroke Severity				
Major	2.1%	3.9%	2.5%	0.06
Minor	1.1%	5.9%	2.1%	
Valve Criteria				
Aortic valve area index (cm^2/m^2)	0.4 ± 0.10	0.4 ± 0.08	0.4 ± 0.10	0.02

	Observed MRI (N=189)	Missing MRI (N=51)	Total (N=240)	p-value[1]
Mean aortic valve gradient (mmHg)	41.0 ± 13.81	48.2 ± 14.62	42.5 ± 14.26	0.001
Baseline Neurological Status				
mRS Score	0.9 ± 1.05	1.1 ± 1.35	0.9 ± 1.12	0.21
NYHA				
I	2.7%	5.9%	3.4%	0.28
II	13.6%	9.8%	12.8%	
III	58.2%	49.0%	56.2%	
IV	25.5%	35.3%	27.7%	

Note: Continuous data presented as Mean ± SD. Categorical data presented using %.
[1] 1 p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.
[2] Defined as neurological deficit lasting more than 24 hours confirmed by imaging.

7.2. Procedural Characteristics

Procedural characteristics were similar across all study arms for the ITT population with TAVR procedure time (p = 0.01) and flouro time (p = 0.05) being lower in the Control Arm, as would be expected (Table 8 and Table 9). When comparing in-window and out-of-window patients within the ITT analysis population, a greater than anticipated number of patients were unable to complete the follow-up MRI assessment due to implantation of a permanent pacemaker (PPM) during or after the index procedure. A PPM is contraindicated for 3 Tesla magnet MRI, and thus these patients could not receive the 2-7 day MRI follow-up exam. Expanded Procedural Characteristics tables are available in Appendix I.

Table 8: Abbreviated Procedural Characteristics

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Sentinel Device Placement					
Radial	95.0%	91.2%	N/A	93.2%	0.49
Brachial	4.2%	7.0%	N/A	5.6%	
Other	0.8%	1.8%	N/A	1.3%	
TAVR Fluoro Time (min)	18.0 ± 10.78	20.9 ± 13.01)	16.7 ± 11.50	18.6 ± 11.91	0.05
TAVR Device					
Medtronic CoreValve	3.3%	2.5%	5.9%	3.9%	0.72
Medtronic CoreValve Evolut R	29.8%	24.2%	23.7%	25.9%	
Edwards SAPIEN XT	19.0%	17.5%	16.9%	17.8%	
Edwards SAPIEN 3	47.9%	55.8%	53.4%	52.4%	
Procedural Outcomes					
Total TAVR Procedure Time (min)	81.7 ± 36.59	93.2 ± 51.53	74.2 ± 40.98	83.3 ± 44.12	0.01
PPM implanted (≤7 days)	20.3%	15.7%	12.6%	16.9%	0.28
New onset of Atrial Fibrillation	3.3%	4.1%	7.6%	4.9%	0.29

[1] 1 p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test. Where applicable, mean ± SD information is provided.

Table 9: Procedural Characteristics, Observed MRI vs Missing

	Observed MRI (N=189)	Missing (N=51)	Total (N=240)	p-value[1]
Sentinel Device Placement				
Radial	92.2%	87.5%	91.2%	0.05
Brachial	7.8%	4.2%	7.0%	
Other	0%	8.3%	1.8%	
TAVR Fluoro Time (min)	18.3 ± 12.47	21.4 ± 12.36	18.9 ± 12.47	0.20

	Observed MRI (N=189)	Missing (N=51)	Total (N=240)	p-value[1]
TAVR Device				
Medtronic CoreValve	3.7%	6.1%	4.2%	0.28
Medtronic CoreValve Evolut R	23.8%	24.5%	23.9%	
Edwards SAPIEN XT	15.3%	24.5%	17.2%	
Edwards SAPIEN 3	57.1%	44.9%	54.6%	
Procedural Outcomes				
Total TAVR Procedure Time (min)	81.3 ± 44.62	94.6 ± 56.77	84.0 ± 47.58	0.10
PPM implanted (≤7 days)	6.3%	43.1%	14.2%	<.0001
New onset of Atrial Fibrillation	5.8%	5.9%	5.8%	1.00

[1] 1 p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test. Where applicable, mean ± SD information is provided.

7.3. Safety Outcomes

7.3.1. Summary

- The primary safety endpoint of the rate of MACCE at 30-days was met (7.4%) and was significant (p <.0001, 95% CI 10.7%-11.1%) when compared to the non-inferiority performance goal of 18.3%, this finding was true in all populations analyzed.
- The in-hospital MACCE rate for Sentinel was numerically lower than the Control.
- The 30-day MACCE rate for Sentinel was numerically lower than the Control.
- The 30-day stroke rate was 5.6% with Sentinel compared to 9.1% in the Control, all strokes occurred within the first 7 days and rates did not change out to 90 days
- No major vascular events at the Sentinel access site were observed during the procedure and the rate at 30 days was 0.4%.

7.3.2. Primary Safety Endpoint (Non-Inferiority Hypothesis)

The primary safety endpoint for the study evaluated the rate of adjudicated MACCE [All Death, All Stroke, and Acute Kidney Injury (Class 3)] within 30 days compared to a historical performance goal.

The primary safety endpoint was met across all analysis populations, see **Table 10**. The MACCE rate was 7.4% for the imputed ITT population, 7.3% in the ITT population, and 7.6% in the As Treated population, with a p-value of p < .0001 (95% CI 10.7%-11.1%) in all populations when compared to the non-inferiority performance goal of 18.3%. Given that the upper bound of the exact one-sided 95% confidence interval for the primary endpoint event rate is less than the pre-specified threshold of 18.3%, the null hypothesis was rejected in favor of the alternative, therefore meeting the study's primary safety endpoint.

Table 10: 30-Day MACCE Rate (Primary Safety Endpoint)

	Safety Cohort (Safety + Test)				
Population	**Total Events**	**Patients w/Event(s) n/N, (%)**	**Performance Goal**	**Upper 95% Confidence Interval[1]**	**p-value[1]**
ITT, with imputation	N/A[2]	18/244 (7.4%)	18.3%	10.7%	<.0001
ITT	17	17/234 (7.3%)	18.3%	10.7%	<.0001
As Treated	17	17/225 (7.6%)	18.3%	11.1%	<.0001

[1]Upper confidence interval and p-value based on exact one-sided test for alternative hypothesis: rate <PG with 0.05 alpha level
[2]Binary outcome based on imputation analysis, number of events does not apply

A sensitivity/tipping point analysis using the ITT population was performed to determine how many additional patients would have been needed for the MACCE rate to exceed 18.3%. All possible scenarios were analyzed as if each of the 10 patients missing the MACCE endpoint would have experienced an event. This analysis reveals that greater than 10 additional MACCE events would have been necessary for the study to have failed to meet the 18.3% performance goal, confirming the positive outcome of the study's primary safety endpoint (Table 11).

Table 11: Primary Safety Endpoint Sensitivity/Tipping Point

Scenario	**Patients w/Event(s) n/N, (%)**	**Performance Goal (%)**	**Upper 95% Confidence Interval[1]**	**p-value[1]**
1 additional MACCE	18/244 (7.4%)	18.3	10.7%	<.0001
2 additional MACCE	19/244 (7.8%)	18.3	11.2%	<.0001
3 additional MACCE	20/244 (8.2%)	18.3	11.7%	<.0001
4 additional MACCE	21/244 (8.6%)	18.3	12.2%	<.0001
5 additional MACCE	22/244 (9.0%)	18.3	12.6%	<.0001
6 additional MACCE	23/244 (9.4%)	18.3	13.1%	<.0001
7 additional MACCE	24/244 (9.8%)	18.3	13.6%	0.0002
8 additional MACCE	25/244 (10.2%)	18.3	14.0%	0.0004
9 additional MACCE	26/244 (10.7%)	18.3	14.5%	0.0007
10 additional MACCE	27/244 (11.1%)	18.3	14.9%	0.001

[1]Upper confidence interval and p-value based on exact one-sided test for alternative hypothesis: rate < PG with 0.05 alpha level

7.3.3. Secondary Endpoints

There are four non-hierarchical secondary safety analyses that were performed for labeling purposes using descriptive statistics. Each endpoint was evaluated using the ITT and As Treated populations.

The secondary safety endpoints support the primary safety endpoint result by demonstrating numerically lower MACCE rates in the Safety Cohort when compared to the study's Control Arm, which served as a contemporary control for the study. Additional secondary endpoint analysis may be found in Appendix J.

7.3.3.1. Incidence of in-hospital MACCE

Safety Cohort compared to Control Arm procedure through discharge

The ITT In-hospital MACCE rate was numerically lower (32% relative reduction) between the Safety Cohort [5.7% (14/244)] and Control Arm [8.4% (10/119)]; a statistical difference was not observed (p = 0.37). Specifically, there was a 42% reduction in stroke between the Safety Cohort (4.9%) and the Control Arm (8.4%) though it was not statistically significant (p = 0.24) (Table 12).

Table 12: In-Hospital MACCE Rate

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients) [exact 95% CI]	Control Arm % patients with event (n patients with event/N patients) [exact 95% CI]	p-value[1]
ITT			
Any MACCE	5.7% (14/244) [3.2%, 9.4%]	8.4% (10/119) [4.1%, 14.9%]	0.37
Death (all)	0.4% (1/244) [0.0%, 2.3%]	0.8% (1/119) [0.0%, 4.6%]	0.55
Stroke (all)	4.9% (12/244) [2.6%, 8.4%]	8.4% (10/119) [4.1%, 14.9%]	0.24
Disabling Stroke	0.8% (2/244) [0.1%, 2.9%]	0.8% (1/119) [0.0%, 4.6%]	1.00
Non-disabling Stroke	4.1% (10/244) [2.0%, 7.4%]	7.6% (9/119) [3.5%, 13.9%]	0.21
AKI (Class 3)	0.4% (1/244) [0.0%, 2.3%]	0% [0.0%, 3.1%]	1.00
As Treated			
Any MACCE	6.1% (14/231) [3.4%, 10.0%]	7.8% (10/128) [3.8%, 13.9%]	0.52
Death (all)	0.4% (1/231) [0.0%, 2.4%]	0.8% (1/128) [0.0%, 4.3%]	1.00
Stroke (all)	5.2% (12/231) [2.7%, 8.9%]	7.8% (10/128) [3.8%, 13.9%]	0.36
Disabling Stroke	0.9% (2/231) [0.1%, 3.1%]	0.8% (1/128) [0.0%, 4.3%]	1.00
Non-disabling Stroke	4.3% (10/231) [2.1%, 7.8%]	7.0% (9/128) [3.3%, 12.9%]	0.33
AKI (Class 3)	0.4% (1/231) [0.0%, 2.4%]	0% [0.0%, 2.8%]	1.00

[1]p-value based on two-sided Fisher's exact test for Safety Cohort compared to the Control Arm.

7.3.3.2. 30-Day MACCE Rates, All Arms

Safety Cohort compared to Control Arm at 30 days post procedure.

The ITT 30-Day MACCE [7.3% (17/234)] and stroke rates [5.6% (13/231)] in the Safety Cohort were numerically lower than the Control Arm, [9.9% (11/111) and 9.1% (10/110) respectively]. A statistical difference was not achieved, but the observed rates represent a 26% reduction in MACCE and 38% reduction in stroke (Table 13).

Table 13: 30-Day MACCE and Component Rates, Safety Cohort and Control Arm

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients) [exact 95% CI]	Control % patients with event (n patients with event/N patients) [exact 95% CI]	P-value[1]
ITT			
Any MACCE	7.3% (17/234) [4.3%,11.4%]	9.9% (11/111) [5.1%,17.0%]	0.41
Death	1.3% (3/234) [0.3%,3.7%]	1.8% (2/111) [0.2%,6.4%]	0.66
Stroke	5.6% (13/231) [3.0%,9.4%]	9.1% (10/110) [4.4%,16.1%]	0.25
Disabling	0.9% (2/231) [0.1%,3.1%]	0.9% (1/109) [0.0%,5.0%]	1.0000
Non-disabling	4.8% (11/231) [2.4%,8.4%]	8.2% (9/110) [3.8%,15.0%]	0.22
AKI (Class 3)	0.4% (1/231) [0.0%,2.4%]	0% [0.0%,3.3%]	1.00
As Treated			
Any MACCE	7.6% (17/225) [4.5%,11.8%]	9.2% (11/120) [4.7%,15.8%]	0.68
Death	1.3% (3/225) [0.3%,3.8%]	1.7% (2/120) [0.2%,5.9%]	1.00
Stroke	5.9% (13/222) [3.2%,9.8%]	8.4% (10/119) [4.1%,14.9%]	0.37
Disabling	0.9% (2/222) [0.1%,3.2%]	0.8% (1/118) [0.0%,4.6%]	1.00
Non-disabling	5.0% (11/222) [2.5%,8.7%]	7.6% (9/119) [3.5%,13.9%]	0.34
AKI (Class 3)	0.5% (1/222) [0.0%,2.5%]	0% [0.0%,3.1%]	1.00

[1]P-Value based on two-sided Fisher's exact test for Test compared to Control.

Test Arm compared to Control Arm at 30 days post procedure.

Similar to the In-hospital MACCE results, in the Test Arm ITT 30-Day MACCE [6.0% (7/117)] and stroke rates [4.3% (5/116)] were numerically lower than the Control Arm, [9.9% (11/111) and 9.1% (10/110) respectively]. A statistical difference was not achieved, but the observed rates represent a 39% reduction in MACCE and 53% reduction in stroke (Table 14).

Table 14: 30-Day MACCE and Component Rates, Test and Control Arms

	Test Arm % patients with event (n patients with event/N patients) [exact 95% CI]	Control Arm % patients with event (n patients with event/N patients) [exact 95% CI]	p-value[1]
ITT			
Any MACCE	6.0% (7/117) [2.4%,11.9%]	9.9% (11/111) [5.1%,17.0%]	0.62
Death	0.9% (1/117) [0.0%,4.7%]	1.8% (2/111) [0.2%,6.4%]	1.00
Stroke (all)	4.3% (5/116) [1.4%,9.8%]	9.1% (10/110) [4.4%,16.1%]	0.41
Disabling Stroke	0% [0.0%,3.1%]	0.9% (1/109) [0.0%,5.0%]	0.25
Non-disabling Stroke	4.3% (5/116) [1.4%,9.8%]	8.2% (9/110) [3.8%,15.0%]	0.77
AKI (Class 3)	0.9% (1/116) [0.0%,4.7%]	0% [0.0%,3.3%]	1.00
As Treated			
Any MACCE	6.4% (7/110) [2.6%,12.7%]	9.9% (11/111) [5.1%,17.0%]	0.62
Death	0.9% (1/110) [0.0%,5.0%]	1.8% (2/111) [0.2%,6.4%]	1.00
Stroke (all)	4.6% (5/109) [1.5%,10.4%]	9.1% (10/110) [4.4%,16.1%]	0.57
Disabling Stroke	0% [0.0%,3.3%]	0.9% (1/109) [0.0%,5.0%]	0.4979
Non-disabling Stroke	4.6% (5/109) [1.5%,10.4%]	8.2% (9/110) [3.8%,15.0%]	1.0000
AKI (Class 3)	0.9% (1/109) [0.0%,5.0%]	0% [0.0%,3.3%]	0.4910

[1]P-Value based on two-sided Fisher's exact test for Test compared to Control.

7.3.3.3. Incidence of major vascular complications

Sentinel related major vascular complications within 30 days post procedure.

Major vascular complications were defined as any thoracic aortic dissection; access site or access-related vascular injury (dissection, stenosis, perforation, etc.) leading to either death, need for significant blood transfusion, unplanned interventions, or irreversible end organ damage; distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.

Incidence of adjudicated major vascular events were low in all analysis populations during the index procedure with no radial or brachial (Sentinel access) events during the procedure, and only one brachial (Sentinel access) event (0.4%) within 30 days of the index procedure, see Table 15.

Table 15: Incidence of Sentinel Related Major Vascular Complications

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients per arm)
ITT	
During the index procedure	0% (0/244)
Sentinel Access, Radial	0% (0/244)
Sentinel Access, Brachial	0% (0/244)
Within 30 days of the index procedure	0.4% (1/244)[1]
Sentinel Access, Radial	0% (0/244)
Sentinel Access, Brachial	0.4% (1/244)[1]
As Treated	
During the index procedure	0% (0/231)
Sentinel Access, Radial	0% (0/231)
Sentinel Access, Brachial	0% (0/231)
Within 30 days of the index procedure	0.4% (1/231)[1]
Sentinel Access, Radial	0% (0/231)
Sentinel Access, Brachial	0.4% (1/231)[1]

[1] Pseudoaneurysm, treated with thrombin injection

7.3.3.4. Incidence of Serious Adverse Events

Safety Cohort compared to Control Arm within 30 days post procedure.

There were no unanticipated adverse device effects (UADE) in the study. Site reported serious adverse events in the ITT population were similar between the two groups, and did not exceed serious adverse event (SAE) rates reported from contemporary TAVR studies[24], with 42.6% (104/244) being reported for the Safety Cohort and 42.9% (51/119) for the Control Arm (Table 16). Additional serious adverse event information may be found in Appendix K.

Table 16: Incidence of Serious Adverse Events within 30 Days

	Safety Cohort (Safety + Test) n=244			Control Arm n=119		
	Total Events	Patients w/Event(s) % (n/N)	95% CI	Total Events	Patients w/Event(s) % (n/N)	95% CI
ITT	170	42.6% (104/244)	(36.3%, 49.1%)	89	42.9% (51/119)	(33.8%, 52.3%)
As Treated	162	42.9% (99/231)	(36.4%, 49.5%)	97	43.8% (56/128)	(35.0%, 52.8%)

[24] SAPIEN® THV – High Risk Surgical Cohort Briefing Document

Of the 11 SAEs reported by sites to be potentially related to the Sentinel System, only 1 was adjudicated by the CEC as possibly related, reference Table 17.

Table 17: Incidence of Site-Reported Potentially Sentinel Related Serious Adverse Events

Site-Reported SAE	CEC Adjudicated as Possible Relation to Sentinel System?
Vascular Pseudoaneurysm (n=1)	Yes[1]
Conduction System Injury (n=4)	No
Neurological Event - Imaging Only (n=1)	No
Stroke/CVA (n=3)	No
Access Site Complication, Injury Including Infection, or Thrombus (n=1)	No
Ataxia Right Arm (n=1)	No
Total = 11	

[1] Pseudoaneurysm, treated with thrombin injection

7.4. Sentinel System Delivery

7.4.1. Summary

- Sentinel was successfully delivered and retrieved in 94.4% of procedures (Device Success).
- At least one filter was successfully deployed in 99% of cases (Procedural Success).
- No significant learning curve was observed.

7.4.2. Device Malfunction, Acute Delivery and Retrieval Success

Of the 231 patients in whom placement of a Sentinel System was attempted, 15 experienced a malfunction or failure of the Sentinel System. Of these, 13 were distal filter not deployed at the time of TAVR, 2 were difficulties advancing the guidewire, and only 1 failed to have a successful Sentinel System deployment of either filters.

Acute delivery and retrieval success was defined as deployment and retrieval of the proximal and distal filters in accessible anatomies. Accessible anatomies are those which are not excessively tortuous or calcified that would prevent cannulation of the device to its position. Procedural success was defined as deployment of at least one filter (with either the first or second device) during the TAVR procedure without any incidence of investigational device related MACCE.

Acute delivery and retrieval success was achieved in 94.4% (218/231) of patients treated with the Sentinel System and Procedural Success was achieved in 99.6% (230/231) of the treated patients.

Table 18: ITT Acute Delivery and Retrieval Success

	Safety Arm %, (n/N)	Test Arm %, (n/N)	Control Arm %, (n/N)	Total %, (n/N)	p-value[1]
Acute Delivery and Retrieval Success	96.6% (115/119)	92.0% (103/112)	N/A	94.4% (218/231)	0.16

[1]p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.

7.5. Histopathological Outcomes

7.5.1. Summary

- Embolic material was captured in 99% of patients.
- Acute thrombus was almost always associated with tissue and/or foreign material and constituted 98% of captured debris.
- Foreign material (catheter coating) was captured in 35% of patients.
- Large debris (≥ 0.5 mm) were captured in a high percentage of patients.

7.5.2. Histopathology

A total of 210 filters (105 proximal, 105 distal) were assessed for debris. Almost all study patients assessed (99%) were found to have tissue fragments in either the proximal or distal filter. Among all filters, acute thrombus with tissue and foreign material was the most commonly captured debris (98%) followed by arterial wall (96%), valve tissue or calcification (70%), foreign material (35%) and myocardium (17%) (**Figure 15**).

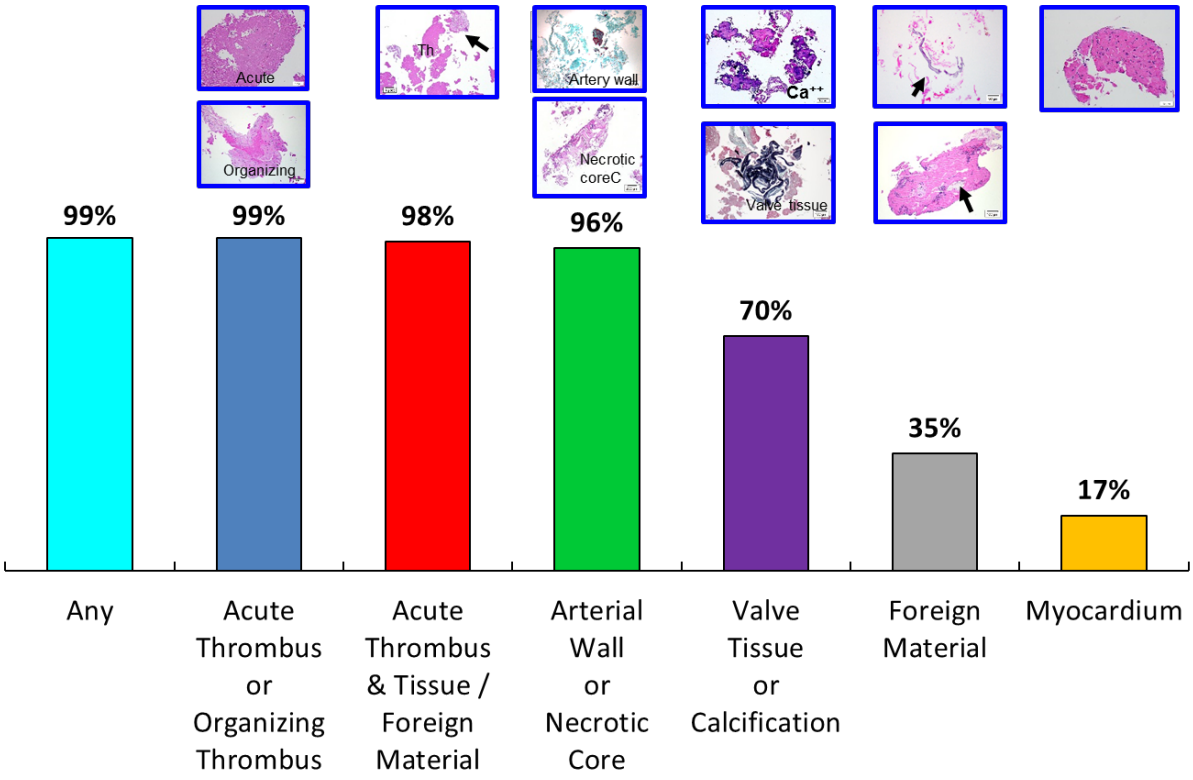


Figure 15: Rate of Debris Capture

The percentage of particles captured >0.15 mm in maximum diameter by patient is provided in **Figure 16** while the embolic material by particle size is provided in **Figure 17** (automated measuring system).

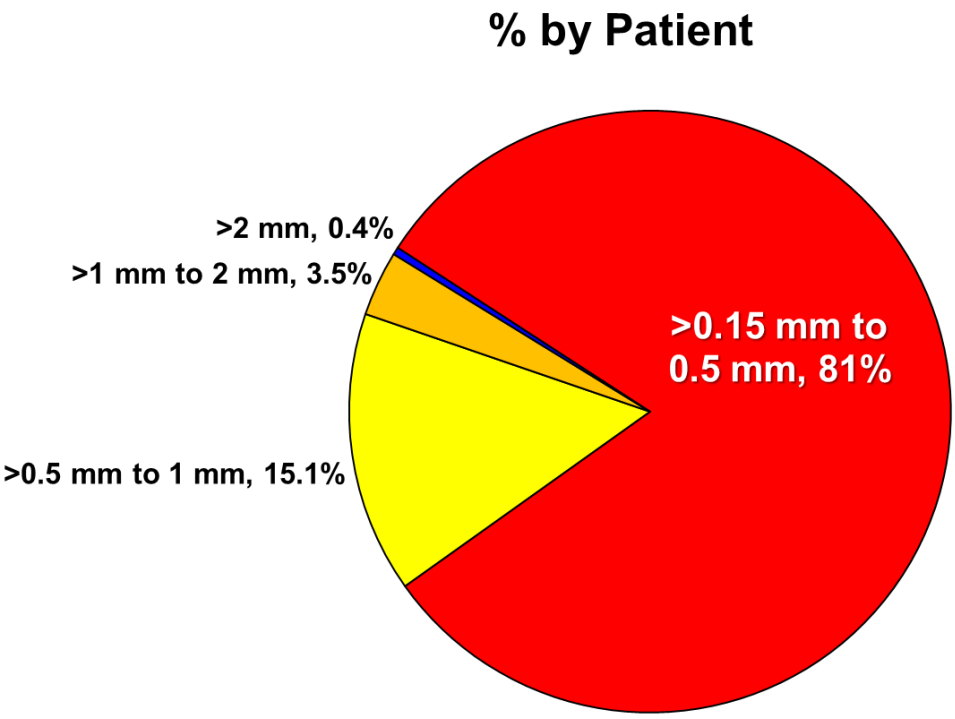


Figure 16: Percentage of Particles Captured by Patient

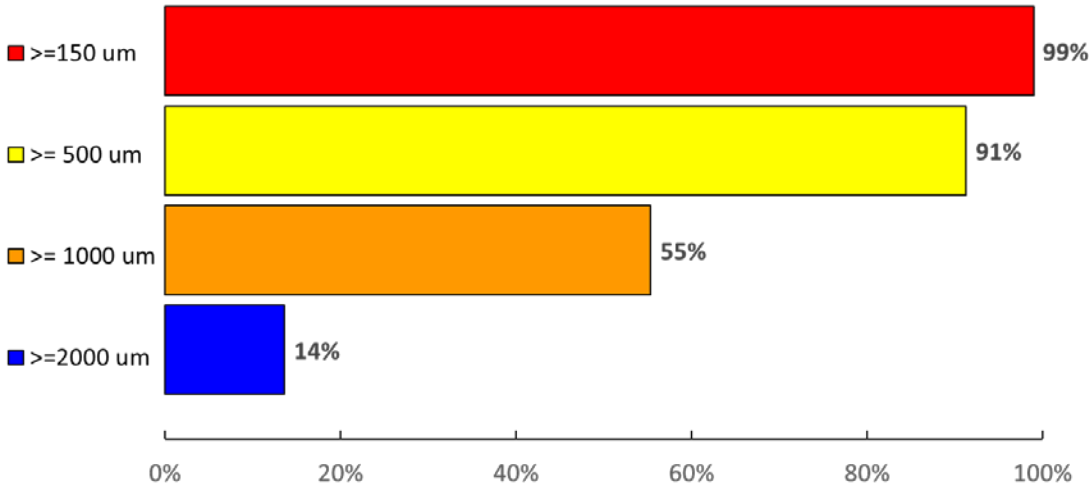


Figure 17: Percent of Patients with at Least One Particle of Given Size

7.6. Effectiveness Outcomes

7.6.1. Summary

- The primary endpoint of a statistically significant reduction in new lesion volume between the Test and Control Arms was not met (p = 0.24).
- A 42% reduction (confidence intervals overlap zero) in new lesion volume was observed
- (b)(4) [redacted]
- A post hoc multivariable analysis helped explain the nature and extent of variance observed in the study.

7.6.2. Primary Superiority Efficacy Endpoint

A reduction in new lesion volume in protected territories between the Test and Control Arms was observed but did not reach statistical significance, p = 0.24 (ITT with imputation). The results are similar across all populations, with a trend in favor of the test arm, but statistical significance was not reached in any population. However, it is important to note the p-value improves in relation to sample size as seen in the below in ascending order from Per protocol to ITT with imputation population. This finding in part led to the post hoc meta-analysis discussed in Section 7.6.5.1.

Table 19: New Lesion Volume in Protected Territories (Primary Efficacy Endpoint)

	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	Observed Treatment Difference (Test - Control)	Hodges-Lehmann Estimate of Location Shift (95% CI)	Bootstrapped Estimate of Treatment Difference (95% CI)	p-value[1]
ITT with Imputation, mm³	109.1 (36.9, 379.7), n=121 0 min, 5175.9 max	174 (39.6, 469.3), n=119 0 min, 24300 max	-64.9	-23.7 (-81.7, 13.2)	-65.9 (-118.7, 10.5)	0.24
ITT, mm³	102.8 (36.9, 423.2), n=91 0 min, 5175.9 max	178 (34.3, 482.5), n=98 0 min, 24300 max	-75.1	-21.1 (-94.9, 21.8)	-70.5 (-136.5, 16.8)	0.33
Per Protocol, mm³	118.7 (50.1, 435.1), n=83 0 min, 5175.9 max	181.9 (47.5, 482.5), n=89 0 min, 24300 max	-63.3	-13.2 (-85.7, 35.6)	-57.3 (-119.9, 40.9)	0.57

[1]Based on two-sided Wilcoxon test

7.6.3. Observational Success Criteria

The Observational Success Criteria was met with an observed new lesion volume reduction of 42% in the Treatment Arm as compared to the Control Arm in protected brain areas (compared to the pre-specified 30% performance goal), see Table 20.

Table 20: Reduction in New Lesion Volume (Protected Territories)

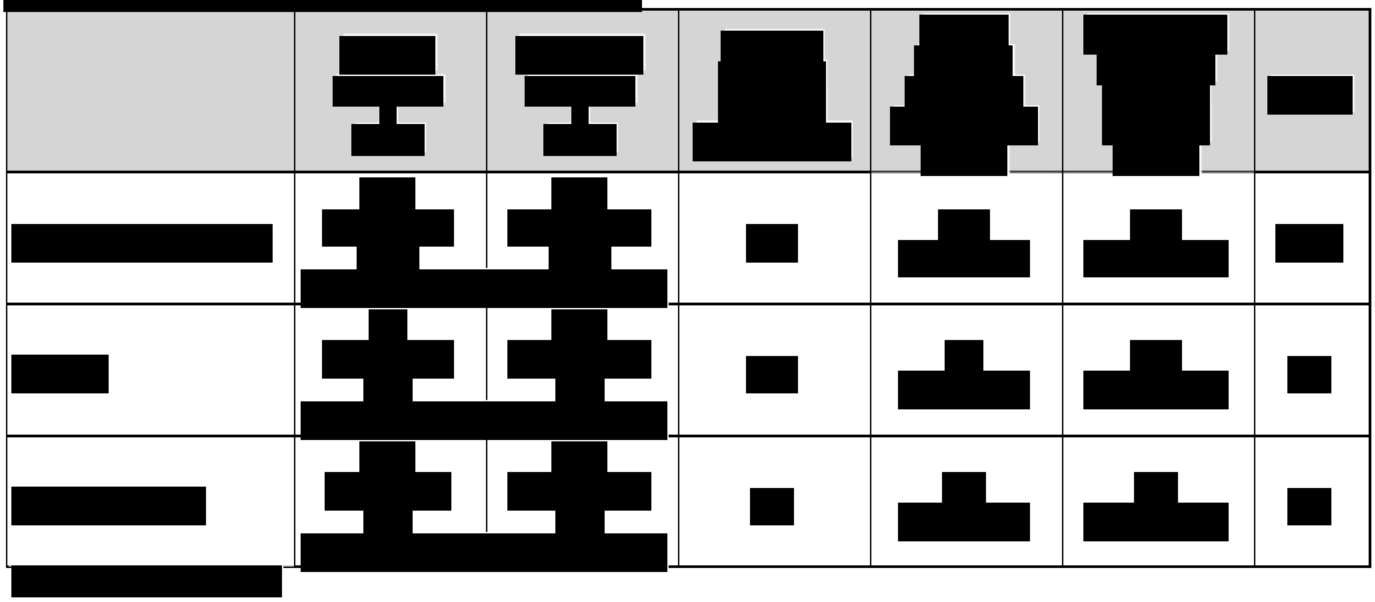
	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	Performance Goal	%, 95% CI[1]
ITT, mm³	102.8 (36.9, 423.2), n=91 0 min, 5175.9 max	178 (34.3, 482.5), n=98 0 min, 24300 max	30%	42.2 (-3.2, 67.6)
Per Protocol, mm³	118.7 (50.1, 435.1), n=83 0 min, 5175.9 max	181.9 (47.5, 482.5), n=89 0 min, 24300 max	30%	34.8 (-8.1, 60.6)

[1]Calculated using the Price, et al. method

7.6.4. Additional DW-MRI Analysis (2-7 Days)

Secondary DW-MRI analysis related to new lesion volume in all territories is provided below. In addition, data on new lesion number in both protected and all territories is also provided. None of the results were found to be statistically significant. Information on all secondary MRI endpoints is provided in **Appendix F** with supplemental MRI information provided in **Appendix M**.

(b)(4)



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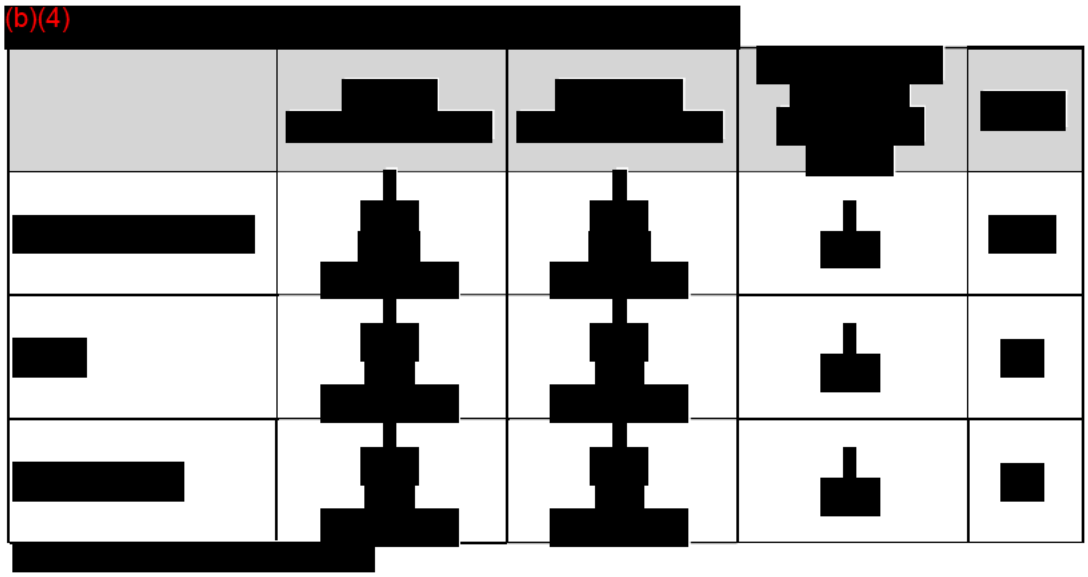
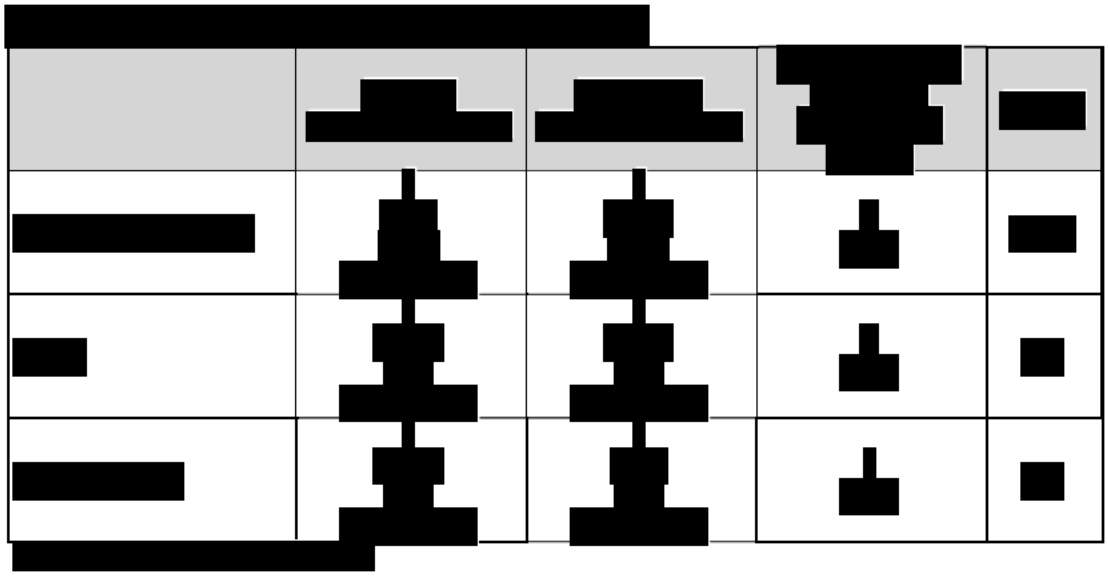
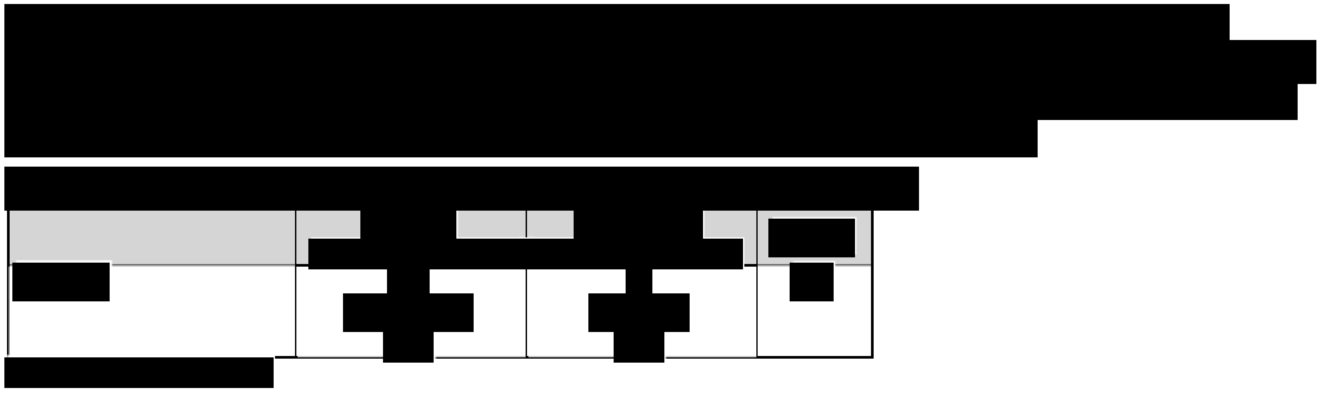






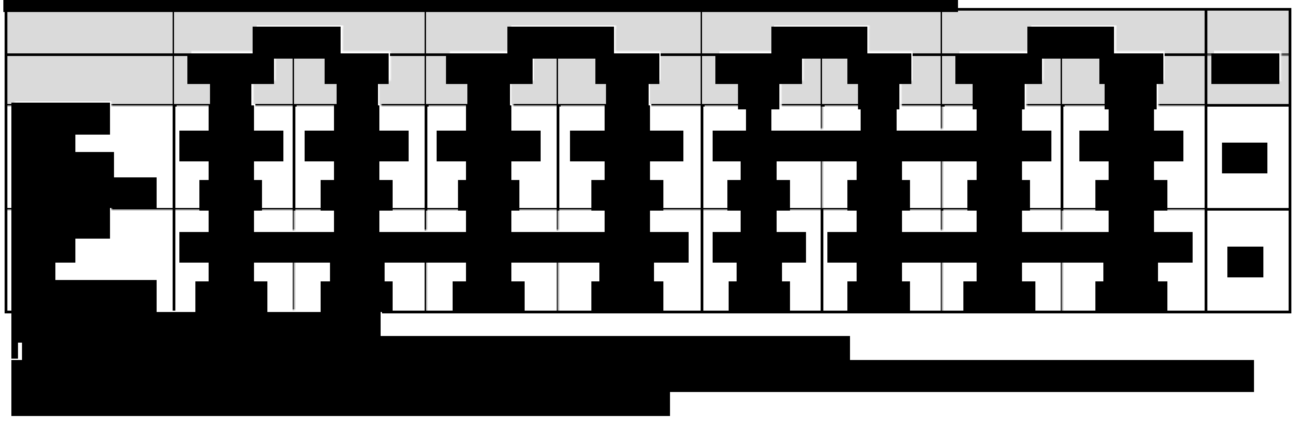
7.6.5. Post Hoc Analyses

(b)(4)

[redacted]

(b)(4)

(b)(4)



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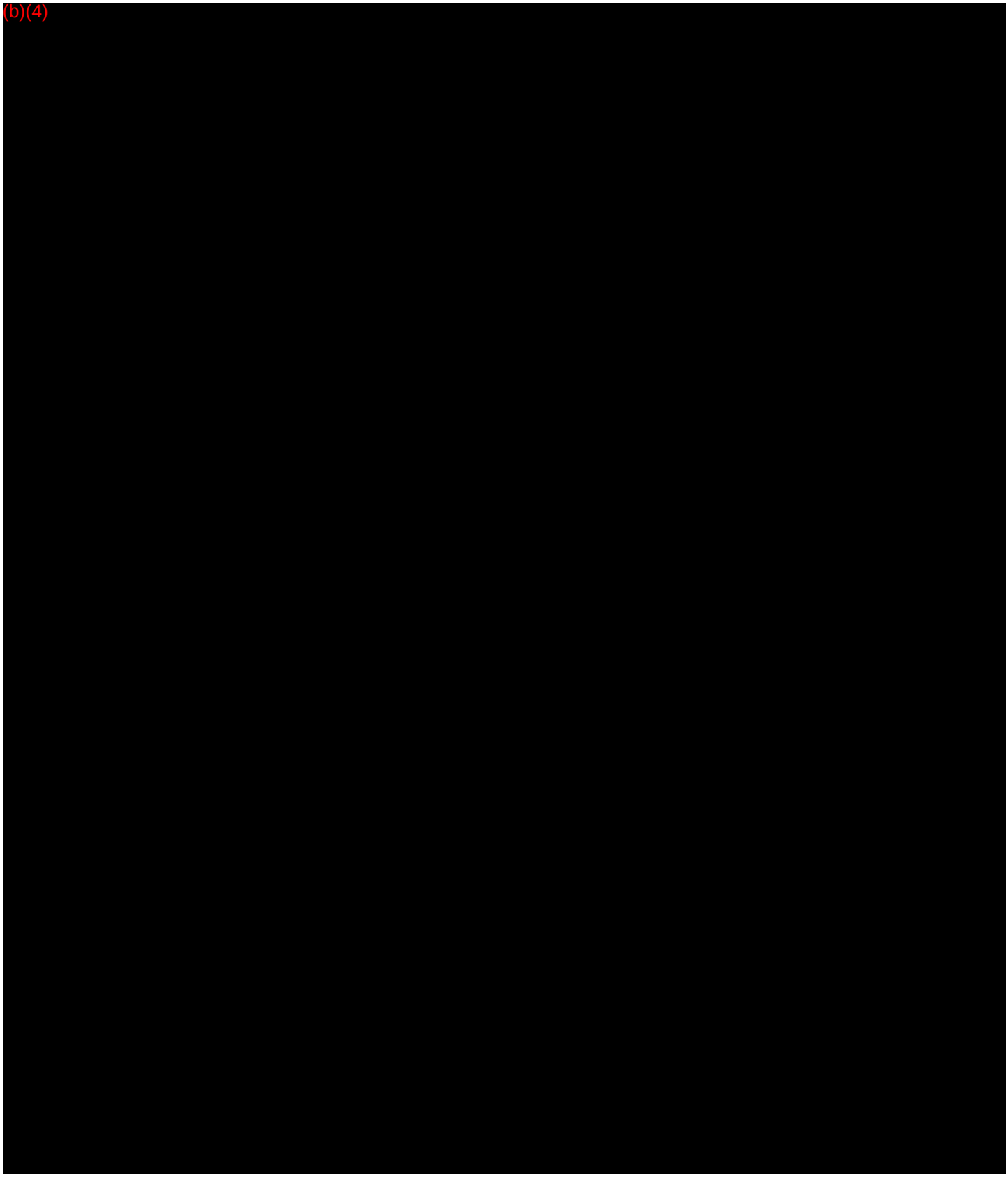


7.6.5.2. Multi-Variable Analysis

The multivariable analysis is useful in helping to interpret and explain the results observed in the SENTINEL study by identifying variances effecting the outcomes, especially in light of the fact the Sentinel System is an accessory device to a complex and highly operator variable procedure. Baseline and procedural characteristics were evaluated in order to predict new lesion volumes using a multivariable step wise regression. The step wise regression model minimized the AIC and variables entered the model if they had a p-value <=0.1 and exited the model if the p-value was > 0.05. The graph below illustrates that 65% of the variance observed in SENTINEL DW-MRI data is attributed to baseline lesion volume which is specific to each patient's medical history. As expected, treatment arm assignment was the largest contributor of non-patient specific variables at 14%. The valve type*treatment arm interaction and valve type alone are less impactful at 12% and 6%, respectively.

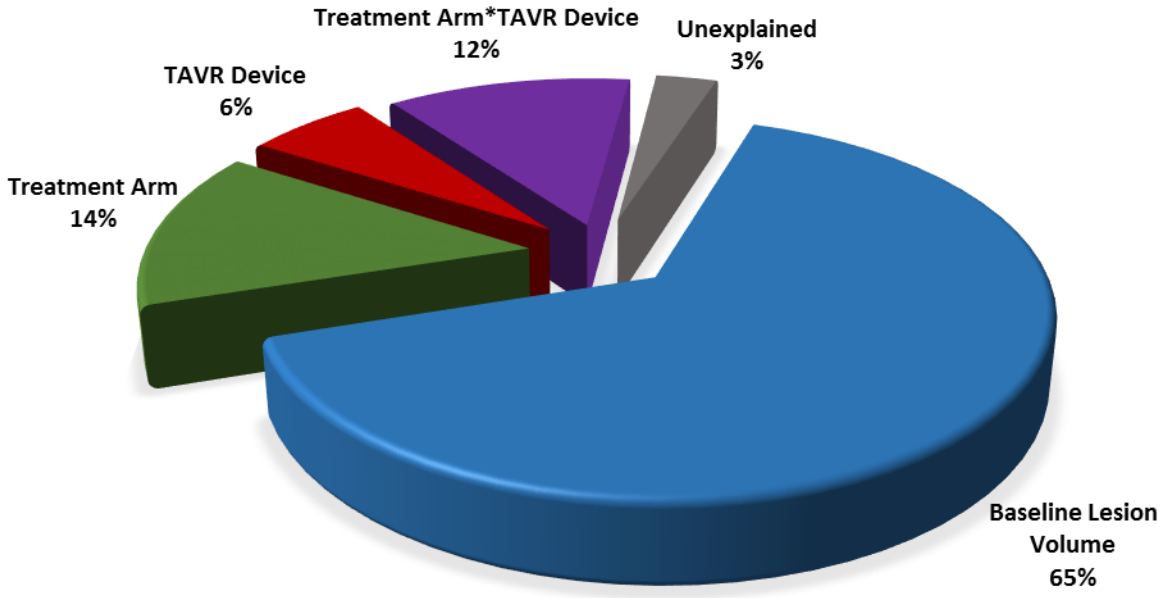


Figure 22: Proportion of Variance Explained by the Multivariable Model

7.7. Neurocognitive Outcomes

7.7.1. Summary

- No differences in neurocognitive results were observed between the test and control groups.
- Patient neurocognition at baseline was impaired as a consequence of the impact of the pre-existing lesion disease (i.e. baseline lesion volume), resulting in a cognition "floor" effect.
- Strong association and a correlation between lesion volume and lesion number with neurocognitive impairment in all territories was observed.

7.7.2. Results

The change in the neurocognitive test battery composite z-scores from baseline to follow-up between the Test and Control Arms was not significant at 30 days. The composite z-score is an overall cognition score that is the average of the z-scores from each of the five cognitive domains assessed: attention, executive function, processing speed, verbal memory and visual memory.

Table 26: Z-Score Results (30 Days)

	Test Arm Mean ± SD, n	Control Arm Mean ± SD, n	p-value
ITT	-0.09 ± 0.44, 93	-0.03 ± 0.37, 92	0.42
Per Protocol (23-45d)	-0.09 ± 0.45, 89	-0.03 ± 0.37, 87	0.45

Note: Data presented as Mean ± SD, n. p-values based on model adjusted for education and baseline Geriatric Depression Score and baseline Mini Mental State Score.

A large percentage of SENTINEL patients entered the study already significantly impaired (>1.5 standards deviations below normal) as compared to the average baseline neurocognitive function for their age group, see figure below for results of executive function at baseline, a key neurocognitive sub-domain.

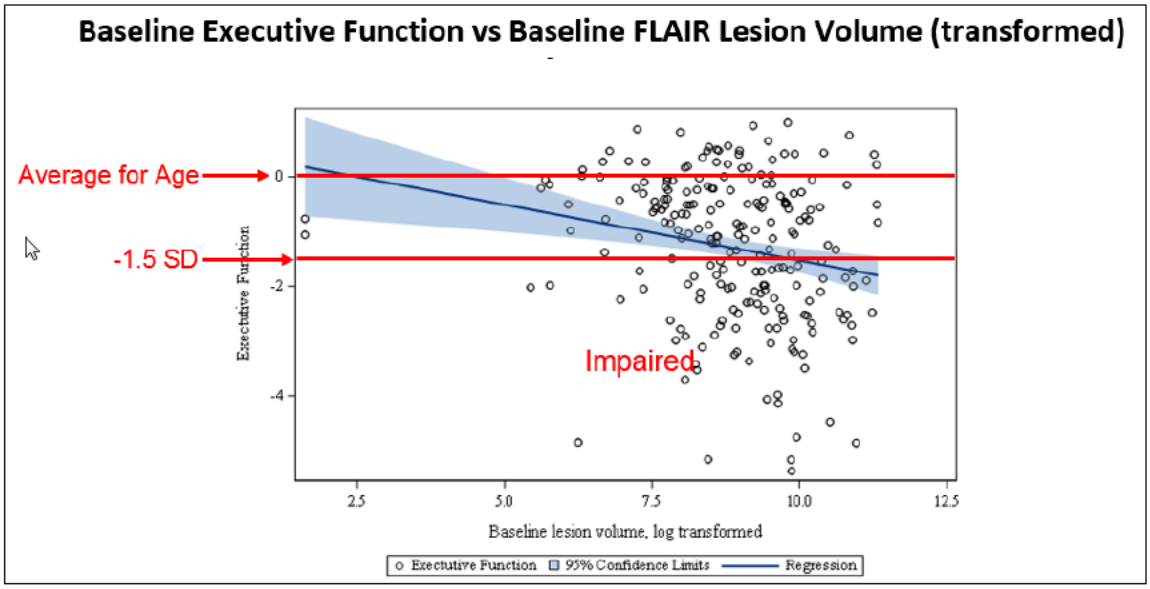


Figure 23: SENTINEL Patient Impairment

It is difficult to demonstrate decline in patients who are already significantly impaired ("floor effect"), and the lack of a significant change in the composite z-score was likely a result of the patient's pre-existing baseline lesion burden. Results were similar in all 7 domains examined for Test and Control Arm patients with no difference in domain z-score from baseline to follow-up. Additional correlative neurocognitive analyses can be found in **Appendix N**.

Given the patient population was found to be impaired at baseline (mean age of 82 and a low average baseline composite z-score of -0.66), combined with the fact that the study was not powered to show a difference in neurocognition, the study results did not demonstrate a significant difference in neurocognition. Additional neurocognitive analyses may be found in **Appendix G**.

The SENTINEL study did demonstrate that new embolic brain lesions as a result of the TAVR procedure, were associated and correlated to neurocognitive dysfunction, while size, frequency, and location of these lesions were all consequential. Decline in neurocognitive z-score at 30 days in the aggregate population (157 patients with paired neurocognitive and MRI assessments) was found to be correlated with an increase in lesion volume and number in the figures below ($p = 0.001$, $r = -0.27$; $p =$

0.0002, r = -0.30, respectively). Note all subjects with clinically apparent stroke have been removed as a conservative measure).

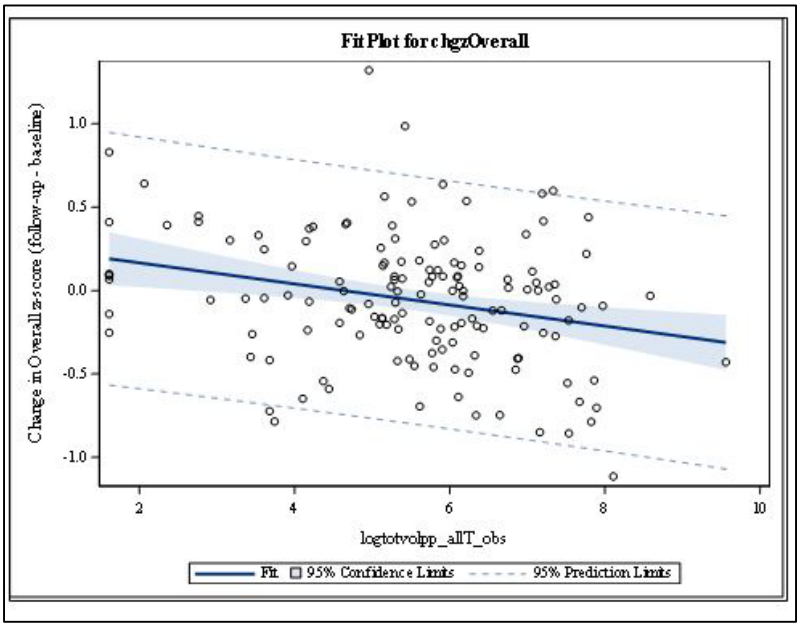


Figure 24: Aggregate Correlation of 2-7 Day DW-MRI Lesion Volume (Log Transformed) with Change in Neurocognitive Battery (All Territories) from Baseline to 30 Days

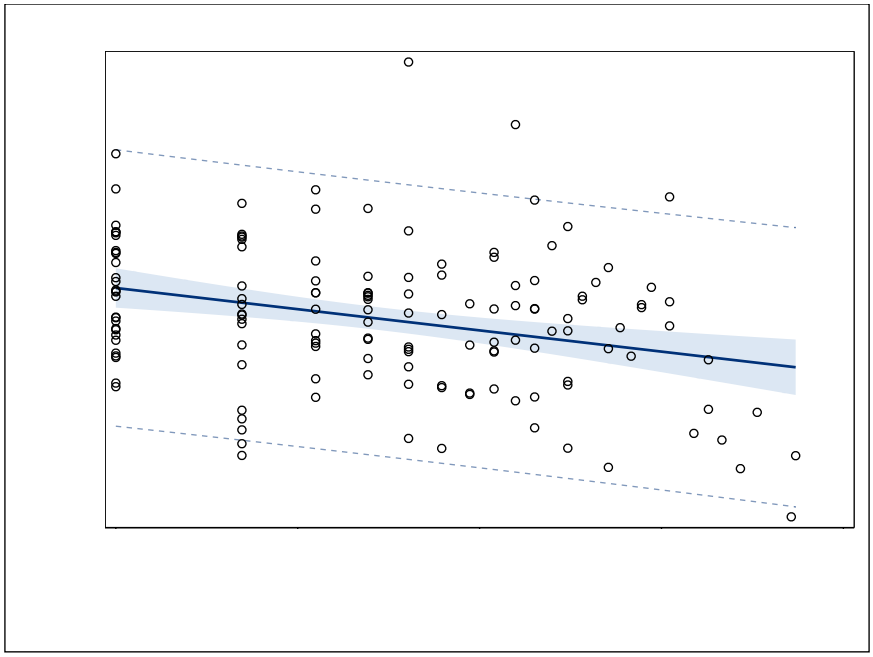


Figure 25: Aggregate Correlation of 2-7 Day DW-MRI Lesion Number (Log Transformed) with Change in Neurocognitive Battery (All Territories) from Baseline to 30 Days

7.8. Additional Analysis, Valve Type

New valves were added during the study as they became commercially available in the United States and thus an enrollment balance between different valve types could not be pre-specified. Valve selection was highly dependent upon site and physician preference leading to a wide variance in the percentage of each valve type used with SAPIEN 3 representing over 52% of the valves in the study. In addition, an interim analysis was not feasible due to temporal non-concordance of the primary safety and efficacy endpoints in order to adjust during the course of enrollment for valve distribution or sample size readjustment.

(b)(4)

[redacted]

[redacted]

For informational purposes, additional histopathology information by valve type is also provided below along with morphometric information (manual measurement by the core laboratory).

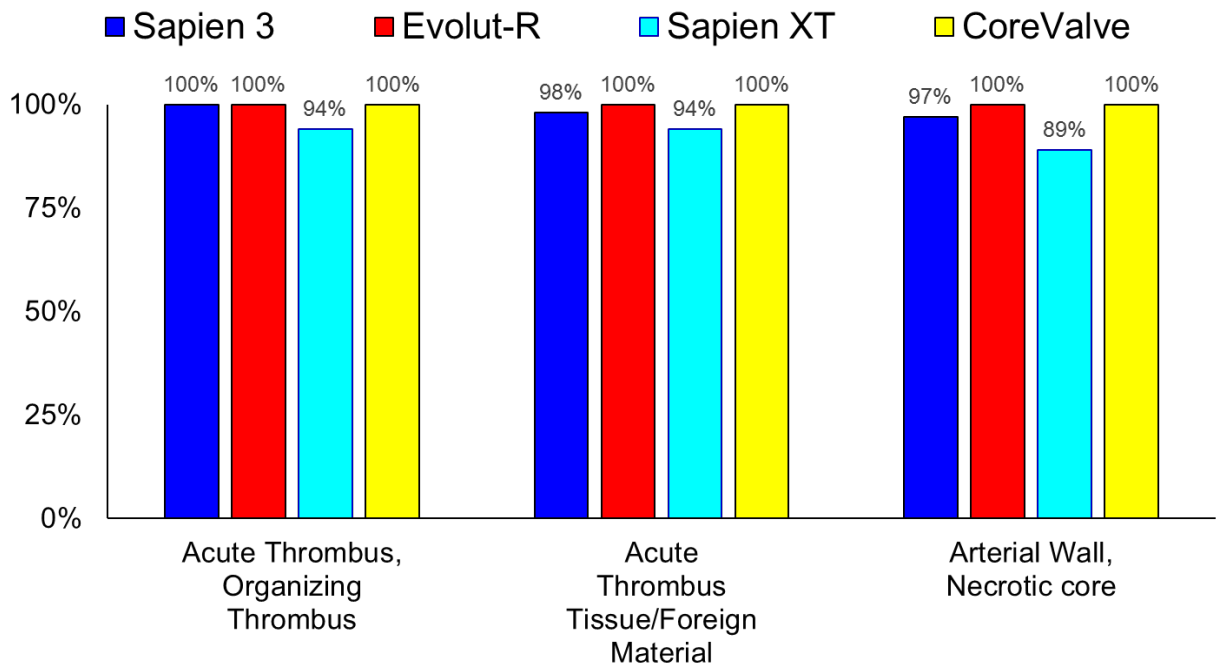


Figure 26: Histopathology Results by Valve Type

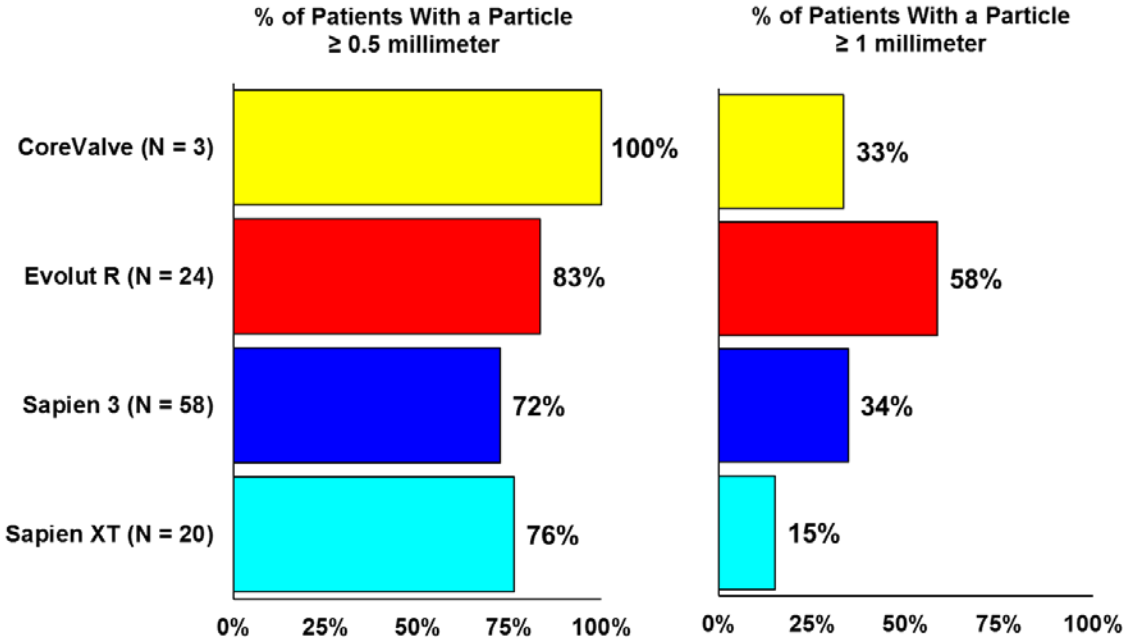


Figure 27: Morphometric Analysis by Valve Type

7.9. Discussion and Conclusions

The SENTINEL study demonstrated that stroke remains a risk of the TAVR procedure with the unprotected arm of the trial experiencing a 9.1% stroke rate. The study also demonstrated the safety of the Sentinel System as the primary safety endpoint was met and clinical events were numerically

lower with the Sentinel System compared to the control arm. The study was not powered to show a significant reduction in stroke or other components of MACCE but the observed stroke rate in the Sentinel System arms were numerically lower compared to the Control Arm (5.6% versus 9.1%). Use of the Sentinel System was intuitive, placement and removal of the device was fast, and the rate of radial or brachial vascular injury procedurally was 0.4%. The device success rate was high at 94.4% and at least one filter was deployed in 99% of eligible patients.

Use of the Sentinel System resulted in the capture of embolic material in 99% of patients, the type and size of captured debris varied by valve type and large debris (≥ 0.5mm) was captured in at least 70% of patients regardless of valve type. This finding confirms that TAVR catheters and devices are not benign since 36% of the captured debris consisted of foreign material most likely liberated from TAVR interventional devices.

A reduction in new lesion volume between the Test and Control Arms was observed but did not reach statistical significance. The failure to achieve statistical significance was likely due to the use of a limited dataset to power the study and the following sources of variance: patients' pre-existing baseline lesion burden, the DW-MR signal decay variability itself, and the inclusion of multiple valves into the study.

(b)(4)

Neurocognition was not shown to be different between the Test and Control Arms most likely due to the study not being sufficiently powered to evaluate this endpoint and the patient's level of cognition already being well below average for their age (floor effect) as a result of pre-existing baseline lesion disease. The study also demonstrated a correlation between neurocognition and new lesion volume and number. The study showed a strong association and a correlation between an increase in new lesion volume and deterioration in neurocognitive function, both in areas of the brain protected by the Sentinel System and in all territories of the brain.

The Sentinel System investigated in this trial was shown to be safe to use and captured and removed embolic material in almost all patients. The Sentinel System introduces minimal risk to the patient or the TAVR procedure and there are currently no approved alternatives.

7.10. SENTINEL Study Limitations

Several limitations of the study likely contributed to the lack of statistical significance of the surrogate imaging efficacy endpoint. First, despite the use of 3T MRI scanners and central core laboratory analysis of the scans, there was considerable variance in MRI post-procedure results, in part due to rapidly changing new lesion volumes and numbers signal detection during the follow-up window as well as site by site and patient by patient variability of follow up imaging acquisition windows. Second, there was little benchmark MRI data on which to base the control arm assumptions and treatment effect, therefore, the observed new lesion volume and number were less than predicted from the foundation CLEAN-TAVI trial. Third, the impact of baseline T2/FLAIR lesion volume on subsequent new lesion volume and number was not accounted for in the trial design. Fourth, different TAVR devices were included in this trial and the randomization scheme was not balanced according to valve type.

8. Benefit-Risk Considerations

When subjected to the general and special controls the probable benefits of using the Sentinel System to capture and remove embolic material/debris from the cerebral circulation during TAVR procedures outweigh the potential risks. This is especially important as there are currently no approved alternative treatment options for cerebral protection during TAVR.

8.1. Summary of Benefit

The CLEAN-TAVI, MISTRAL-C and SENTINEL randomized control trials together demonstrate that ischemic embolic brain lesions are a significant clinical risk that can be reduced by the use of filter based embolic protection devices and can potentially enhance the safety of the TAVR procedure. Histopathological analysis has shown that 99% of patients are likely to receive a benefit through the capture and removal of embolic material/debris from the cerebral circulation and there are currently no approved alternatives to the Sentinel System.

The pivotal SENTINEL study demonstrates the safety and performance of the Sentinel System in a trial that included all commercially available TAVR devices in a high risk severe AS patient population that had a broad range of co-morbidities. The rate of 30 day Major Adverse Cardiovascular and Cerebral Events (MACCE) was not only significantly non-inferior to the pre-specified historical performance goal of 18.3 % (p-value <.0001) but the observed rate of MACCE in the Test Arm was numerically lower than the observed rate in concurrent Control Arm (7.3% vs 9.9%). A lower TAVR procedure MACCE rate observed through the use of the Sentinel System is of benefit to patients especially considering clinically apparent stroke is the main component of MACCE. Recognizing that SENTINEL was not powered as a stroke trial, it is still important to note the study showed a numerically lower stroke rate of 5.6% in the Sentinel arm versus 9.1% in the Control arm.

The SENTINEL study also quantified the amount, type, and frequency of embolic material/debris generated during TAVR along with the ability of the Sentinel System to capture and remove this debris destined for cerebral circulation. The Sentinel System captured and removed debris in 99% of Test patients. The debris captured included acute/organized thrombus, calcification, valve tissue, arterial wall tissue, TAVR catheter hydrogel coating material, and myocardial tissue. Large debris ($\geq$ 0.5 mm) was captured in at least 70% of patients regardless of valve type. Capturing and removing this debris during TAVR is of benefit to patients as it reduces the potential for that debris to cause cerebral ischemic lesions, which as the study reveals, can be of future detriment to the patient's cognition due to the cumulative impact of incremental additions of embolic debris to the brain.

It has been postulated that parenteral intra-procedural pharmacological treatment during TAVR may be an effective strategy in preventing cerebral embolization. The BRAVO-3 MRI[25] study, was the first investigation of the potential benefit of an intra-procedural pharmacological intervention in reducing risk of cerebral emboli in patients undergoing TAVR. This trial was the largest study to date to investigate the occurrence of cerebral emboli after TAVR without the use of an embolic protection device assessment. The primary results indicated that (i) cerebral lesions as detected with DW-MRI are a frequent observation (61.7% among all patients) after contemporary TAVR, and (ii) choice of parenteral anticoagulant during TAVR did not significantly affect or reduce the rate of new cerebral lesions measured by MRI from TAVR. Therefore, the authors conclude that mechanical protection by

[25] Dangas, et al. "Cerebral Embolization During Transcatheter Aortic Valve Replacement: The BRAVO-3 MRI Study." JACC, 2016

use of cerebral protection may be the only way to effectively guard against the migration of embolic debris to the brain.

While the primary surrogate imaging efficacy endpoint of a statistical reduction in new lesion volume did not meet statistical significance, the reduction trend is in favor of the Sentinel System. Though the study did demonstrate a reduction in new lesion volume in Test versus Control patients in areas of the brain protected by the Sentinel System. Any incremental reduction in lesion volume and frequency is a long-term benefit to patients since larger lesion volumes (or more frequent lesions) predispose patients to future neurocognitive decline as demonstrated by the SENTINEL study. This conclusion is further supported by the use of embolic protection devices in carotid stenting which has demonstrated the positive impact of embolic protection on neurocognitive function preservation.[26,27] The importance of this protective effect will continue to increase as TAVR is expanded to lower risk populations who will have longer life expectancy and any cognition deterioration will be of greater concern.

Though the SENTINEL study did not show a significant difference in neurocognition between the test and control arms, it did demonstrate a strong association and a correlation between neurocognition and new lesion volume and number. The study shows relationship between an increase in new lesion volume and deterioration in neurocognitive function in areas of the brain protected by the Sentinel System as well as in all territories of the brain in the aggregate population ($p = 0.002$ and 0.001 respectively).

(b)(4) [redacted]. These findings are congruent with the other clinical data generated by the SENTINEL study such as the reduced adverse events rates, neurocognitive dose-response to lesion burden, and the very high rate of debris capture and removal when a Sentinel System is used.

Patient risk tolerance, while not formally documented in the SENTINEL study, is apparent by the fact patients were willing to participate in a study where they had a 2/3 chance of receiving cerebral protection. This indicates patients place a high value on the potential benefits of cerebral protection during TAVR in order to potentially reduce the chance of brain injury during TAVR. Several patients did not meet the Inclusion/Exclusion criteria for the SENTINEL study, but in conjunction with advice from their physicians, pursued the path of Compassionate and Emergency Use in order to gain access to the investigational Sentinel System. This occurred six times over the course of the trial with successful patient outcomes each time.

8.2. Summary of Risks

The TAVR population studied in the SENTINEL study consisted of high risk severe AS patients, nearly all of whom had significant co-morbidities. Serious adverse events are common in this population and events in the SENTINEL study were similar between the arms. The Sentinel System introduces minimal or no risk to patients as evidenced by a high rate of device deployment and retrieval success (94.4%) and only one access site injury. Sites performed approximately three Roll-In

[26]Park, et al. "Effect of Carotid Artery Stenting on Cognitive Function in Patients with Carotid Artery Stenosis: A Prospective, 3-Month Follow-up Study." Journal of Clinical Neurology. 2015 April; 11(2): 149-156
[27] Zhou, et al. "Effects of carotid artery stenting on cognitive function in patients with mild cognitive impairment and carotid stenosis." Experimental and Therapeutic Medicine. 2013 April; 5(4): 1019-1024

cases prior to randomizing patients in SENTINEL and the data suggests there was not a significant learning curve involved with use of the Sentinel System. Though not significant, stroke rates were recorded with the Test Arm showing a rate 5.6% vs 9.1% in the Control Arm. There were two (2) deaths in the roll-in arm, and five (5) deaths in the randomized arms at the 30-day endpoint, not statistically different between randomized arms. None of the deaths adjudicated by the independent Clinical Events Committee were related to the Sentinel System. The Sentinel System was successfully removed in 100% of cases and only one brachial artery adverse event was noted within 30 days of the index procedure. Although the total TAVR procedure time on average was increased by 10 minutes, this additional time is justified by the potential benefit the patient may receive from the protective use of the Sentinel System.

8.3. Benefit-Risk Conclusion

A survey performed at the ACC 2016 (Hawkey M.) meeting documented that 100% of physicians polled felt cerebral protection may be necessary during TAVR and that 70% of patients fear stroke much more than death when considering TAVR. The SENTINEL study demonstrates that new ischemic embolic brain lesions during TAVR are a clinical risk factor that should be avoided by the use of the Sentinel System. Risks related to these ischemic lesions are likely similar across all patients with severe AS, regardless of surgical risk score since by definition they have severely stenotic valves. The SENTINEL study also shows that the Sentinel System can be safely used during TAVR with minimal learning curve and the patients in the Test Arm categorically had a numerically lower MACCE rate than the Control Arm. The Sentinel System introduces minimal risk to patients. Histopathological analysis demonstrated that 99% of patients are likely to receive a benefit from the capture and removal from the cerebral circulation of embolic material/debris released during TAVR. A reduction in new lesion volume in protected territories was observed while the patient level post hoc meta-analysis demonstrated that when the number of patients is increased and variance is decreased, the precision of the treatment effect is enhanced. As the population for TAVR expands, lower surgical risk, and younger, patients likely have longer life expectancies over which to benefit from reduced neurological injury (stroke and cognitive decline). Physicians and patients have a strong desire for cerebral protection and there are currently no approved alternatives. The Sentinel System provides clinical benefit and the risks can be mitigated by the use of general and the identified special controls.

Appendix A Enrollment and Investigational Sites

A total of three hundred and sixty-three (363) patients were enrolled in the study at 19 sites in the United States and Germany. Based on study randomization, enrollment in each study arm was as follows: 119 Control, 121 Test and 123 Safety. The patients in the Safety and Test Arms combined constituted the Safety Cohort and those in the Test and Control Arms constituted the Imaging Cohort for the purpose of endpoint analysis. The first patient was enrolled on October 2, 1014 and the final patient was enrolled on March 10, 2016.

Table 29: Investigational Site Enrollment

Site Number	Location	Roll-Ins	Randomized Enrollment		
			Safety	Imaging	Control
001	US	5	24	25	24
002	US	5	13	13	12
003	US	6	20	19	18
004	US	4	4	4	4
005	US	3	6	6	7
006	US	3	8	7	8
007	US	3	4	4	4
008	US	3	2	2	2
010	US	4	3	3	2
011	US	3	1	0	1
012	US	5	3	2	1
013	US	6	2	1	2
014	US	3	5	4	6
015	US	5	3	3	4
016	US	4	0	1	0
018	US	2	0	1	1
019	Germany	0	22	22	22
021	Germany	0	3	4	1
024	US	1	0	0	0
Total		65	123	121	119

Appendix B Required Study Assessments by Arm

R=Roll-in, S=Safety, T=Test, C=Control								
	Screening		Treatment	Follow-up				
Visit Number	1	2	3	4	5	6	7	8
Study Procedure	Baseline[1]	Baseline DW-MRI	TAVR Procedure	<24 Hour Follow- up	Post-TAVR DW-MRI (2-7 Days)	Discharge	30 (±7) Day FLAIR- MRI	90 (±10) Day Follow-up
Informed consent	R,S,T,C							
I/E criteria	R,S,T,C							
Medical history	R,S,T,C							
Medication profile	R,S,T,C		R,S,T,C	R,S,T,C	R,S,T,C	R,S,T,C	R,S,T,C	R,S,T,C
Physical Exam	R,S,T,C							
STS Score	R,S,T,C							
Chemistry panel	R,S,T,C					R,S,T,C[2]	R,S,T,C	R,S,T,C
CK, CK-MB, or troponin	R,S,T,C							
ECG	R,S,T,C			R,S,T,C[3]				
Modified Allen's Test	R,S,T,C							
Neuro Assessments	R,S,T,C					R,S,T,C[4]	R,S,T,C	R,S,T,C[5]
Adverse Event (AE) review			R,S,T,C	R,S,T,C		R,S,T,C	R,S,T,C	R,S,T,C[6]
CT[7]	R,S,T,C[8]							
Angiogram	R,S,T,C[9]							
DW-MRI		T,C			T,C		T,C	
SF-12 QoL	T,C						T,C	T,C
Neurocognitive Test Battery[9]	T,C				T,C (Optional)		T,C	T,C
Sentinel insertion/removal times			R,S,T					
Sentinel contrast use			R,S,T					
Sentinel access site evaluation			R,S,T	R,S,T		R,S,T		
Filter spec. prep and ship			R[10],T					
Study Exit								R,S,T,C

1 Baseline visit and data collection can occur anytime within 14 days of TAVR procedure
2 Creatinine and BUN to be drawn per institution standard of care, at least once prior to discharge. Collect values as close to 24hr, 48hr and 72hrs and/or discharge if AKI is suspected.
3 ECG if cardiac event is suspected
4 Must be done prior to discharge and must be done by a neurologist
5 Only for subjects experiencing a stroke ≤ 30 days, must be completed by a neurologist
6 AE review in Roll-In and Safety Arms at 90 day may be done via telephone follow-up (unless the subject suffered a stroke within 30 days post procedure)
7 CT should include imaging from chin to diaphragm
8 CT to be done prior per institution standard of care ≤ 1 year of the procedure
9 An angiogram is not required, however, if one is done wait a minimum of 3-5 days between diagnostic catheterization and DW-MRI
10 First Roll-In subject may have histopathology done

Appendix C SENTINEL Inclusion/Exclusion Criteria

INCLUSION CRITERIA:

Subjects eligible to participate must meet all of the following at screening and/or baseline visits:

1. Approved indications for commercially available transcatheter aortic valves. Refer to the selected valve IFU for additional details.
2. Compatible left common carotid artery (6.5 – 10 mm) and brachiocephalic artery (9 – 15 mm) diameters without significant stenosis (> 70%) as determined by Multi-Slice Computed Tomography (MSCT) scan or equivalent imaging modality
3. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visit
4. The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site

EXCLUSION CRITERIA

General

1. Vasculature in the right extremity precluding 6Fr sheath radial or brachial access
2. Inadequate circulation to the right extremity as evidenced by signs of artery occlusion (modified Allen's test) or absence of radial/brachial pulse
3. Hemodialysis shunt, graft, or arterio-venous fistula involving the upper extremity vasculature
4. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment
5. Aortic valve is a congenital unicuspid or bicuspid valve; or is non-calcified
6. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+)
7. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease)
8. Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency
9. Blood dyscrasias as defined: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis or coagulopathy
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery for any reason
12. Hypertrophic cardiomyopathy with or without obstruction
13. Severe ventricular dysfunction with LVEF ≤20%
14. Echocardiographic evidence of intracardiac or aortic mass, thrombus, or vegetation
15. Symptomatic or asymptomatic severe occlusive carotid disease requiring concomitant CEA/stenting
16. Subject has undergone carotid stenting or carotid endarterectomy within the previous 6 weeks
17. Active peptic ulcer or upper GI bleeding within the prior 3 months
18. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, clopidogrel, or sensitivity to contrast media, which cannot be adequately pre-medicated
19. Recent (within 6 months) CVA or a TIA
20. Renal insufficiency (creatinine > 3.0 mg/dL or GFR < 30) and/or renal replacement therapy at the time of screening

21. Life expectancy < 12 months due to non-cardiac co-morbid conditions
22. Subjects in whom anti-platelet and/or anticoagulant therapy is contraindicated, or who will refuse transfusion
23. Subjects who have active bacterial endocarditis or other active infections
24. Currently participating in an investigational drug or another device study
25. Subjects who have a planned treatment with any other investigational device or procedure during the study follow-up period (90 days)
26. Subject with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation during the study follow-up period (90 days)
27. Any subject with a balloon valvuloplasty (BAV) within 30 days of the procedure

Neurologic (Randomized subjects only)

28. Subject had active major psychiatric disease
29. Subject has severe visual, auditory, or learning impairment and who are unable to comprehend English and therefore unable to be consented for the study
30. Subjects with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities

Angiographic

31. Excessive tortuosity in the right radial/brachial/subclavian artery preventing Sentinel System access and insertion
32. Subject whose brachiocephalic or left carotid artery reveals significant stenosis, calcification, ectasia, dissection, or aneurysm at the ostium or within 3 cm of the ostium

Magnetic Resonance Imaging (Randomized subjects only)

33. Subject Body Mass Index (BMI) precluding imaging in scanner
34. Contraindications to MRI (subjects with any implantable temporary or permanent pacemaker or defibrillator, metal implants in field of view, metallic fragments, clips, or devices in the brain or eye before TAVR procedure)
35. Planned implantation of a pacemaker or defibrillator implantation after TAVR
36. Claustrophobia

Appendix D Roll-In Results

Each investigational site participated in a formal, documented training program prior to enrollment of the first treated patient. The training program included a didactic presentation and training in deployment of the device in an anatomical glass model.

Following completion of the training program, each site enrolled up to five non-randomized "Roll-In" TAVR patients utilizing the Sentinel System. All implanting physicians at each site had to be present for at least one roll-in case. "Roll-In" patients underwent assessments that were identical to those performed on all Safety and Test Arm patients. A total of 65 Roll-In patients were enrolled. 63 received a Sentinel System; 59 were available for clinical follow-up.

Safety results for Roll-In patients were similar to those from randomized patients, confirming that training on the Sentinel System was sufficient, and no significant learning curve that operators must go through in order to be proficient in the safe and successful use of the Sentinel System. See Table 30 to Table 37.

Table 30: Baseline Demographics (Roll-In Patients)

	Roll-In Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
Demographics	
Age	82.2 ± 9.38 (65); 51, 95; (95% CI: 79.9, 84.6)
Male	52.3% (34/65)
Hispanic or Latino	3.1% (2/65)
Race	
Asian	0%
American Indian or Alaskan Native	0%
Black/African or African American	4.6% (3/65)
Native Hawaiian or Pacific Islander	0%
White/Caucasian	95.4% (62/65)
Physical Exam	
Weight (lbs)	176.8 ± 49.01 (65); 95, 362; (95% CI: 164.7, 188.9)
Height (in)	66.0 ± 3.99 (65); 56, 76; (95% CI: 65.0, 67.0)
BMI	28.3 ± 6.41 (65); 20, 51; (95% CI: 26.7, 29.9)
Systolic Blood Pressure	135.6 ± 22.97 (65); 94, 187; (95% CI: 130.0, 141.3)
Diastolic Blood Pressure	68.0 ± 10.10 (65); 46, 96; (95% CI: 65.5, 70.5)
Heart Rate	73.1 ± 11.38 (65); 51, 103; (95% CI: 70.2, 75.9)
Modified Allen's Test	
Normal	98.5% (64/65)

	Roll-In Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
Abnormal	1.5% (1/65)
STS PROM Score	6.4 ± 3.68 (65); 1, 22; (95% CI: 5.5, 7.4)
STS PROM Score (Categorized)	
<4	21.5% (14/65)
4-7	41.5% (27/65)
8-15	33.8% (22/65)
>15	3.1% (2/65)
Medical History	
History of Atrial Fibrillation	36.9% (24/65)
Paroxysmal	54.2% (13/24)
Permanent	12.5% (3/24)
Persistent	33.3% (8/24)
History of Peripheral Vascular Disease	21.5% (14/65)
History of Coronary Artery Disease	49.2% (32/65)
History of Diabetes	
Diabetes Type I	1.5% (1/65)
Diabetes Type II	30.8% (20/65)
Stroke Severity	
Major	3.1% (2/65)
Minor	0%
Previous Stroke with Permanent Deficit[1]	3.1% (2/65)
Previous Transient Ischemic Attack (TIA)	12.3% (8/65)
Porcelain Aorta	3.1% (2/65)
Previous CABG	20.0% (13/65)
Previous PCI	21.5% (14/65)
Valve Criteria	
Valve Area (cm2)	0.7 ± 0.18 (64); 0, 1; (95% CI: 0.7, 0.8)

	Roll-In Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
Aortic valve area index (cm2/m2)	0.4 ± 0.10 (64); 0, 1; (95% CI: 0.4, 0.4)
Mean aortic valve gradient (mmHg)	44.2 ± 14.47 (64); 19, 103; (95% CI: 40.6, 47.8)
Peak aortic-jet velocity (m/sec)	4.2 ± 0.65 (63); 3, 6; (95% CI: 4.0, 4.4)
Neurological, Neurocognitive, Neuroimaging Baseline Exams	
mRS Score	1.1 ± 1.25 (63); 0, 4; (95% CI: 0.8, 1.4)
NIHSS Score (total)	0.6 ± 1.37 (64); 0, 7; (95% CI: 0.2, 0.9)
Neurocognitive Z-Score	NA
NYHA	
I	3.1% (2/64)
II	28.1% (18/64)
III	48.4% (31/64)
IV	20.3% (13/64)

[1]Defined as neurological deficit lasting more than 24 hours confirmed by imaging.

Table 31: Procedural Characteristics (Roll-In Patients)

	Roll-in Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
Arch	
Normal	84.6% (55/65)
Bovine	13.8% (9/65)
Other	1.5% (1/65)
Nominal Vessel Diameters (20mm range)	
Brachiocephalic (mm)	12.9 ± 1.94 (65); 8, 18; (95% CI: 12.4, 13.3)
LCC (mm)	7.5 ± 1.07 (65); 5, 11; (95% CI: 7.2, 7.8)
Sentinel Device Placement	
Radial	95.3% (61/64)
Brachial	4.7% (3/64)
Other	0%
Activated Clotting Time[1] (sec)	295.1 ± 71.74 (64); 166, 600; (95% CI: 277.2, 313.0)

	Roll-in Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
Fluoro Time[2] (min)	25.4 ± 13.36 (50); 0, 52; (95% CI: 21.6, 29.2)
TAVR Device Placement	
Transfemoral	87.7% (57/65)
Transapical	12.3% (8/65)
TAVR Device	
Medtronic CoreValve Evolut R	4.6% (3/65)
Edwards SAPIEN XT	86.2% (56/65)
Edwards SAPIEN 3	9.2% (6/65)
Procedural Outcome	
Total TAVR Procedure Time (min)	116.9 ± 55.13 (62); 47, 287; (95% CI: 102.9, 130.9)
Total TAVR contrast (cc)	39.8 ± 60.30 (62); 0, 427; (95% CI: 24.5, 55.1)
Activated Clotting Time[3] (sec)	271.0 ± 98.84 (60); 111, 760; (95% CI: 245.4, 296.5)
Permanent pacemaker implanted (within 7 days from procedure)	4.6% (3/65)
New onset of Atrial Fibrillation	0%
Acute Delivery and Retrieval Success[4]	92.1% (58/63)
Distal filter successfully deployed	91.9% (57/62)
Proximal filter successfully deployed	96.8% (61/63)
Sentinel device retrieved successfully	100.0% (63/63)
TAVR procedure considered complete5	95.2% (60/63)

[1]After heparin has been given and prior to Sentinel device insertion.
[2]Fluoro used during entire TAVR procedure.
[3]At the time of Sentinel device retrieval.
[4]Deployment and retrieval of the proximal and distal filters in accessible anatomies. Accessible anatomies are those which are not excessively tortuous or calcified that would prevent cannulation of the device to its position.
[5]Deployment of at least one filter (with either the first or second device) during the TAVR procedure without any incidence of investigational device related MACCE.

Table 32: Study Exit Summary (Roll-In Patients)

	Roll-in % (n/N)
Completion of Study as Planned	84.6% (55/65)
Voluntary Withdrawal	3.08% (2/65)
Lost to Follow-Up	1.54% (1/65)
Physician's Decision	0% (0/65)
Death	6.15% (4/65)
Other	4.62% (3/65)
Overall	100% (65/65)

Table 33: In-hospital MACCE Rate (Roll-In Patients)

	Roll-in % patients with event (n patients with event/N patients) [exact 95% CI]
Any MACCE	3.4% (2/59) [0.4%, 11.7%]
Death (all)	1.7% (1/59) [0.0%, 9.1%]
Stroke (all)	1.7% (1/59) [0.0%, 9.1%]
Disabling Stroke	0% [0.0%, 6.1%]
Non-disabling Stroke	1.7% (1/59) [0.0%, 9.1%]
AKI (Class 3)	0% [0.0%, 6.1%]

Table 34: 30-day MACCE Rate (Roll-In Patients)

	Roll-in % patients with event (n patients with event/N patients) [exact 95% CI]]
Any MACCE	6.8% (4/59) [1.9%, 16.5%]
Death (all)	3.4% (2/59) [0.4%, 11.7%]
Stroke (all)	3.4% (2/59) [0.4%, 11.7%]
Disabling Stroke	1.7% (1/59) [0.0%, 9.1%]
Non-disabling Stroke	1.7% (1/59) [0.0%, 9.1%]
AKI (Class 3)	0% [0.0%, 6.1%]

Table 35: 90-day MACCE Rate (Roll-In Patients)

	Roll-in % patients with event (n patients with event/N patients) [exact 95% CI]]
Any MACCE	9.1% (5/55) [3.0%,20.0%]
Death (all)	5.5% (3/55) [1.1%,15.1%]
Stroke (all)	3.8% (2/52) [0.5%,13.2%]
Disabling Stroke	1.9% (1/52) [0.0%,10.3%]
Non-disabling Stroke	1.9% (1/52) [0.0%,10.3%]
AKI (Class 3)	0% [0.0%,6.8%]

Note: Data based on subjects with 90 day follow-up or an event experienced within 90 days

Table 36: Incidence of Major Vascular Complications (Roll-In Patients)

	Roll-in % patients with event (n patients with event/N patients) [exact 95% CI]]
During the index procedure[1]	5.1% (3/59) [1.1%, 14.1%]
Radial Artery	0% [0.0%, 6.1%]
Brachial Artery	0% [0.0%, 6.1%]
Within 30 days of the index procedure[1]	1.7% (1/59) [0.0%, 9.1%]
Radial Artery	0% [0.0%, 6.1%]
Brachial Artery	0% [0.0%, 6.1%]

[1]All major vascular complications, including TAVR access as well as Sentinel (radial, brachial)

Table 37: Incidence of Serious Adverse Events at 30 days (Roll-In Patients)

	Total Events	Patients w/Event(s) % (n/N)
Incidence of Serious AE	46	45.8% (27/59)

Appendix E Study Oversight

1. Clinical Events Committee

The Clinical Events Committee (CEC) was an independent committee composed of physicians familiar with the representative subject population, transcatheter aortic valve replacement procedures and their outcomes. The CEC was responsible for the review and adjudication of events that were considered to be potential MACCE or unanticipated. CEC adjudicated events were used in the analysis of study data.

2. Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) was responsible for oversight of study progress and trial operations. The DSMB reviewed study progress and study conduct and was responsible for the decision to stop recruitment or modify the study design, as necessary, throughout the course of the study. The DSMB was also responsible for review of aggregate AE listings to determine the presence of a trend that may be unexpected in severity or degree of incidence.

The DSMB was privy to, at a minimum, the study's enrollment status, subject demographics, adverse events, and protocol deviations.

3. Medical Monitor

The Medical Monitor for the study was responsible for providing safety oversight and reviewing the protocol (e.g., study halting rules) and information about the study product as it became available, including reported safety events.

The Medical Monitor, in consultation with the Claret Medical clinical affairs team and safety oversight committees (Data Safety Monitoring Committee and Clinical Events Committee), provided safety review during the execution of the clinical trial. This oversight included reviewing safety information and providing applicable recommendations.

The Medical Monitor was independent from Claret Medical and independent of anyone involved in the clinical care of the study subjects. The Medical Monitor did not have scientific, financial, or other conflicts of interest related to Claret Medical or the participating clinical investigators.

4. Study Operations Committee

The SENTINEL Study Operations Committee provided the overall supervision of the trial, monitored trial progress and conduct and advised on safety and scientific credibility. The operations committee engaged in collaborative and cooperative shared decision-making regarding the operational activities of the SENTINEL study by providing clinical, medical and discipline specific expertise from their fields of knowledge.

The SENTINEL Study Operations Committee was composed of the following:

- Residing chair of the Claret Medical Clinical Steering Committee
- Claret Medical clinical affairs department
- Co-Principal Investigators
- Medical Monitor for the SENTINEL study
- Monitoring and data management organizations

5. MRI Core Laboratory

Buffalo Neuroimaging Analysis Center

An independent MRI core laboratory was used for computation of MRI findings at the patient and individual lesion level. The core laboratory findings were used in the analysis and reporting of the neuroimaging data. A standardized MRI acquisition and measurement process was designed by the core laboratory specifically for the SENTINEL Study, and each investigative site received training on the acquisition and transmission of images. All MRI scanners used in the study were required to have 3 Tesla magnets, and all scanners were qualified by the core laboratory through approval of a qualification scan on a healthy volunteer. A site could have more than one MRI scanner certified by the core laboratory, however, all serial scans for a single patient were required to be performed on the same scanner.

6. Histopathology Core Laboratory

CVPath Institute, Inc.

An independent histopathology core laboratory was used for the analysis and quantification of the debris captured by the Sentinel Systems used in the Test arm.

7. Neurocognitive Core Laboratory

Tananbaum Stroke Center, Neurological Institute; Columbia University Medical Center

An independent neurocognitive core laboratory was used for independent review and scoring of neurocognitive examination results performed on all Test and Control Arm patients. All test administrators at each site were certified by the core laboratory prior to administering patient assessments.

8. CT Core Laboratory

Cedars-Sinai Medical Center

The CT core laboratory performed CT assessments for final determination of clinical and anatomical study suitability. CT images were uploaded by sites to a central CT core laboratory. Three-dimensional CT reconstruction was performed blindly by the core laboratory on all potential study patients so that consistent and standardized determination of anatomical suitability was employed across study sites and patients.

9. Data Management

Medpace, Inc.

Data management was performed by a contracted data management organization. A validated electronic data capture system (EDC) was used to manage and house the study data as collected on the standardized case report form. Conventional data verification routines were performed. Data management was performed according to Good Clinical Practice (GCP) guidelines, and standard operating procedures (SOP).

10. Statistical Analysis

North American Science Associates, Inc. (NAMSA) / Duke Clinical Research Institute (DCRI)

All study statistical analysis was performed by a contract medical research organization in accordance with GCP guidelines and the organization’s applicable SOPs.

11. Site Monitoring

Chellew Clinical Outsourcing, LLC

Routine monitoring of clinical site records was conducted throughout the course of the trial. A contract research monitoring organization was employed to conduct monitoring according to GCP guidelines and applicable SOPs.

12. Blinding

All patients were blinded to their randomization assignments. The CT Core Laboratory was blinded to the patient's treatment assignment as they analyzed the patient CTs. Similarly, neuroimaging and neurocognitive core laboratories remained blinded to the patient's randomization assignment until after all MRI scans and neurocognitive assessments were complete and were entered into the study database. The sponsor remained blinded to the study data until all patients reached the study required follow-up time points and all MRI and neurocognitive assessments were entered in the database. The CEC also remained blinded throughout the conduct of the trial. The principal investigator(s), interventionalist (TAVR implanter), study site coordinators, data management administrator, DSMB members, independent safety reporting statistician, and histopathology core laboratory were not blinded during the study.

Appendix F Secondary Efficacy Endpoints

All secondary endpoints were evaluated using the ITT and PP populations. In the ITT population, the majority of secondary efficacy endpoints trended numerically lower in the Test Arm compared to the Control Arm, although statistical significance was not reached (see Table 38 - Table 42). 2-7 day results utilize DW-MRI while 30 day results utilize T2/FLAIR.

Table 38: 2-7 Day Max & Average Single Lesion Volume (Protected & All Territories)

	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	Hodges-Lehmann Estimate of Location Shift (95% CI)	p-value[1]
ITT: Maximum single new lesion volume per patient – protected territories (mm3)	63.3 (29, 199.7), n=91 0 min, 1945.9 max	85.7 (31, 226.8), n=98 0 min, 24244.6 max	-5.3 (-34.3, 17.1)	0.57
Per Protocol: Maximum single new lesion volume per patient – protected territories (mm3)	64.6 (36.9, 201.7), n=83 0 min, 1945.9 max	84.4 (33, 226.8), n=89 0 min, 24244.6 max	0 (-27.7, 24.4)	0.94
ITT: Maximum single new lesion volume per patient – all territories (mm3)	128.5 (56, 282.1), n=91 0 min, 13563.9 max	116 (55.4, 302.6), n=98 0 min, 24244.6 max	3.3 (-34.3, 40.2)	0.84
Per Protocol: Maximum single new lesion volume per patient – all territories (mm3)	137.1 (64.6, 315.1), n=83 0 min, 13563.9 max	113.4 (55.4, 300.6), n=89 0 min, 24244.6 max	18.5 (-21.8, 58)	0.35
ITT: Average single new lesion volume per patient – protected territories (mm3)	48.8 (25.7, 87), n=91 0 min, 386 max	49.2 (25.2, 79.1), n=98 0 min, 8100 max	0 (-11.5, 11.7)	0.94
Per Protocol: Average single new lesion volume per patient – protected territories (mm3)	52 (30.3, 87.9), n=83 0 min, 386 max	48.3 (30.1, 73.5), n=89 0 min, 8100 max	3 (-7.3, 16.2)	0.49
ITT: Average single new lesion volume per patient – all territories (mm3)	65.2 (36.9, 99.8), n=91 0 min, 1772.4 max	56.4 (36.5, 94.6), n=98 0 min, 8100 max	6.6 (-6.4, 19.8)	0.30
Per Protocol: Average single new lesion volume per patient – all territories (mm3)	65.9 (46.4, 103.7), n=83 0 min, 1772.4 max	54.5 (35.3, 92.3), n=89 0 min, 8100 max	12.3 (-0.3, 25.5)	0.06

[1]Based on two-sided Wilcoxon test

Table 39: 30 Day New Lesion Volume (Protected Territories)

	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	Observed Treatment Difference (Test - Control)	Hodges-Lehmann Estimate of Location Shift (95% CI)	p-value[1]
ITT, mm3	0 (0, 52.7), n=78 0 min, 4920.1 max	0 (0, 83.1), n=80 0 min, 26575.4 max	0.0	0 (0, 0)	0.83
Per Protocol, mm3	0 (0, 52.7), n=73 0 min, 4920.1 max	0 (0, 76.5), n=65 0 min, 26575.4 max	0.0	0 (0, 0)	0.84

[1]Based on two-sided Wilcoxon test

(b)(4)

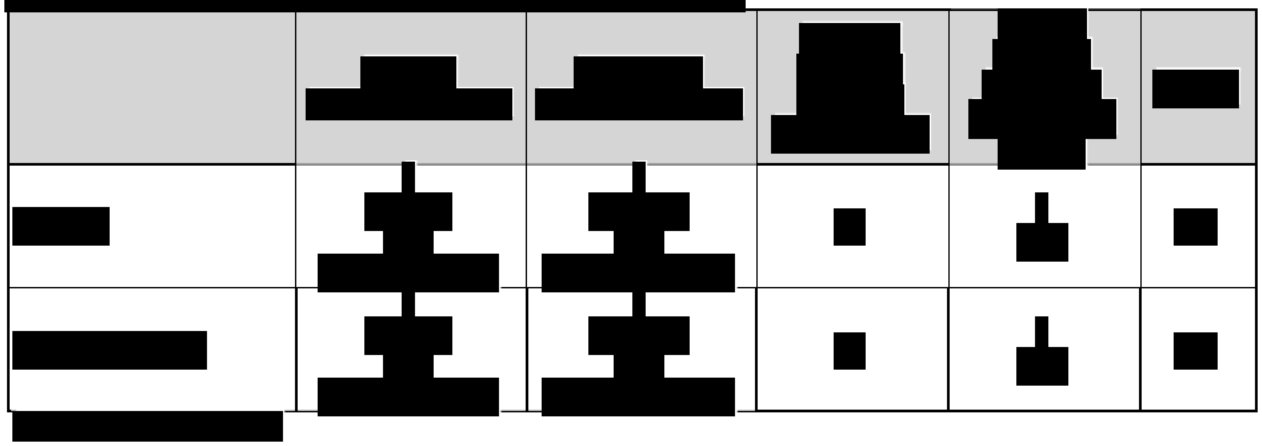
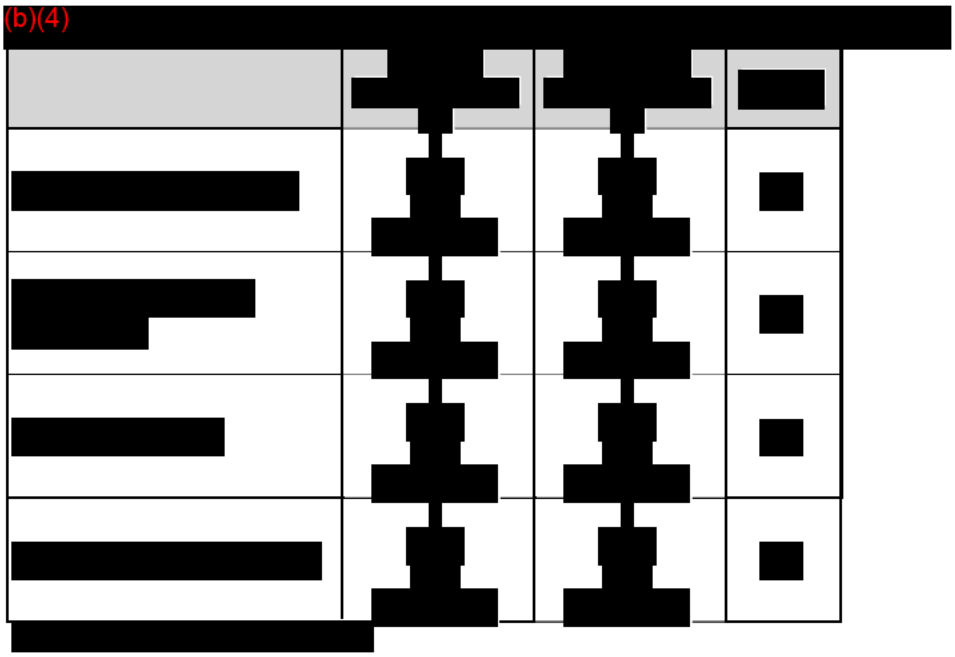


Table 41: 30 Day Max & Average Single Lesion Volume (Protected & All Territories)

	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	p-value[1]
ITT: Maximum single new lesion volume per patient – protected territories (mm3)	0 (0, 38.8), n=78 0 min, 4079 max	0 (0, 67.9), n=80 0 min, 26575.4 max	0.85
Per Protocol: Maximum single new lesion volume per patient – protected territories (mm3)	0 (0, 38.8), n=73 0 min, 4079 max	0 (0, 59.3), n=65 0 min, 26575.4 max	0.88
ITT: Maximum single new lesion volume per patient – all territories (mm3)	0 (0, 71.2), n=78 0 min, 4079 max	0 (0, 89.5), n=80 0 min, 26575.4 max	0.83
Per Protocol: Maximum single new lesion volume per patient – all territories (mm3)	0 (0, 71.2), n=73 0 min, 4079 max	0 (0, 89.4), n=65 0 min, 26575.4 max	0.72
ITT: Average single new lesion volume per patient – protected territories (mm3)	0 (0, 36.9), n=78 0 min, 820 max	0 (0, 50.3), n=80 0 min, 26575.4 max	0.75
Per Protocol: Average single new lesion volume per patient – protected territories (mm3)	0 (0, 36.9), n=73 0 min, 820 max	0 (0, 47.5), n=65 0 min, 26575.4 max	0.78
ITT: Average single new lesion volume per patient – all territories (mm3)	0 (0, 50.1), n=78 0 min, 573.3 max	0 (0, 68.2), n=80 0 min, 26575.4 max	0.93
Per Protocol: Average single new lesion volume per patient – all territories (mm3)	0 (0, 50.1), n=73 0 min, 573.3 max	0 (0, 59.9), n=65 0 min, 26575.4 max	0.81

[1]Based on two-sided Wilcoxon test

(b)(4)



Appendix G Secondary Neurocognitive Endpoints

Table 43: Change in Neurocognitive Battery Composite Z-Score from Baseline

	Test Arm	Control Arm	p-value
ITT 90 days	0.18 ± 0.38, 77	0.18 ± 0.35, 76	0.94
Per Protocol 90 days (46-100d)	0.16 ± 0.38, 68	0.19 ± 0.36, 70	0.65
ITT 2-7 days	-0.33 ± 0.65, 66	-0.16 ± 0.58, 66	0.19
Per Protocol 2-7 days	-0.29 ± 0.64, 58	-0.15 ± 0.59, 62	0.38

Note: Data presented as Mean ± SD, n. p-values based on model adjusted for education and baseline Geriatric Depression Score and baseline Mini Mental State Score.

Table 44: Neurocognitive Test Battery Z-Scores – ITT (All Available Data)

		Test Arm		Control Arm		
		Mean ± SD (min, max), n	Change from Baseline	Mean ± SD (min, max), n	Change from Baseline	p-value1
Attention	Baseline	-0.14 ± 0.96 (-2.84, 1.71), 117	N/A	-0.17 ± 0.88 (-2.32, 1.62), 117	N/A	N/A
	30 Day Follow-Up	-0.14 ± 0.93 (-2.66, 1.91), 93	0.03 ± 0.55 (-1.54, 1.35), 93	0.03 ± 0.88 (-2.39, 1.69), 92	0.14 ± 0.51 (-1.45, 1.32), 92	0.18
	90 Day Follow-Up	0.06 ± 0.87 (-1.91, 2.02), 77	0.2 ± 0.49 (-0.77, 1.55), 77	0.11 ± 0.87 (-2.44, 1.73), 76	0.23 ± 0.55 (-0.95, 1.76), 76	0.61
Executive Function	Baseline	-1.28 ± 1.3 (-5.16, 0.93), 117	N/A	-1.36 ± 1.36 (-5.38, 0.99), 117	N/A	N/A
	30 Day Follow-Up	-1.2 ± 1.4 (-4.73, 0.68), 93	0.14 ± 0.86 (-2.28, 2.77), 93	-0.99 ± 1.34 (-5.79, 0.77), 91	0.25 ± 0.86 (-3.72, 4.35), 91	0.45
	90 Day Follow-Up	-0.94 ± 1.16 (-3.97, 0.78), 77	0.32 ± 0.79 (-1.59, 2.16), 77	-0.79 ± 1.21 (-4.63, 1.07), 76	0.39 ± 0.86 (-1.39, 4.49), 76	0.4585
Processing Speed	Baseline	-0.24 ± 0.91 (-2.31, 2.04), 117	N/A	-0.23 ± 0.95 (-2.35, 2.09), 117	N/A	N/A
	30 Day Follow-Up	-0.11 ± 1 (-2.14, 2.12), 92	0.14 ± 0.43 (-0.91, 1.32), 92	-0.01 ± 0.86 (-2.1, 1.98), 90	0.12 ± 0.39 (-1.05, 0.81), 90	0.56
	90 Day Follow-Up	-0.05 ± 0.86 (-1.81, 1.91), 77	0.21 ± 0.46 (-0.94, 1.47), 77	0.14 ± 0.81 (-1.59, 1.76), 76	0.27 ± 0.43 (-0.93, 1.39), 76	0.73
Verbal Memory	Baseline	-0.85 ± 0.94 (-3.12, 1.11), 117	N/A	-0.64 ± 1.07 (-4.08, 1.04), 117	N/A	N/A
	30 Day Follow-Up	-1.09 ± 1.13 (-3.46, 1.11), 93	-0.28 ± 0.85 (-2.17, 1.92), 93	-0.88 ± 1.18 (-4.01, 1.03), 91	-0.32 ± 0.8 (-2.64, 1.55), 91	0.46
	90 Day Follow-Up	-0.86 ± 1.05 (-3.76, 1.24), 77	-0.02 ± 0.78 (-1.64, 2.17), 77	-0.61 ± 1.11 (-3.24, 1.17), 76	-0.13 ± 0.78 (-1.71, 2.1), 76	0.29
Visual Memory	Baseline	-0.83 ± 0.85 (-3.89, 0.78), 115	N/A	-0.72 ± 0.96 (-3.28, 1.59), 117	N/A	N/A
	30 Day Follow-Up	-1.28 ± 0.94 (-3.67, 0.68), 93	-0.46 ± 0.91 (-2.29, 1.56), 92	-1.02 ± 1.03 (-2.94, 1.4), 92	-0.36 ± 0.79 (-1.86, 1.4), 92	0.43
	90 Day Follow-Up	-0.58 ± 0.98 (-3.73, 1.33), 77	0.17 ± 0.86 (-1.7, 2.03), 77	-0.53 ± 0.98 (-3.44, 1.7), 76	0.12 ± 0.81 (-2.01, 1.63), 76	0.69
Mental Status[2]	Baseline	26.12 ± 2.95 (15, 30), 114	N/A	26.07 ± 3.32 (13, 30), 116	N/A	N/A
	30 Day Follow-Up	26.24 ± 2.84 (16, 30), 92	0.41 ± 2.67 (-6, 9), 91	26.82 ± 2.74 (18, 30), 89	0.52 ± 2.55 (-6, 8), 89	N/A
	90 Day Follow-Up	26.56 ± 2.6 (19, 30), 77	0.3 ± 2.76 (-7, 8), 76	27.24 ± 2.47 (18, 30), 76	0.96 ± 2.42 (-5, 8), 76	N/A

		Test Arm		Control Arm		
		Mean ± SD (min, max), n	Change from Baseline	Mean ± SD (min, max), n	Change from Baseline	p-value1
Depression[2]	Baseline	3.33 ± 2.62 (0, 11), 114	N/A	2.7 ± 2.28 (0, 11), 116	N/A	N/A
	30 Day Follow-Up	2.38 ± 2.43 (0, 10), 91	-0.68 ± 2.02 (-6, 4), 90	2.07 ± 2.14 (0, 9), 89	-0.73 ± 1.57 (-8, 4), 89	N/A
	90 Day Follow-Up	2.53 ± 2.66 (0, 11), 77	-0.75 ± 2.22 (-8, 8), 76	2.37 ± 2.75 (0, 12), 76	-0.49 ± 2.16 (-8, 5), 76	N/A
Overall Composite Score	Baseline	-0.66 ± 0.75 (-2.59, 0.88), 117	N/A	-0.63 ± 0.79 (-2.83, 0.91), 117	N/A	N/A
	30 Day Follow-Up	-0.77 ± 0.82 (-2.66, 0.7), 93	-0.09 ± 0.44 (-1.45, 0.99), 93	-0.59 ± 0.79 (-2.55, 0.95), 92	-0.03 ± 0.37 (-1.19, 1.32), 92	0.42
	90 Day Follow-Up	-0.47 ± 0.76 (-2.18, 1), 77	0.18 ± 0.38 (-0.58, 1.1), 77	-0.34 ± 0.72 (-2.86, 0.87), 76	0.18 ± 0.35 (-0.76, 1.12), 76	0.94

[1]p-values based on model adjusted for education, baseline Geriatric Depression Score, and baseline Mini Mental State Score.
[2]Raw score provided for Mental State and Depression.

Appendix H Baseline Demographics and Medical History

Table 45: Baseline Demographics and Medical History

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Demographics					
Age (years)	81.5 ± 8.98 44, 98	82.0 ± 7.95 57, 99	83.4 ± 7.90 54, 98	82.3 ± 8.31 44, 99	0.18
Male	44.7%	47.9%	51.3%	47.9%	0.61
Ethnicity, Hispanic or Latino	0%	2.5% (3/119)	0.8% (1/119)	1.1% (4/358)	0.13
Race					
White/Caucasian	90.8% (109/120)	96.6% (115/119)	96.6% (115/119)	94.7% (339/358)	0.04
Black/African or African American	6.7% (8/120)	0.8% (1/119)	0.8% (1/119)	2.8% (10/358)	
Other	0.8% (1/120)	1.7% (2/119)	1.7% (2/119)	1.4% (5/358)	
Asian	1.7% (2/120)	0.8% (1/119)	0%	0.8% (3/358)	
American Indian or Alaskan Native	0%	0%	0.8% (1/119)	0.3% (1/358)	
Native Hawaiian or Pacific Islander	0%	0%	0%	0%	
Physical Exam					
Weight (lbs)	165.8 ± 43.30 (121)	173.9 ± 52.88 (119)	167.3 ± 38.34 (117)	169.0 ± 45.28 (357)	0.34
Height (in)	65.3 ± 4.25 (121); 54, 77;	65.0 ± 3.68 (119); 57, 75;	65.4 ± 4.15 (118); 57, 74;	65.2 ± 4.03 (358); (95% CI: 64.8, 65.6)	0.76
BMI (kg/m^2)	27.2 ± 5.76 (121); 18, 44; (95% CI: 26.1, 28.2)	28.8 ± 7.48 (119); 14, 60; (95% CI: 27.4, 30.1)	27.4 ± 5.25 (117); 16, 48; (95% CI: 26.5, 28.4)	27.8 ± 6.26 (357); 14, 60; (95% CI: 27.1, 28.4)	0.11
Systolic Blood Pressure (mmHg)	140.5 ± 19.82 (121); (95% CI: 136.9, 144.1)	137.3 ± 21.89 (120);; (95% CI: 133.4, 141.3)	135.1 ± 19.56 (119); 94, 187; (95% CI: 131.6, 138.7)	137.7 ± 20.52 (360); 91, 218; (95% CI: 135.5, 139.8)	0.12
Diastolic Blood Pressure (mmHg)	70.4 ± 12.66 (121); 45, 124; (95% CI: 68.1, 72.7)	68.3 ± 12.86 (120); 43, 108; (95% CI: 66.0, 70.7)	66.3 ± 12.08 (119); 41, 110; (95% CI: 64.1, 68.5)	68.3 ± 12.61 (360); 41, 124; (95% CI: 67.0, 69.7)	0.04

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Heart Rate (beats/minute)	74.6 ± 13.75 (121); 49, 122; (95% CI: 72.1, 77.1)	72.9 ± 14.16 (120); 44, 124; (95% CI: 70.3, 75.4)	71.6 ± 12.63 (118); 45, 108; (95% CI: 69.3, 73.9)	73.0 ± 13.55 (359); 44, 124; (95% CI: 71.6, 74.4)	0.24
Modified Allen's Test					
Normal	99.2% (122/123)	98.3% (119/121)	99.2% (118/119)	98.9% (359/363)	0.85
Abnormal	0.8% (1/123)	1.7% (2/121)	0.8% (1/119)	1.1% (4/363)	
STS Predicted Risk of Mortality Score (PROM)	6.2 ± 3.17 (122); 1, 17; (95% CI: 5.6, 6.7)	6.4 ± 3.28 (121); 1, 20; (95% CI: 5.8, 7.0)	7.5 ± 4.66 (119); 1, 33; (95% CI: 6.7, 8.3)	6.7 ± 3.79 (362); 1, 33; (95% CI: 6.3, 7.1)	0.01
STS PROM Score (Categorized)					
<4	18.0% (22/122)	13.2% (16/121)	10.1% (12/119)	13.8% (50/362)	0.19
4-7	54.1% (66/122)	56.2% (68/121)	53.8% (64/119)	54.7% (198/362)	
8-15	25.4% (31/122)	28.9% (35/121)	28.6% (34/119)	27.6% (100/362)	
>15	2.5% (3/122)	1.7% (2/121)	7.6% (9/119)	3.9% (14/362)	
Medical History					
History of Atrial Fibrillation	30.1% (37/123)	34.7% (42/121)	30.3% (36/119)	31.7% (115/363)	0.69
Paroxysmal	48.6% (18/37)	62.5% (25/40)	50.0% (18/36)	54.0% (61/113)	0.44
Permanent	21.6% (8/37)	7.5% (3/40)	13.9% (5/36)	14.2% (16/113)	
Persistent	29.7% (11/37)	30.0% (12/40)	36.1% (13/36)	31.9% (36/113)	
History of Peripheral Vascular Disease	16.3% (20/123)	14.0% (17/121)	15.1% (18/119)	15.2% (55/363)	0.90
History of Coronary Artery Disease	53.7% (66/123)	50.4% (61/121)	55.5% (66/119)	53.2% (193/363)	0.73
History of Diabetes					
Diabetes Type I	0%	1.7% (2/121)	0%	0.6% (2/363)	0.22
Diabetes Type II	26.8% (33/123)	38.8% (47/121)	37.8% (45/119)	34.4% (125/363)	0.09

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Stroke Severity					
Major	3.3% (4/123)	4.1% (5/121)	0.8% (1/119)	2.8% (10/363)	0.04
Minor	4.9% (6/123)	0%	4.2% (5/119)	3.0% (11/363)	
Previous Transient Ischemic Attack (TIA)	8.1% (10/123)	7.4% (9/121)	6.7% (8/119)	7.4% (27/363)	0.97
Previous Stroke with Permanent Deficit[2]	8.1% (10/123)	4.1% (5/121)	5.0% (6/119)	5.8% (21/363)	0.44
Porcelain Aorta	3.3% (4/123)	1.7% (2/121)	2.5% (3/119)	2.5% (9/363)	0.78
Previous CABG	14.6% (18/123)	18.2% (22/121)	21.0% (25/119)	17.9% (65/363)	0.43
Previous PCI	15.4% (19/123)	17.4% (21/121)	16.8% (20/119)	16.5% (60/363)	0.94
Valve Criteria					
Valve Area (cm^2)	0.7 ± 0.18 (122); 0, 1; (95% CI: 0.7, 0.8)	0.7 ± 0.17 (119); 0, 1; (95% CI: 0.7, 0.7)	0.7 ± 0.20 (118); 0, 1; (95% CI: 0.7, 0.8)	0.7 ± 0.18 (359); 0, 1; (95% CI: 0.7, 0.7)	0.66
Aortic valve area index (cm^2/m^2)	0.4 ± 0.09 (120); 0, 1; (95% CI: 0.4, 0.4)	0.4 ± 0.10 (117); 0, 1; (95% CI: 0.4, 0.4)	0.4 ± 0.10 (116); 0, 1; (95% CI: 0.4, 0.4)	0.4 ± 0.10 (353); 0, 1; (95% CI: 0.4, 0.4)	0.41
Mean aortic valve gradient (mmHg)	41.8 ± 14.65 (121); 3, 89; (95% CI: 39.2, 44.5)	44.2 ± 14.81 (118); 18, 86; (95% CI: 41.5, 46.9)	40.9 ± 13.56 (118); 3, 93; (95% CI: 38.4, 43.3)	42.3 ± 14.38 (357); 3, 93; (95% CI: 40.8, 43.8)	0.18
Peak aortic-jet velocity (m/sec)	4.0 ± 1.00 (97); 0, 6; (95% CI: 3.8, 4.2)	4.1 ± 1.11 (103); 0, 8; (95% CI: 3.9, 4.3)	4.1 ± 0.84 (94); 0, 6; (95% CI: 3.9, 4.2)	4.1 ± 0.99 (294); 0, 8; (95% CI: 3.9, 4.2)	0.55
Neurological, Neurocognitive, Neuroimaging Baseline Exams					
mRS Score	1.0 ± 1.27 (118); 0, 4; (95% CI: 0.8, 1.2)	0.8 ± 1.13 (118); 0, 4; (95% CI: 0.6, 1.1)	1.0 ± 1.11 (115); 0, 4; (95% CI: 0.8, 1.2)	0.9 ± 1.17 (351); 0, 4; (95% CI: 0.8, 1.1)	0.53
NIHSS Score (total)	0.5 ± 1.06 (118); 0, 6; (95% CI: 0.3, 0.7)	0.4 ± 1.52 (118); 0, 14; (95% CI: 0.1, 0.7)	0.3 ± 0.80 (115); 0, 5; (95% CI: 0.2, 0.5)	0.4 ± 1.17 (351); 0, 14; (95% CI: 0.3, 0.5)	0.38
Neurocognitive Z-Score	N/A	-0.7 ± 0.75 (117); -3, 1; (95% CI: -0.8, -0.5)	-0.6 ± 0.79 (117); -3, 1; (95% CI: -0.8, -0.5)	-0.6 ± 0.76 (240); -3, 1; (95% CI: -0.7, -0.5)	0.70

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
T2/FLAIR MRI Lesion Volume (mm^3)	N/A	7377.5 (2562.9, 19181.5), n=114 0.0 min, 205956.7 max	7916.7 (3865.4, 17315.3), n=114 0.0 min, 83153.5 max	7847.9 (3243.2, 17854.5), n=228 0.0 min, 205956.7 max	0.43
NYHA					
I	3.3% (4/120)	3.4% (4/119)	3.4% (4/116)	3.4% (12/355)	0.97
II	15.0% (18/120)	11.8% (14/119)	13.8% (16/116)	13.5% (48/355)	
III	56.7% (68/120)	58.8% (70/119)	53.4% (62/116)	56.3% (200/355)	
IV	25.0% (30/120)	26.1% (31/119)	29.3% (34/116)	26.8% (95/355)	

Note: Continuous data presented as Mean ± SD (n); Min, Max. Categorical data presented using % (n/N).
1 p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.
2 Defined as neurological deficit lasting more than 24 hours confirmed by imaging.

Table 46: Baseline Demographics & Medical History, Observed MRI vs Missing MRI

	Observed MRI (N=189)	Missing MRI (N=51)	Total (N=240)	p-value[1]
Demographics				
Age (years)	82.9 ± 7.62 (189); 54, 98; (95% CI: 81.8, 84.0)	82.0 ± 9.05 (51); 60, 99; (95% CI: 79.4, 84.5)	82.7 ± 7.94 (240); 54, 99; (95% CI: 81.7, 83.7)	0.46
Male (%)	47.6% (90/189)	56.9% (29/51)	49.6% (119/240)	0.27
Ethinicity, Hispanic or Latino	1.1% (2/188)	4.0% (2/50)	1.7% (4/238)	0.20
Race				
White/Caucasian	98.4% (185/188)	90.0% (45/50)	96.6% (230/238)	0.002
Other	0%	8.0% (4/50)	1.7% (4/238)	
Black/African or African American	0.5% (1/188)	2.0% (1/50)	0.8% (2/238)	
Asian	0.5% (1/188)	0%	0.4% (1/238)	
American Indian or Alaskan Native	0.5% (1/188)	0%	0.4% (1/238)	
Native Hawaiian or Pacific Islander	0%	0%	0%	

	Observed MRI (N=189)	Missing MRI (N=51)	Total (N=240)	p-value[1]
Physical Exam				
Weight (lbs)	166.6 ± 38.53 (186); 79, 289; (95% CI: 161.0, 172.	185.6 ± 66.12 (50); 100, 450; (95% CI: 166.8, 204.	170.6 ± 46.27 (236); 79, 450; (95% CI: 164.7, 176.	0.01
Height (in)	65.0 ± 3.74 (187); 57, 75; (95% CI: 64.5, 65.6)	65.8 ± 4.52 (50); 58, 74; (95% CI: 64.5, 67.1)	65.2 ± 3.92 (237); 57, 75; (95% CI: 64.7, 65.7)	0.24
BMI (kg/m²)	27.6 ± 5.57 (186); 14, 49; (95% CI: 26.8, 28.4)	29.8 ± 9.00 (50); 19, 60; (95% CI: 27.3, 32.4)	28.1 ± 6.49 (236); 14, 60; (95% CI: 27.3, 28.9)	0.03
Systolic Blood Pressure (mmHg)	137.2 ± 20.29 (188); 91, 198; (95% CI: 134.3, 140.	132.5 ± 22.19 (51); 94, 192; (95% CI: 126.2, 138.7	136.2 ± 20.75 (239); 91, 198; (95% CI: 133.6, 138.	0.15
Diastolic Blood Pressure (mmHg)	67.6 ± 12.64 (188); 41, 110; (95% CI: 65.8, 69.4)	66.3 ± 12.00 (51); 43, 91; (95% CI: 62.9, 69.6)	67.3 ± 12.49 (239); 41, 110; (95% CI: 65.7, 68.9)	0.50
Heart Rate (beats/minute)	72.2 ± 13.29 (187); 45, 120; (95% CI: 70.3, 74.1)	72.5 ± 13.98 (51); 44, 124; (95% CI: 68.6, 76.5)	72.2 ± 13.41 (238); 44, 124; (95% CI: 70.5, 74.0)	0.87
Modified Allen's Test				
Normal	99.5% (188/189)	96.1% (49/51)	98.8% (237/240)	0.12
Abnormal	0.5% (1/189)	3.9% (2/51)	1.3% (3/240)	
STS PROM Score	6.8 ± 3.94 (189); 1, 33; (95% CI: 6.3, 7.4)	7.4 ± 4.46 (51); 1, 20; (95% CI: 6.1, 8.6)	6.9 ± 4.06 (240); 1, 33; (95% CI: 6.4, 7.5)	0.39
STS PROM Score (Categorized)				
<4	12.2% (23/189)	9.8% (5/51)	11.7% (28/240)	0.55
4-7	56.1% (106/189)	51.0% (26/51)	55.0% (132/240)	
8-15	28.0% (53/189)	31.4% (16/51)	28.8% (69/240)	
>15	3.7% (7/189)	7.8% (4/51)	4.6% (11/240)	
Medical History				
History of Atrial Fibrillation	33.3% (63/189)	29.4% (15/51)	32.5% (78/240)	0.74
Paroxysmal	54.1% (33/61)	66.7% (10/15)	56.6% (43/76)	0.41
Permanent	13.1% (8/61)		10.5% (8/76)	
Persistent	32.8% (20/61)	33.3% (5/15)	32.9% (25/76)	
History of Peripheral Vascular Disease	14.8% (28/189)	13.7% (7/51)	14.6% (35/240)	1.00
History of Coronary Artery Disease	53.4% (101/189)	51.0% (26/51)	52.9% (127/240)	0.76
History of Diabetes				
Diabetes Type I	0.5% (1/189)	2.0% (1/51)	0.8% (2/240)	0.38

	Observed MRI (N=189)	Missing MRI (N=51)	Total (N=240)	p-value[1]
Diabetes Type II	37.6% (71/189)	41.2% (21/51)	38.3% (92/240)	0.63
Previous Stroke with Permanent Deficit[2]	3.2% (6/189)	9.8% (5/51)	4.6% (11/240)	0.06
Stroke Severity				
Major	2.1% (4/189)	3.9% (2/51)	2.5% (6/240)	0.06
Minor	1.1% (2/189)	5.9% (3/51)	2.1% (5/240)	
Previous Transient Ischemic Attack (TIA)	7.4% (14/189)	5.9% (3/51)	7.1% (17/240)	1.00
Porcelain Aorta	2.1% (4/189)	2.0% (1/51)	2.1% (5/240)	1.00
Previous CABG	23.3% (44/189)	5.9% (3/51)	19.6% (47/240)	0.005
Previous PCI	15.9% (30/189)	21.6% (11/51)	17.1% (41/240)	0.40
Valve Criteria				
Valve Area (cm^2)	0.7 ± 0.18 (187); 0, 1; (95% CI: 0.7, 0.7)	0.7 ± 0.18 (50); 0, 1; (95% CI: 0.6, 0.7)	0.7 ± 0.18 (237); 0, 1; (95% CI: 0.7, 0.7)	0.30
Aortic valve area index (cm^2/m^2)	0.4 ± 0.10 (184); 0, 1; (95% CI: 0.4, 0.4)	0.4 ± 0.08 (49); 0, 1; (95% CI: 0.3, 0.4)	0.4 ± 0.10 (233); 0, 1; (95% CI: 0.4, 0.4)	0.02
Mean aortic valve gradient (mmHg)	41.0 ± 13.81 (186); 3, 86; (95% CI: 39.0, 43.0)	48.2 ± 14.62 (50); 21, 93; (95% CI: 44.1, 52.4)	42.5 ± 14.26 (236); 3, 93; (95% CI: 40.7, 44.4)	0.001
Peak aortic-jet velocity (m/sec)	4.0 ± 0.94 (154); 0, 6; (95% CI: 3.9, 4.2)	4.4 ± 1.11 (43); 0, 8; (95% CI: 4.0, 4.7)	4.1 ± 0.99 (197); 0, 8; (95% CI: 4.0, 4.2)	0.04
Neurological, Neurocognitive, Neuroimaging Baseline Exams				
mRS Score	0.9 ± 1.05 (184); 0, 4; (95% CI: 0.7, 1.0)	1.1 ± 1.35 (49); 0, 4; (95% CI: 0.7, 1.5)	0.9 ± 1.12 (233); 0, 4; (95% CI: 0.8, 1.0)	0.21
NIHSS Score (total)	0.3 ± 0.76 (184); 0, 5; (95% CI: 0.2, 0.4)	0.7 ± 2.19 (49); 0, 14; (95% CI: 0.1, 1.3)	0.4 ± 1.22 (233); 0, 14; (95% CI: 0.2, 0.5)	0.03
Neurocognitive Z-Score	-0.6 ± 0.78 (187); -3, 1; (95% CI: -0.7, -0.5)	-0.8 ± 0.73 (47); -2, 0; (95% CI: -1.0, -0.6)	-0.6 ± 0.77 (234); -3, 1; (95% CI: -0.7, -0.5)	0.13
NYHA				
I	2.7% (5/184)	5.9% (3/51)	3.4% (8/235)	0.28
II	13.6% (25/184)	9.8% (5/51)	12.8% (30/235)	
III	58.2% (107/184)	49.0% (25/51)	56.2% (132/235)	
IV	25.5% (47/184)	35.3% (18/51)	27.7% (65/235)	

Note: Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
[1]p-values are testing for statistical differences for in-window vs missing. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.
[2]Defined as neurological deficit lasting more than 24 hours confirmed by imaging.

Appendix I Procedural Characteristics

Table 47: Procedural Characteristics

	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Arch					
Normal	87.6% (106/121)	86.7% (104/120)	78.8% (93/118)	84.4% (303/359)	0.34
Bovine	11.6% (14/121)	12.5% (15/120)	18.6% (22/118)	14.2% (51/359)	
Other	0.8% (1/121)	0.8% (1/120)	2.5% (3/118)	1.4% (5/359)	
Sentinel Device Placement					
Radial	95.0% (114/120)	91.2% (104/114)	N/A	93.2% (218/234)	0.49
Brachial	4.2% (5/120)	7.0% (8/114)	N/A	5.6% (13/234)	
Other	0.8% (1/120)	1.8% (2/114)	N/A	1.3% (3/234)	
TAVR Fluoro Time[2] (min)	18.0 ± 10.78 (91); 2, 42; (95% CI: 15.8, 20.3)	20.9 ± 13.01 (93); 0, 58; (95% CI: 18.3, 23.6)	16.7 ± 11.50 (83); 5, 80; (95% CI: 14.2, 19.2)	18.6 ± 11.91 (267); 0, 80; (95% CI: 17.2, 20.0)	0.05
TAVR Device					
Medtronic CoreValve	3.3% (4/121)	2.5% (3/120)	5.9% (7/118)	3.9% (14/359)	0.72
Medtronic CoreValve Evolut R	29.8% (36/121)	24.2% (29/120)	23.7% (28/118)	25.9% (93/359)	
Edwards SAPIEN XT	19.0% (23/121)	17.5% (21/120)	16.9% (20/118)	17.8% (64/359)	
Edwards SAPIEN 3	47.9% (58/121)	55.8% (67/120)	53.4% (63/118)	52.4% (188/359)	
Procedural Outcome					
Total TAVR Procedure Time (min)	81.7 ± 36.59 (105); 30, 204; (95% CI: 74.6, 88.8)	93.2 ± 51.53 (106); 28, 332; (95% CI: 83.3, 103.1)	74.2 ± 40.98 (99); 15, 228; (95% CI: 66.0, 82.4)	83.3 ± 44.12 (310); 15, 332; (95% CI: 78.3, 88.2)	0.01
Permanent pacemaker implanted (within 7 days from procedure)	20.3% (25/123)	15.7% (19/121)	12.6% (15/119)	16.9% (62/366)	0.28
New onset of Atrial Fibrillation	3.3% (4/123)	4.1% (5/121)	7.6% (9/119)	4.9% (18/366)	0.29
TAVR procedure considered complete[3]	95.8% (114/119)	98.2% (110/112)	N/A	97.0% (224/231)	0.45

Note: Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).
1 p-values are testing for statistical differences across randomized arms. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.
2 Fluoro used during entire TAVR procedure.
3 Deployment of at least one filter (with either the first or second device) during the TAVR procedure without any incidence of investigational device related MACCE.

Table 48: Procedural Characteristics, Observed MRI vs Missing

	Observed MRI (N=189)	Missing (N=51)	Total (N=240)	p-value[1]
Arch				
Normal	80.4% (152/189)	91.8% (45/49)	82.8% (197/238)	0.08
Bovine	18.0% (34/189)	6.1% (3/49)	15.5% (37/238)	
Other	1.6% (3/189)	2.0% (1/49)	1.7% (4/238)	
Sentinel Device Placement				
Radial	92.2% (83/90)	87.5% (21/24)	91.2% (104/114)	0.05
Brachial	7.8% (7/90)	4.2% (1/24)	7.0% (8/114)	
Other	0%	8.3% (2/24)	1.8% (2/114)	
TAVR Fluoro Time[2] (min)	18.3 ± 12.47 (142); 0, 80; \ (95% CI: 16.3, 20.4)	21.4 ± 12.36 (34); 4, 47; (95% CI: 17.1, 25.7)	18.9 ± 12.47 (176); 0, 80; (95% CI: 17.1, 20.8)	0.20
TAVR Device				
Medtronic CoreValve	3.7% (7/189)	6.1% (3/49)	4.2% (10/238)	0.28
Medtronic CoreValve Evolut R	23.8% (45/189)	24.5% (12/49)	23.9% (57/238)	
Edwards SAPIEN XT	15.3% (29/189)	24.5% (12/49)	17.2% (41/238)	
Edwards SAPIEN 3	57.1% (108/189)	44.9% (22/49)	54.6% (130/238)	
Procedural Outcome				
Total TAVR Procedure Time (min)	81.3 ± 44.62 (162); 15, 332; (95% CI: 74.3, 88.2)	94.6 ± 56.77 (43); 32, 276; (95% CI: 77.1, 112.0)	84.0 ± 47.58 (205); 15, 332; (95% CI: 77.5, 90.6)	0.1033
Permanent pacemaker implanted (within 7 days from procedure)	6.3% (12/189)	43.1% (22/51)	14.2% (34/240)	<.0001
New onset of Atrial Fibrillation	5.8% (11/189)	5.9% (3/51)	5.8% (14/240)	1.00
TAVR procedure considered complete[3]	97.8% (88/90)	100.0% (22/22)	98.2% (110/112)	1.00

Note: Continuous data presented as Mean ± SD (n); Min, Max; 95% CI. Categorical data presented using % (n/N).

[1] p-values are testing for statistical differences across regions. Continuous data are compared using ANOVA; categorical data are compared using Fisher's exact test.

[2] Fluoro used during entire TAVR procedure.

[3] Deployment of at least one filter (with either the 1st or 2nd device) during TAVR without any incidence of investigational device related MACCE.

Appendix J Supplementary Safety Tables

Table 49: Adjudicated Adverse Event Summary by Study Arm (Days 0-100)

	Safety Cohort (Safety + Test) N=244		Control Arm N=119	
Event Type	Total Events	**Patients w/Event(s)**	**Total Events**	**Patients w/Event(s)**
Acute Kidney Injury (I, II, and III)	7	2.9% (7)	5	2.5% (3)
Vascular Complication[1]	21	8.6% (21)	9	7.6% (9)
Stroke	13	5.3% (13)	12	9.2% (11)
TIA	1	0.4% (1)	1	0.8% (1)
Death	11	4.5% (11)	4	3.4% (4)
Other[2]	68	23.0% (56)	33	21.0% (25)
Overall	121	34.4% (84)	64	32.8% (39)

[1]All vascular complications, including Sentinel (radial, brachial) and TAVR access
[2]Conduction system injuries, peri-procedural encephalopathy, and misc.

Table 50: Adjudicated Sentinel System-related Serious Adverse Event Summary (Days 0-100)

	Safety Cohort (Safety + Test) N=244	
Event Type	**Total Events**	**Patients w/Event(s)**
Vascular Complication	1	0.4% (1)
Other	1	0.4% (1)
Overall	2	0.8% (2)

Note: Includes events with Probable or Highly Probable relation to the Sentinel system

Table 51: 30-Day MACCE (ITT with all subjects, treating missing as no event)

	Test (Safety+Test)	Control	P-value[1]
ITT			
Any MACCE	7.0% (17/244) [17] (4.1%,10.9%)	9.2% (11/119) [12] (4.7%,15.9%)	0.5299
Death	1.2% (3/244) [3] (0.3%,3.6%)	1.7% (2/119) [2] (0.2%,5.9%)	0.6644
Stroke	5.3% (13/244) [13] (2.9%,8.9%)	8.4% (10/119) [10] (4.1%,14.9%)	0.2600
Disabling	0.8% (2/244) [2] (0.1%,2.9%)	0.8% (1/119) [1] (0.0%,4.6%)	1.0000
Non-disabling	4.5% (11/244) [11] (2.3%,7.9%)	7.6% (9/119) [9] (3.5%,13.9%)	0.2312
AKI (Class 3)	0.4% (1/244) [1] (0.0%,2.3%)	0% (0.0%,3.1%)	1.0000

Note: Data presented as: % of subjects with event (number of subjects with event/subjects per arm) [number of events] (exact 95% CI)
[1] P-Value based on two-sided Fisher's exact test for combined safety and test arms compared to the control arm.

Table 52: 30-day MACCE Rate (Site Comparison)

	Top 4 Sites % patients with event (n patients with event/N patients) [exact 95% CI]	Remaining Sites % patients with event (n patients with event/N patients) [exact 95% CI]	p-value[1]
Per Protocol			
Any MACCE	8.3% (19/230) [5.0%, 12.6%)	7.6% (9/119) [3.5%, 13.9%]	1.00
Death	1.7% (4/230) [0.5%, 4.4%]	0.8% (1/119) [0.0%, 4.6%]	0.67
Stroke	7.0% (16/230) [4.0%, 11.1%]	5.9% (7/119) [2.4%, 11.7%]	0.82
Disabling	0.9% (2/230) [0.1%, 3.1%]	0.8% (1/119) [0.0%, 4.6%]	1.00
Non-disabling	6.1% (14/230) [3.4%, 10.0%]	5.0% (6/119) [1.9%, 10.7%]	0.81
AKI (Class 3)	0% [0.0%, 1.6%]	0.8% (1/119) [0.0%, 4.6%]	0.34

[1]p-value based on two-sided Fisher's exact test for top 4 enrolling sites vs the remaining sites.

Table 53: 90-Day MACCE Rate

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients) [exact 95% CI]	Control Arm % patients with event (n patients with event/N patients) [exact 95% CI]	P-value[1]
ITT			
Any MACCE	11.3% (24/213) [7.4%,16.3%]	12.9% (12/93) [6.8%,21.5%]	0.70
Death	5.2% (11/213) [2.6%,9.1%]	3.3% (3/92) [0.7%,9.2%]	0.56
Stroke (all)	6.4% (13/202) [3.5%,10.8%]	12.0% (11/92) [6.1%,20.4%]	0.11
Disabling Stroke	1.0% (2/202) [0.1%,3.5%]	3.3% (3/90) [0.7%,9.4%]	0.17
Non-disabling Stroke	5.4% (11/202) [2.7%,9.5%]	9.9% (9/91) [4.6%,17.9%]	0.21
AKI (Class 3)	0.5% (1/203) [0.0%,2.7%]	0% [0.0%,4.1%]	1.00
As Treated			

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients) [exact 95% CI]	Control Arm % patients with event (n patients with event/N patients) [exact 95% CI]	P-value[1]
Any MACCE	9.8% (20/205) [6.1%,14.7%]	15.8% (16/101) [9.3%,24.4%]	0.13
Death	3.4% (7/205) [1.4%,6.9%]	7.0% (7/100) [2.9%,13.9%]	0.24
Stroke (all)	6.6% (13/198) [3.5%,11.0%]	11.5% (11/96) [5.9%,19.6%]	0.17
Disabling Stroke	1.0% (2/198) [0.1%,3.6%]	3.2% (3/94) [0.7%,9.0%]	0.33
Non-disabling Stroke	5.6% (11/198) [2.8%,9.7%]	9.5% (9/95) [4.4%,17.2%]	0.22
AKI (Class 3)	0.5% (1/199) [0.0%,2.8%]	0% [0.0%,3.9%]	1.00

Note: Based on patients with 90-day follow-up or who experienced an event within 90 days
[1]P-Value based on two-sided Fisher's exact test for combined safety and Test Arms compared to the Control Arm.

Table 54: Incidence of Major Vascular Complications

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients per arm) [number of events] (exact 95% CI)	Control Arm % patients with event (n patients with event/N patients per arm) [number of events] (exact 95% CI)
ITT		
During the index procedure[1]	6.1% (15/244) [15] (3.5%, 9.9%)	5.0% (6/119) [6] (1.9%, 10.7%)
Radial Artery	0% (0.0%, 1.5%)	N/A
Brachial Artery	0% (0.0%, 1.5%)	N/A
Within 30 days of the index procedure[1]	2.5% (6/244) [6] (0.9%, 5.3%)	0.8% (1/119) [1] (0.0%, 4.6%)
Radial Artery	0% (0.0%, 1.5%)	N/A
Brachial Artery	0.4% (1/244) [1] (0.0%, 2.3%)	N/A
As Treated		
During the index procedure[1]	6.5% (15/231) [15] (3.7%, 10.5%)	4.7% (6/128) [6] (1.7%, 9.9%)

	Safety Cohort (Safety + Test) % patients with event (n patients with event/N patients per arm) [number of events] (exact 95% CI)	**Control Arm** % patients with event (n patients with event/N patients per arm) [number of events] (exact 95% CI)
Radial Artery	0% (0.0%, 1.6%)	N/A
Brachial Artery	0% (0.0%, 1.6%)	N/A
Within 30 days of the index procedure[1]	2.6% (6/231) [6] (1.0%, 5.6%)	0.8% (1/128) [1] (0.0%, 4.3%)
Radial Artery	0% (0.0%, 1.6%)	N/A
Brachial Artery	0.4% (1/231) [1] (0.0%, 2.4%)	N/A

Note: All randomized patients who received a TAVR evaluable for this analysis
[1]All major vascular complications, including TAVR access as well as Sentinel (radial, brachial)

Appendix K Serious Adverse Events

Site reported rates of events for Safety Cohort patients that received the Sentinel System were similar to rates reported for patients in the Control Arm who did not receive the Sentinel System. No findings were noted by the DSMB.

Table 55: Serious Adverse Event Summary – Site Reported (Days 0-100)

	Safety Cohort (Safety + Test) N=244		Control Arm N=119	
Event Type	**Total Events**	**Patients w/Event(s)**	**Total Events**	**Patients w/Event(s)**
Abnormal Lab Value	5	2.0% (5)	1	0.8% (1)
Access Site Complication or Injury Including Infection or Thrombus	12	4.9% (12)	5	4.2% (5)
Access Site Hematoma	2	0.8% (2)	0	0% (0)
Acute Kidney Injury, Stage 1	2	0.8% (2)	0	0% (0)
Acute Kidney Injury, Stage 3	2	0.8% (2)	0	0% (0)
Anemia	8	3.3% (8)	1	0.8% (1)
Arrhythmia	9	3.3% (8)	6	5.0% (6)
Bleed, Operative or Post-Operative	3	1.2% (3)	1	0.8% (1)
Cardiac Arrest	4	1.6% (4)	6	5.0% (6)
Cardiac Failure or Low Cardiac Output	2	0.8% (2)	0	0% (0)
Cardiogenic Shock	0	0% (0)	1	0.8% (1)
Conduction System Injury	55	21.7% (53)	19	16.0% (19)
Congestive Heart Failure (CHF)	10	4.1% (10)	4	3.4% (4)
Death, Cardiovascular	4	1.6% (4)	2	1.7% (2)
Death, Non-Cardiovascular	1	0.4% (1)	0	0% (0)
Diarrhea	3	0.8% (2)	0	0% (0)
Dyspnea	1	0.4% (1)	0	0% (0)
Embolism	0	0% (0)	1	0.8% (1)
Endocarditis	1	0.4% (1)	0	0% (0)
Epistaxis	1	0.4% (1)	0	0% (0)
Exercise Intolerance or Weakness	1	0.4% (1)	0	0% (0)
Fever	2	0.8% (2)	1	0.8% (1)
GI Bleed	4	1.2% (3)	2	1.7% (2)
Hematoma	0	0% (0)	1	0.8% (1)
Hematuria	1	0.4% (1)	1	0.8% (1)
Hypertension	3	1.2% (3)	1	0.8% (1)
Hypotension	6	2.5% (6)	0	0% (0)
Infection, Including Systemic	4	1.6% (4)	2	0.8% (1)
Ischemia, Coronary	0	0% (0)	1	0.8% (1)
Ischemia, Limb	2	0.4% (1)	0	0% (0)
Myocardial Infarction	1	0.4% (1)	0	0% (0)
Nausea	1	0.4% (1)	1	0.8% (1)
Neurological Event – Imaging Only	1	0.4% (1)	1	0.8% (1)
Other	24	9.4% (23)	11	9.2% (11)
Pain, Specify	4	1.6% (4)	2	1.7% (2)
Paravalvular or Transvalvular Leak	0	0% (0)	1	0.8% (1)
Pericardial Effusion	0	0% (0)	1	0.8% (1)
Pleural Effusion	4	1.6% (4)	3	2.5% (3)
Pneumonia	1	0.4% (1)	4	3.4% (4)
Renal Insufficiency or Renal Failure	0	0% (0)	1	0.8% (1)
Respiratory Failure	2	0.8% (2)	1	0.8% (1)
Respiratory Insufficiency	1	0.4% (1)	1	0.8% (1)

	Safety Cohort (Safety + Test) N=244		Control Arm N=119	
Event Type	**Total Events**	**Patients w/Event(s)**	**Total Events**	**Patients w/Event(s)**
Stroke CVA	6	2.5% (6)	4	3.4% (4)
Stroke CVA/TIA	1	0.4% (1)	2	1.7% (2)
Syncope	2	0.8% (2)	2	1.7% (2)
TIA	0	0% (0)	2	1.7% (2)
Urinary Retention	5	2.0% (5)	4	3.4% (4)
Urinary Tract Infection	1	0.4% (1)	2	1.7% (2)
Vascular Procedure Complication	3	1.2% (3)	0	0% (0)
Vascular Pseudoaneurysm	2	0.8% (2)	1	0.8% (1)
Vessel Injury	3	1.2% (3)	2	1.7% (2)
Overall	210	48.4% (118)	102	47.9% (57)

Note: Includes events with Probable or Definite relation to the TAVR procedure (or Sentinel procedure for vascular complication events)

Appendix L Poolability

The primary efficacy endpoint data across study sites was determined to be poolable.

Poolability across sites for safety data showed differences at the site level. Institutional differences in valve choice, anesthesia practice, and other TAVR standards of care were found and may have contributed to the individual site safety profiles

The effect of site-to-site safety outcome variability was likely minimal given that there were no significant differences seen from site to site in new lesion volume measured by DW-MRI, a robust and highly quantitative measure of embolic events leading to subtle neurological symptoms. The study had 3 disabling strokes which were evenly distributed across 3 sites.

Table 56: Poolability Analyses for New Lesion Volume (Protected Territories)

Variable	Test Arm Median (IQR), n	Control Arm Median (IQR), n	Interaction p-value
Site			
001	118.7 (50.1, 435.1), n=25	172.7 (40.9, 350.7), n=24	0.31
002	196.4 (64.6, 559.6), n=13	98.2 (33.3, 233.3), n=12	
003	97.6 (55.4, 379.7), n=19	208.3 (65.3, 527.3), n=18	
004	130.5 (81.7, 299.3), n=4	50.1 (33.0, 120.0), n=4	
005	179.3 (60.4, 274.2), n=6	166.1 (0.0, 519.4), n=7	
006	118.7 (35.6, 619.6), n=7	66.9 (0.0, 265.0), n=8	
007	756.4 (108.4, 2000.6), n=4	568.2 (34.3, 1149.6), n=4	
008	300.9 (242.6, 359.3), n=2	309.8 (52.7, 566.9), n=2	
010	414.0 (7.9, 414.0), n=3	2.6 (0.0, 5.3), n=2	
011	n=0	1176.0 (1176.0, 1176.0), n=1	
012	200.4 (55.4, 345.4), n=2	0.0 (0.0, 0.0), n=1	
013	64.6 (64.6, 64.6), n=1	2222.4 (199.7, 4245.1), n=2	
014	1368.8 (592.3, 2259.7), n=4	541.8 (239.9, 1260.4), n=6	
015	435.1 (97.6, 2214.8), n=3	856.9 (106.8, 1500.3), n=4	
016	319.0 (319.0, 319.0), n=1	n=0	
018	20.2 (20.2, 20.2), n=1	205.9 (205.9, 205.9), n=1	
019	136.1 (24.4, 468.0), n=22	227.1 (137.1, 465.4), n=22	
021	129.6 (84.8, 659.4), n=4	1793.8 (1793.8, 1793.8), n=1	
Site (small sites combined)			

Variable	Test Arm Median (IQR), n	Control Arm Median (IQR), n	Interaction p-value
001	118.7 (50.1, 435.1), n=25	172.7 (40.9, 350.7), n=24	0.36
002	196.4 (64.6, 559.6), n=13	98.2 (33.3, 233.3), n=12	
003	97.6 (55.4, 379.7), n=19	208.3 (65.3, 527.3), n=18	
004	130.5 (81.7, 299.3), n=4	50.1 (33.0, 120.0), n=4	
005	179.3 (60.4, 274.2), n=6	166.1 (0.0, 519.4), n=7	
006	118.7 (35.6, 619.6), n=7	66.9 (0.0, 265.0), n=8	
007	756.4 (108.4, 2000.6), n=4	568.2 (34.3, 1149.6), n=4	
010	414.0 (7.9, 414.0), n=3	2.6 (0.0, 5.3), n=2	
014	1368.8 (592.3, 2259.7), n=4	541.8 (239.9, 1260.4), n=6	
015	435.1 (97.6, 2214.8), n=3	856.9 (106.8, 1500.3), n=4	
019	136.1 (24.4, 468.0), n=22	227.1 (137.1, 465.4), n=22	
021	129.6 (84.8, 659.4), n=4	1793.8 (1793.8, 1793.8), n=1	
Combined sites with n<5	242.6 (55.4, 345.4), n=7	205.9 (52.7, 1176.0), n=7	
Sex			
Female	129.9 (50.1, 435.1), n=63	208.6 (65.3, 520.8), n=58	0.35
Male	148.8 (55.4, 468.0), n=58	171.4 (35.6, 303.2), n=61	
Valve Type			
Medtronic CoreValve	1560.9 (7.9, 1930.1), n=3	216.2 (0.0, 1500.3), n=7	0.15
Medtronic CoreValve Evolut R	147.7 (64.6, 435.1), n=29	277.5 (141.1, 543.8), n=28	
Edwards SAPIEN XT	1560.9 (7.9, 1930.1), n=3	216.2 (0.0, 1500.3), n=7	
Edwards SAPIEN 3	147.7 (64.6, 435.1), n=29	277.5 (141.1, 543.8), n=28	

Table 57: Poolability Analyses for 30-Day MACCE

Variable	Safety Cohort (Safety + Test) n/N (%)	p-value[1]
Site		
001	1/49 (2.0%)	0.0230
002	1/26 (3.8%)	
003	1/39 (2.6%)	
004	0/8 (0.0%)	
005	1/12 (8.3%)	
006	1/15 (6.7%)	
007	0/8 (0.0%)	
008	0/4 (0.0%)	
010	2/6 (33.3%)	
011	1/1 (100.0%)	
012	0/5 (0.0%)	
013	1/3 (33.3%)	
014	0/9 (0.0%)	
015	0/6 (0.0%)	
016	0/1 (0.0%)	
018	0/1 (0.0%)	
019	8/44 (18.2%)	
021	1/7 (14.3%)	
Site (small sites combined)		
001	1/49 (2.0%)	0.0597
002	1/26 (3.8%)	
003	1/39 (2.6%)	
004	0/8 (0.0%)	
005	1/12 (8.3%)	
006	1/15 (6.7%)	
007	0/8 (0.0%)	
010	2/6 (33.3%)	
014	0/9 (0.0%)	
015	0/6 (0.0%)	
019	8/44 (18.2%)	
021	1/7 (14.3%)	
Combined sites with n<5	2/15 (13.3%)	

Variable	Safety Cohort (Safety + Test) n/N (%)	p-value[1]
Sex		
Female	13/131 (9.9%)	0.1403
Male	5/113 (4.4%)	
Valve Type		
Medtronic CoreValve	2/7 (28.6%)	0.0411
Medtronic CoreValve Evolut R	7/65 (10.8%)	
Edwards SAPIEN XT	4/44 (9.1%)	
Edwards SAPIEN 3	5/125 (4.0%)	

[1]P-values based on Fisher's exact test for sex and valve type and MC approximation for exact test for Site

(b)(4)

Appendix N Supplemental Neurocognitive Correlation Tables

Includes only MRI scans and Neurocognitive exams within window.

Table 60: Correlation of 2-7 Day DW-MRI New Lesion Volume (log transformed) with Change in Neurocognitive Battery Composite Z-Score

	Test Arm r, (n), p-value	Control Arm r, (n), p-value
2 to 7 Days Post-TAVR	-0.53 (49) p = <.0001	-0.25 (53) p = 0.08
30 Day Follow-Up[1]	-0.21 (74) p = 0.07	-0.20 (72) p = 0.09
90 Day Follow-Up[2]	-0.24 (54) p = 0.08	-0.10 (55) p = 0.45

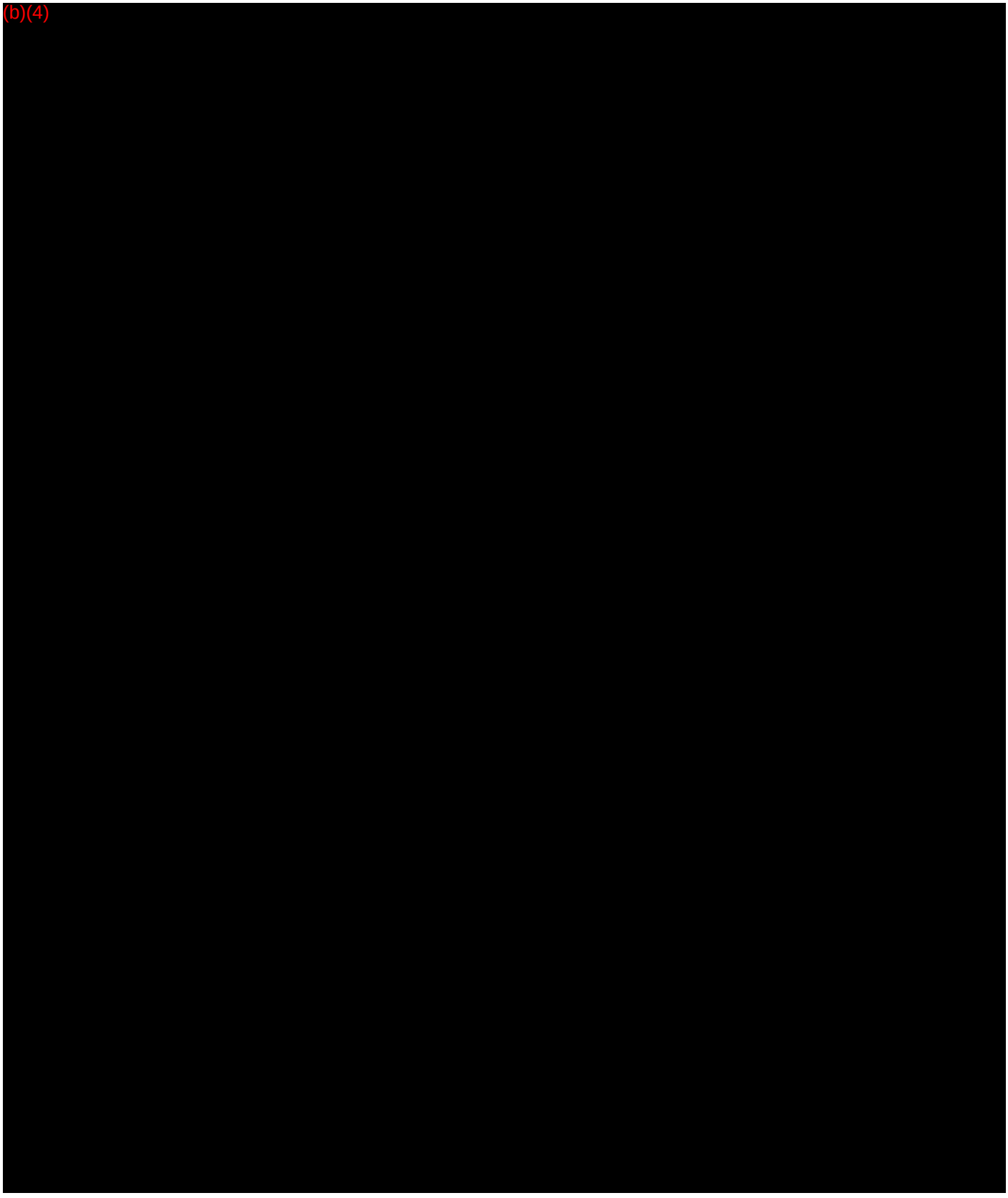
[1]23-45 days
[2]46-100 days

Table 61: Correlation of Day 30 T2/FLAIR New Lesion Volume (log transformed) with Change in Neurocognitive Battery Composite Z-Score

	Test Arm r, (n), p-value	Control Arm r, (n), p-value
30 Day Follow-Up[1]	-0.04 (68) p = 0.74	-0.16 (63) p = 0.20
90 Day Follow-Up[2]	-0.06 (50) p = 0.70	-0.07 (47) p = 0.64

[1]23-45 days
[2]46-100 days

(b)(4)



Appendix P MRI Acquisition and Analysis Methodology

Brain MRI assessments were performed at baseline, 2-7 days and 30 days post procedure. MRI scans were obtained according to a protocol provided by the MRI reading center (Buffalo Neuroimaging Analysis Center, Buffalo, NY, USA) that also performed all quantitative analysis of MRI scans in a blinded manner. MR images at each site were acquired only on a 3 Tesla certified and validated system at 0, 2-7 and 30 days. Diffusion weighted images (DWI) were acquired with a 2D echo planar sequence with one b=0 image and 3 orthogonal diffusion directions with b=1000 s/mm^1. Additional recommended parameters were: repetition time (TR) = 13000ms, echo time (TE) = 100ms, slice thickness = 3mm (no gap), acquisition matrix 204 x 156, final voxel size = 1.25mm x 1.25mm x 3.0mm. DWI images were required at baseline and 2-7 days post procedure on all evaluable imaging cohort patients. Fluid attenuated inversion recovery (FLAIR) images were acquired with a 2D spin echo inversion recovery sequence with the following recommended parameters: inversion time (TI) of 2580ms, TR = 9730ms, TE=92ms, slice thickness = 2mm (no gap), acquisition matrix 256 x 186, final voxel size = 0.94mm x 1.17mm x 2.0mm. The FLAIR images were required at baseline and 30 days post procedure on all evaluable imaging cohort patients. High resolution T1-weighted images (hires-T1) recall gradient-echo (GRE) recommended parameters were: TR = 1690ms, TE=2.57ms, flip angle (FA) = 12, TI=1100ms, slice thickness = 1.5mm (no gap), acquisition matrix 256 x 224, final voxel size = 1.00mm x 1.00mm x 1.5mm. Finally, either a manufacturer-based dual-echo GRE sequence was used to acquire B0 field maps, or the DWI images were acquired with two opposite phase encoding directions. Minor site-specific deviations were allowed to accommodate individual scanner capabilities, provided they were approved by MR physicists at the reading center and were acquired consistently within the site.

DWI acquisitions are subject to artifacts, including eddy current distortions, susceptibility-induced warping, and signal dropout. Although these do not have a substantial impact on clinical assessment of large lesions associated with stroke or transient ischemic attack (TIA), they can be large relative to the small embolic lesions resulting from the TAVI procedure (distortions may be on the order of 1cm, while lesions may be as small as a few mm). Therefore, additional pre-processing steps were taken to control for this. First, the raw DWI images were corrected for distortions using FMRIB's FSL FDT library.[2] This was accomplished using either directly acquired fieldmaps or by computing the field map from paired, phase-reversed DWI acquisitions.[3] Next, the diffusion b=0 (b0) and three corrected b=1000 diffusion-encoded raw images were combined to create trace and apparent diffusivity coefficient (ADC) images.

To facilitate direct longitudinal analysis, all within-subject scans were co-registered to each subject's baseline FLAIR image using FLIRT with 6 degrees of freedom.[7] Because the lesions are often small, subtraction imaging was also employed to increase lesion salience.[4] Aligned baseline DWI and FLAIR images were voxel-wise subtracted from follow-up images to produce direct change maps. To facilitate this subtraction approach, additional pre-processing steps were performed. First, low-frequency spatial intensity inhomogeneities on FLAIR images were corrected using N3.[5] Corrected FLAIR and DWI trace images were further standardized by applying a piecewise-linear histogram adjustment method to compensate for scan-to-scan variability in absolute intensity.[6]

Lesions were delineated on corrected and aligned 2-7, and 30 day DWI trace images and 30 day FLAIR images using a semi-automated contouring technique provided by the JIM software package, with simultaneous reference to the ADC and subtraction images (Figure 1).[8] Using this approach, a

trained operator identified lesions individually, and for each lesion an assistive algorithm delineated a highly reproducible iso-contour at the maximum local gradient. The operator viewed all images and change maps simultaneously to increase confidence, and also coded lesions as new or persistent.

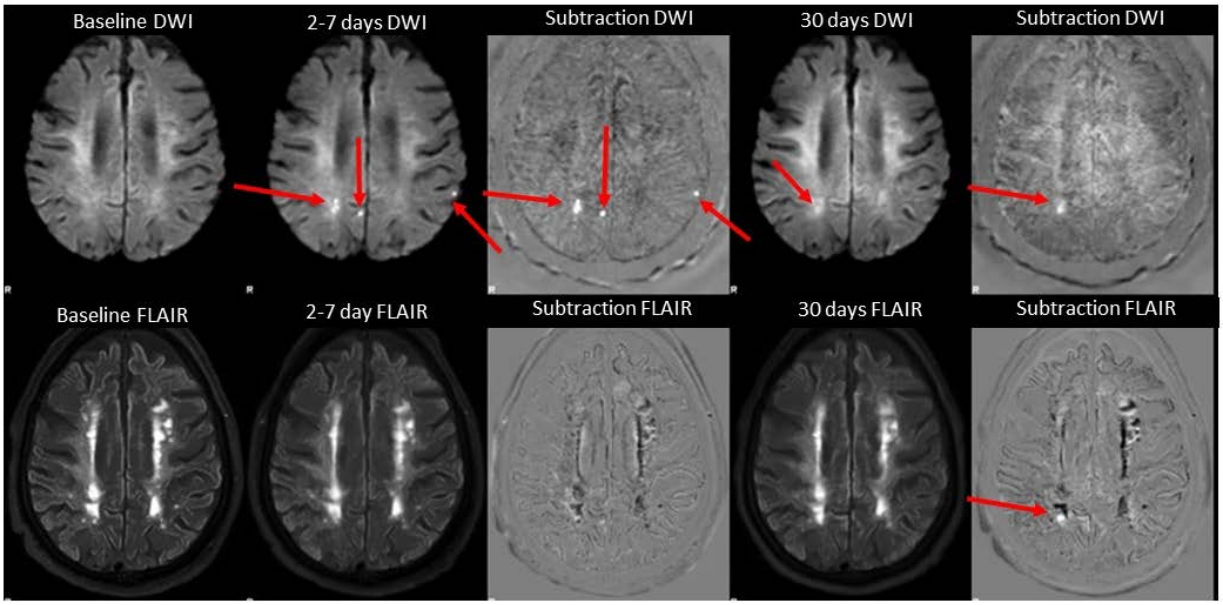


Figure 1. MRI analysis of new DWI lesion volume and number. Lesions were delineated on corrected and aligned DWI and FLAIR images using a semi-automated contouring technique provided by the JIM software package, with simultaneous reference to the subtraction images. **Legend:** FLAIR-fast attenuated inversion recovery, DWI-diffusion-weighted image.

In addition to lesion counts and volumetry, vascular territory was assessed using an atlas-based technique (Figure 2). For this purpose, a vascular territory atlas was manually created in the standard MNI 152 template space[9] based on existing literature,[10] and including 28 separate regions. Individual hires-T1 images were used to non-linearly align this atlas to individual lesion maps. First, individuals' hires-T1 images were corrected for intensity inhomogeneity using N3, then aligned to the MNI 152 template using a two-stage process consisting of an initial rigid-body co-registration followed by composition with a warp field obtained from a non-linear warping technique.[11] These transforms were then inverted, and applied to the original atlas. Lesion number and volume within each vascular territory were than assessed separately.

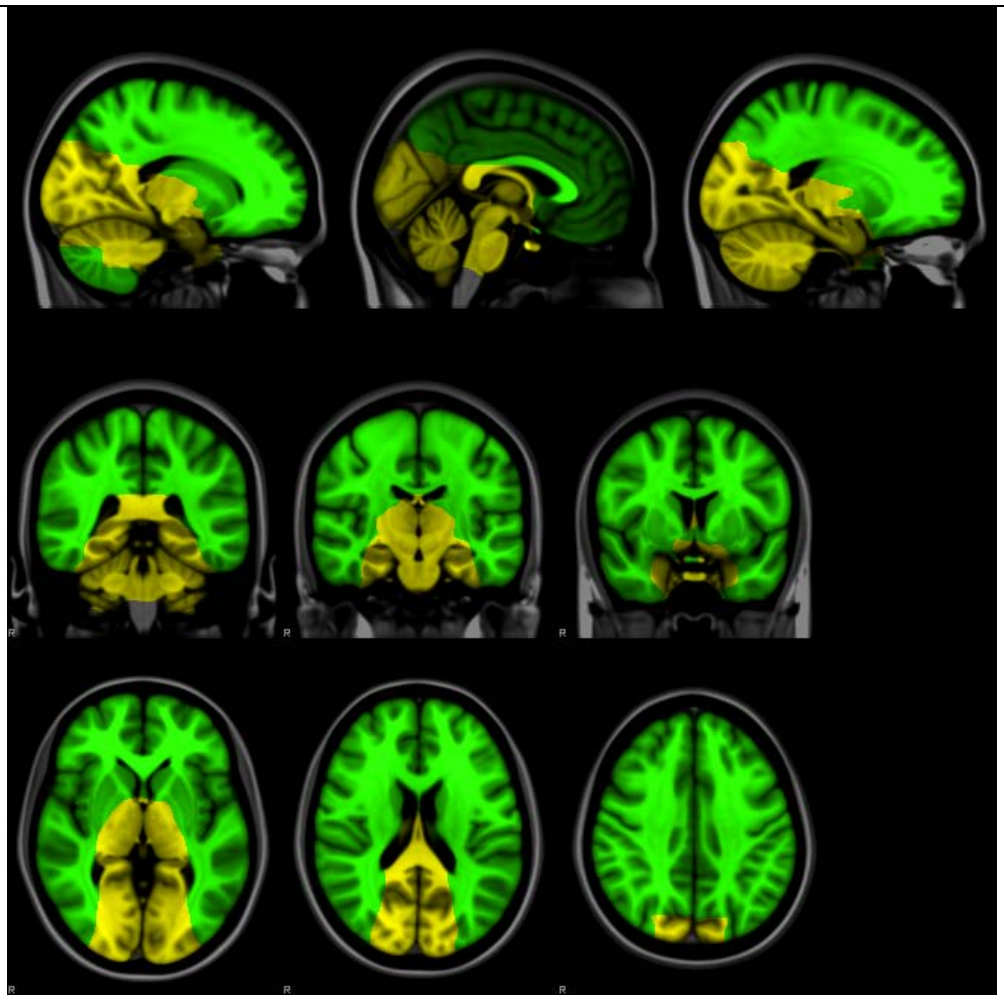


Figure 2. Protected and unprotected territories by Sentinel filter. In green (~ 74% of the brain volume) are shown protected vascular territories belonging to anterior and middle cerebral central and terminal branches, and right posterior inferior cerebellar arteries; in yellow (representing vascular territories of posterior cerebral central and terminal branches, anterior choroidal, superior cerebellar, anterior inferior cerebellar, basilar and left posterior inferior cerebellar arteries) are shown unprotected territories (~ 26% of the brain volume). Individual hires-3D-T1 images were used to non-linearly align the atlas to individual lesion maps.

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