FDA Executive Summary

Circulatory System Devices Panel Meeting

February 23, 2017

DEN160043

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

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1 Introduction

This is an Executive Summary for DEN160043. The submission was reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

Claret Medical, Inc. is requesting their De Novo submission be granted in order to market their Sentinel® Cerebral Protection System (hereinafter referred to as the Sentinel System) for use in patients undergoing transcatheter aortic valve replacement (TAVR). The sponsor proposed the device be 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 patients must meet criteria per the labeling of the TAVR system being used and must also have diameters of the arteries at the site of filter placement between 9-15mm for the brachiocephalic artery and 6.5-10mm in the left common carotid artery.

This request is based upon the results of the Cerebral Protection in Transcatheter Aortic Valve Replacement – The SENTINEL Study, which was a clinical study conducted under IDE G130276. This was a prospective, multi-center, randomized trial that compared outcomes in TAVR patients who had cerebral protection with the Sentinel System versus those who did not have protection. A total of four hundred twenty eight (428) subjects (65 roll-in and 363 randomized) were enrolled at 19 sites in the United States and Germany. Three hundred and sixty-three (363) patients were randomized and enrolled into three study arms using a 1:1:1 randomization ratio (Test=121; Safety=123; Control=119). The Safety Cohort (Test and Safety Arms) received the Sentinel System and patients in the Control Arm did not receive the Sentinel System during TAVR. The primary safety endpoint for the study compared the rate of adjudicated Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days to a performance goal (PG) derived from historical data. The results show that the pre-specified safety criterion was met. The primary effectiveness assessment included a combination of two criteria: statistical superiority (Criterion #1) and observed clinical treatment effect (Criterion #2) in reducing DW-MRI (diffusion-weighted magnetic resonance imaging) lesions post-TAVR in protected territories. Study success required that both criteria be met. The data

did not show a statistically significant reduction in median total new lesion volume in protected territories between the Imaging Cohort Arms (Test and Control) as assessed by DW-MRI at Day 2-7 post-procedure; therefore the statistical superiority criterion (Criterion #1) was not met. The sponsor did demonstrate that the observed ratio of the median total new lesion volumes in protected territories showed ≥ 30% reduction in favor of the Test Arm as compared to the Control Arm; therefore, the observed clinical treatment effect criterion (Criterion #2) was met.

In addition to the endpoints assessed above, multiple additional analyses were performed that provide important information about relevant clinical and imaging outcomes.

2 Device Description

The Sentinel System (Figure 1) is a 6 French, 95cm working length, single use, temporary, percutaneously delivered embolic protection catheter inserted into the right radial or brachial artery. The Sentinel System employs two embolic filters (nitinol frames with laser drilled (140 micron) polyurethane film), one delivered to the brachiocephalic artery (Proximal Filter), and one to the left common carotid artery (Distal Filter). The Proximal Filter measures 15mm in diameter while the Distal Filter measures 10mm in diameter. Target vessel sizes are shown in Table 1 and Figure 2. Following the percutaneous valve placement procedure, the system is removed.

Figure 1: Sentinel Cerebral Protection System

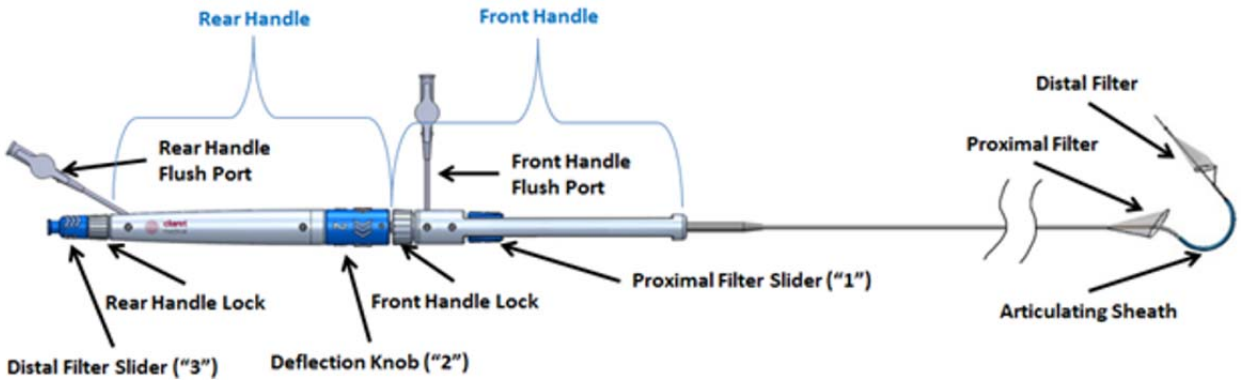


Figure 2: Sentinel System Target Vessel Sizes

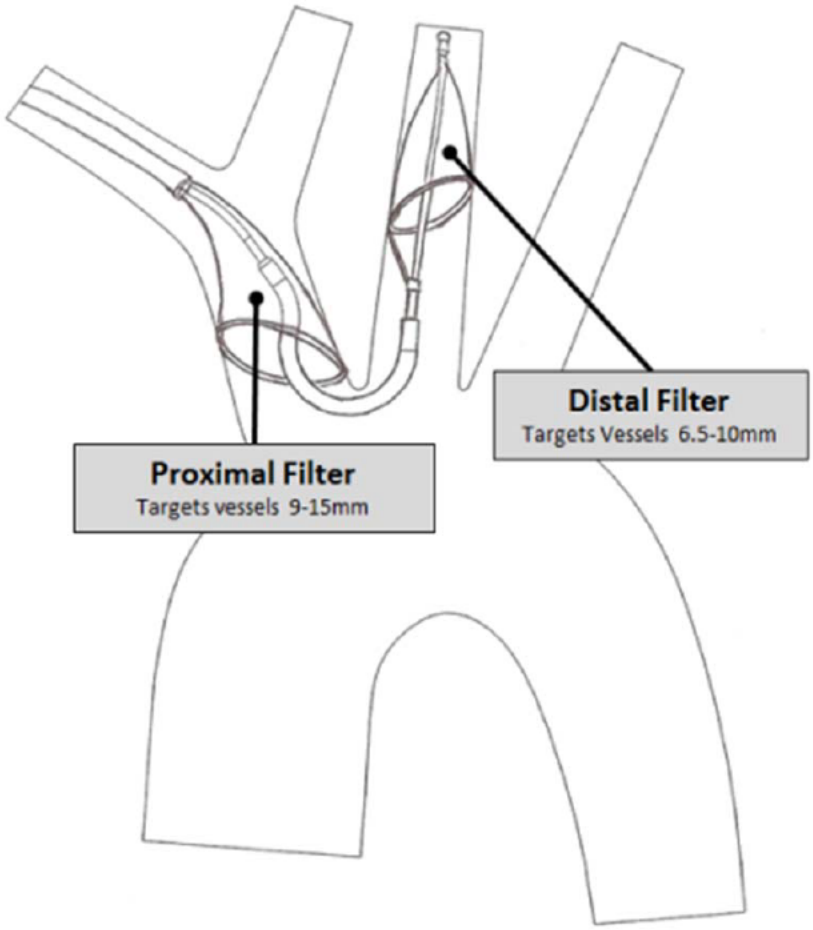


Table 1: Sentinel System Filter Sizing

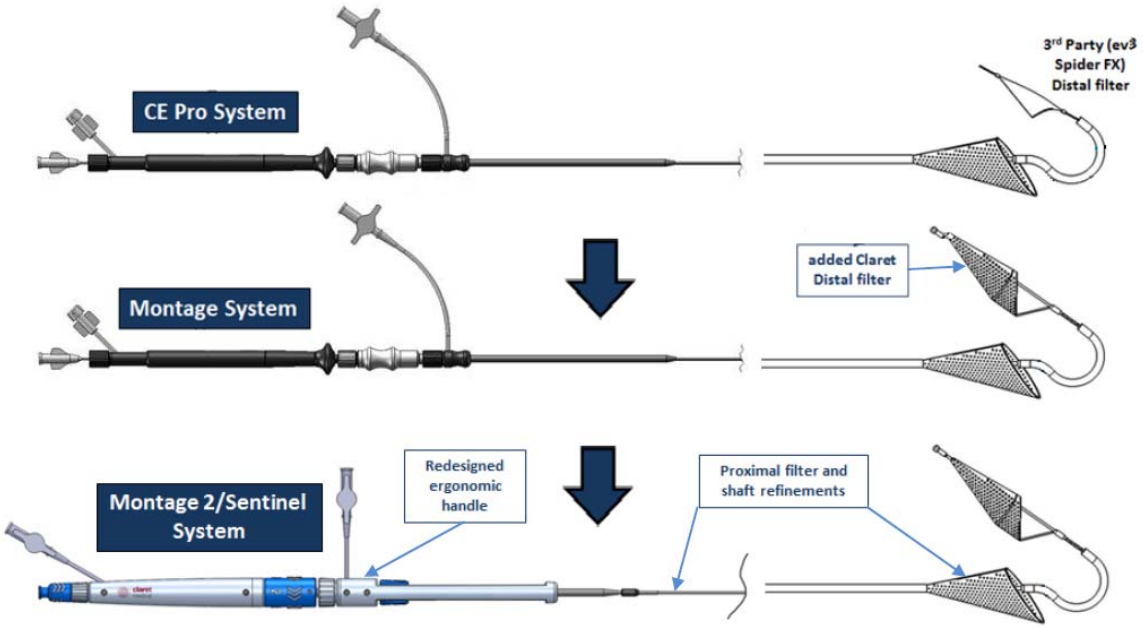
Proximal Filter Size (mm)	Target Proximal Vessel Size (mm)	Distal Filter Size (mm)	Target Distal Vessel Size (mm)
15	9.0 – 15.0	10	6.5 – 10.0

FDA Comment 1: The device is designed to "protect" three of the four cerebral vessels. Protected vessels include the right carotid and right vertebral arteries with proximal filter placement in the brachiocephalic artery as well as the left carotid artery with distal filter placement in the left common carotid artery. There is no protection of the cerebral circulation supplied by the left vertebral artery.

The Sentinel System is a 3rd generation embolic protection device and is a design evolution of the original CE Pro Embolic Protection System (hereinafter referred to as the CE Pro System), as shown in Figure 3 below. The original CE Pro System utilized a commercially available third-party single embolic filter (ev3 SpiderFX) for the Distal Filter which was loaded into the CE Pro System in the

sterile field by the operating physician prior to insertion into the patient. The Montage System was the result of integrating a Claret-designed Distal Filter into the CE Pro System as show in Figure 3 below. Finally, modifying the catheter handle resulted in the Montage 2/Sentinel System. The Sentinel System uses the same working (distal) end of the Montage Dual Filter System. The primary difference between the Sentinel System and its direct predecessor Montage System is the ergonomic device handle and an additional 5cm catheter working length. Other minor changes were also made and supported by non-clinical testing. The Montage System received CE Mark in October 2011, and the Montage 2 System received the CE Mark in February 2013. The Sentinel System received CE Mark in December 2013.

Figure 3: Claret Medical, Inc. device development history



3 Clinical Context

Strokes associated with TAVR procedures are known to occur and reducing these events is a particular area of interest. The mechanism of stroke is thought to be related to procedural mechanical manipulation of endovascular devices and is believed to be especially associated with atheroemboli and calcific debris arising from the aortic root[1]. The mechanism of action of the current device is to offer protection against those procedural embolic events. Stroke rates with TAVR have been regularly documented to be higher than those with surgical valve

[1] Athappan G, Gajulapalli RD, Sengodan P, Bhardwaj A, Ellis SG, Svensson L, Tuzcu EM, Kapadia SR. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. J Am Coll Cardiol. 2014;63:2101–2110.

placement[2] currently limiting the patient population considered for TAVR. The reported 30-day clinical stroke rate with TAVR in observational studies and clinical trials is approximately 2-5%[3] and ischemic cerebral infarcts detected by Diffusion-Weighted MR Imaging (DW-MRI) are greater than 80%[4]. Given the differential stroke rates between surgical and percutaneous valve replacement and the evidence that embolic cerebral infarcts by imaging occur in most TAVR patients, both reducing these events and discerning the clinical impact of "non-clinical" stroke events are areas of interest. For example, one issue is whether subtle neurological and neurocognitive deficits result from these "non-clinical" infarcts. The current clinical data collected with the Sentinel Cerebral Protection System provide significant insight into this area of clinical inquiry.

FDA Comment 2: In consideration of the stroke rate during TAVR, discernment of stroke reduction in patients who have protection with the Sentinel System compared to those who do not have protection would necessitate a very large sample size to show a significant difference. In consideration of FDA's "least burdensome principles" for medical device development and the dynamic TAVR field, FDA worked with the sponsor to develop an image-based trial for demonstration of safety and effectiveness. DW-MRI has not been previously included to support clearance of an embolic protection device and the data provided in this application assist in expanding fundamental knowledge in this area. Conceptually, the goal was to demonstrate that overall lesion volumes were reduced on MR and that these data would be further supported by favorable trends in safety. In addition, a secondary goal was to evaluate potential trends with regard to neurocognitive performance, quality of life, and secondary measures.

4 Regulatory Background

While there are embolic protection devices cleared for marketing for carotid and peripheral interventions, the Sentinel System is the first device proposed for marketing that is designed to be used specifically with TAVR procedures in order to reduce the incidence/impact of embolic events during those procedures. FDA and Claret Medical Inc. agreed that the submission of a De Novo request was appropriate as explained below.

[2] Grabert S, Lange R, Bleiziffer S. Incidence and causes of silent and symptomatic stroke following surgical and transcatheter aortic valve replacement: a comprehensive review. Interact Cardiovasc Thorac Surg. 2016 Sep;23(3):469-76.

[3] Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, Calhoon JH, Carabello BA, Desai MY, Edwards FH, Francis GS, Gardner TJ, Kappetein AP, Linderbaum JA, Mukherjee C, Mukherjee D, Otto CM, Ruiz CE, Sacco RL, Smith D, Thomas JD. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol. 2012 Mar 27;59(13):1200-54.

[4] Pagnesi M, Martino EA, Chiarito M, Mangieri A, Jabbour RJ, Van Mieghem NM, Kodali SK, Godino C, Landoni G, Colombo A, Latib A. Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: A systematic review and meta-analysis. International Journal of Cardiology 221 (2016) 97–106.

A device is a candidate for the De Novo pathway if the device does not fall within an existing classification regulation. This includes devices for which there is no legally marketed predicate device or, when compared to other legally marketed predicate devices, the device has a new intended use or different technological characteristics that raise different questions of safety and effectiveness. In addition, the following conditions should be satisfied:

1. The device is a low to moderate risk device.
2. The probable benefits outweigh the probable risks associated with the use of the device.
3. The probable risks to health associated with the use of the device can be mitigated by general controls alone, or a combination of general and special controls.

A reasonable assurance of safety and effectiveness can be achieved if all of the above conditions are satisfied.

The Sentinel System qualified for De Novo request since there is no appropriate legally marketed predicate device to claim substantial equivalence to in a marketing submission. Use of the Sentinel System as an accessory to TAVR introduces new/different risks than carotid embolic protection device use since the vessels in which the filters of the Sentinel System are placed are larger than the carotid arteries and thus pose different risks associated with device manipulation and embolic capture. In addition, the Sentinel System introduces new/different risks because the vessels where the filters of Sentinel System are placed are not cannulated during an unprotected TAVR procedure, whereas carotid embolic protection devices are introduced in the same vessel as the carotid stent delivery system.

FDA Comment 3: The purpose of this Advisory Panel meeting is to obtain input on critical aspects of the supporting clinical data. The Advisory Panel will *not* be asked to provide input on other regulatory aspects of the De Novo pathway.

5 Regulatory History

A chronology of the key regulatory milestones with respect to this De Novo request and the clinical trial (SENTINEL) conducted to support it is provided below.

- **February 14, 2014** – FDA conditionally approved an Investigational Device Exemption (IDE) for the SENTINEL study (G130276), allowing the enrollment of U.S. subjects in the study. Originally, the study was designed only to use the Edwards Sapien XT valve as it was the only commercially available TAVR device in the U.S. at the time. Various modifications to the SENTINEL protocol were implemented over the course of the study.

- **October 2, 1014** – First SENTINEL patient enrolled.

- **May 11, 2015** – FDA approved modifications to the SENTINEL protocol allowing the use of the Medtronic CoreValve TAVR System. Approximately 10% of randomized patients had been enrolled at the time that this request was submitted for FDA review.

- **July 27, 2015** – FDA approved modifications to the SENTINEL protocol allowing the use of any FDA approved TAVR device to accommodate use of newly available TAVR devices in the SENTINEL study as they became commercially available. Approximately 15% of the randomized patients had been enrolled at the time that this request was submitted for FDA review.

- **March 10, 2016** – Final SENTINEL patient enrolled.

- **May 6, 2016** – FDA approved a Continued Access cohort of the SENTINEL study. Ultimately, the sponsor did not initiate the Continued Access portion of the study.

- **September 20, 2016** – FDA received De Novo request DEN160043, the subject of this Advisory Panel meeting. The submission included the clinical study report of subjects enrolled in the SENTINEL study.

6 Proposed Indications for Use

The sponsor has proposed the following Indications for Use statement based on the results of the SENTINEL study:

"The Sentinel® Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain peri-procedurally. The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 mm – 10 mm in the left common carotid."

The indication proposed during the clinical study was "The Sentinel™ Cerebral Protection System is indicated for use as an embolic capture and retrieval system intended to reduce the ischemic burden in the cerebral anterior circulation while performing transcatheter aortic valve replacement."

A copy of the draft labeling is provided in Appendix VI.

FDA Comment 4: The trial was not designed to show that the device reduces clinical stroke. Rather it was designed to provide imaging and corroborating clinical evidence that the device reduces ischemic events in the brain as detected by diffusion-weighted MRI. The indication statement may be further modified to reflect the clinical use of the device as supported by the clinical data. The Advisory Panel will be asked to comment on the appropriateness of the proposed Indications for Use and the adequacy of the proposed labeling.

7 Non-Clinical Studies

The De Novo submission does not include any newly conducted *in-vitro* or animal testing. The sponsor leverages previously conducted non-clinical testing including bench testing, biocompatibility evaluation, and animal studies since the device design has not been significantly modified since FDA review of this testing under the G130276 IDE. FDA has no further questions about the non-clinical studies and as previously noted, the Advisory Panel is requested to focus its discussion on the clinical aspects of the device and SENTINEL study outcomes.

8 Supporting Clinical Information

In addition to the SENTINEL pivotal study, the sponsor provided supportive data from clinical experience with the device from outside the United States (OUS). Table 2 (below) describes these studies, with additional details on each study below.

Table 2: Summary of Clinical Experience

Study	Description	Timeframe	Device Version used	Patient Enrollment; Primary Assessments	Outcome
First-in-Man 3 centers in Germany (n=38) and Brazil (n=2)	Single arm study to evaluate safety and performance of the device	Feb 2010 – May 2011	CE Pro	N=40 Technical success rate	4 device-related vascular complications related to radial access; Debris captured in 19/35 cases (54.3%); 3 strokes at 30d
Histopathological Study Single Center in Germany	Single arm study to evaluate debris captured	Dec 2011 – Sep 2012	Montage	N=40 Histological assessment of captured debris	Device successfully used in all patients w/o complications. Debris captured in 75% (30/40) cases.
MISTRAL-C OUS post-market 4 Centers Multiple Valves used	Randomized 1:1 (protection vs. no protection)	Jan 2013 – July 2015	Sentinel	N= 65 DW-MRI at 5-7d MoCA and MMSE	52% reduction in new lesion volume in the entire brain between test and control; fewer and smaller lesions for test; Mini-Mental Status Exam showed more deterioration in control; debris capture in all cases.
CLEAN- TAVI OUS post-market Single center, single operator CoreValve only	Randomized 1:1 (protection vs. no protection)	Apr 2013 – June 2014	Montage	N= 100 DW-MRI at 2d and 7d	39% (2d) -51% (7d) reduction in new lesion volume in the entire brain between test and control; trends the same for lesion number.
SENTINEL-H 6-center OUS Post-market Registry Multiple Valves used	Non-randomized	Feb 2014 – Nov 2015	Sentinel	N= 217 Histological Assessment	Debris captured in 99% of patients; acute thrombus with tissue or foreign material was the most common debris type.
SENTINEL Pivotal Study in US (17 sites) and Germany (2 sites) Multiple Valves	Randomized (protection vs. no protection)	Oct 2014 – Mar 2016	Sentinel	N= 428 (363 randomized; 65 roll-in)	See discussion in Section 10 below.

8.1 First-in-Man Clinical Study (EU Premarket, Claret Sponsored)

Claret Medical sponsored a premarket clinical study[5] in Europe for purposes of evaluating the safety and performance of the 1st generation CE Pro System. 40 subjects were enrolled between February 2010 and May 2011 in Germany (N=38) and Brazil (N=2). Patients were 81 years old on average. No intraprocedural transient ischemic attacks, minor strokes or major strokes occurred. Thirty day follow-up showed one minor stroke occurring 30 days after the procedure, and two major strokes both occurring after (4 hours and 27 days respectively) the patient had completed TAVR and after the CE Pro System had been removed from the patient. The study demonstrated that the CE Pro System performs as intended. Captured debris was documented in at least 19 of 35 implanted devices (54.3%). There were four vascular complications reported in the study and attributable to the CE Pro System: one radial dissection, one radial hematoma and infection, and two brachial pseudoaneurysms.

8.2 Histopathological Study (EU Postmarket, Non-Claret Sponsored)

A single center in Europe performed a controlled study[6] of a total of 40 consecutive patients (December 2011 – September 2012) undergoing TAVR with the use of the Montage Dual Filter System for embolic protection. The patients were 78 years old on average. The Montage device was inserted via 6F right radial artery entry prior to the start of the TAVR procedure and removed following the completion of the procedure. The Montage System was successfully deployed in all 40 subjects with no reported adverse events or complications (100% technical success). Macroscopic material liberated during the TAVR procedure was captured in the device filter baskets in 30 of 40 (75%) patients and sent for histopathological analysis. The material was then analyzed by two independent pathology laboratories. The captured debris consisted of fibrin or amorphous calcified material and connective tissue derived from the native aortic valve leaflets and the aorta. This study provided documentation of the high frequency, large size and varied content of embolic debris liberated during TAVR that can be captured by the Montage System prior to reaching the brain.

8.3 MISTRAL-C (EU Postmarket, partially Claret Sponsored)

The MISTRAL-C[7] study was a 65-patient, 4-center, multi-operator, multi-valve randomized study assessing primarily DW-MRI outcomes at 5-7 days post-TAVR. These data showed percent reduction in lesion volume in all territories of 52%.

[5] Naber CK, Ghanem A, Abizaid AA et al. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. EuroIntervention 8(1), 43–50(2012).

[6] Van Mieghem NM, Schipper M, Ladich E et al. Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement. Circulation. 2013; 127:2194-2201.

[7] Van Mieghem NM, van Gils L. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. EuroIntervention. 2016 Jul 20;12(4):499-507.

The study was not powered to detect differences in stroke and neurological and neurocognitive assessments were not standardized/blinded. Debris capture was noted in 100% of patients and Mini-Mental Status examinations showed less deterioration in patients who had protection with the Sentinel System.

8.4 CLEAN-TAVI (EU Postmarket, Claret Co-Sponsored)

The CLEAN-TAVI[8] study was a 100-patient, single center, single operator, single-valve (CoreValve) randomized study assessing primarily DW-MRI outcomes at 2, and 7 days post-TAVR. These data showed percent reduction in lesion volume in all territories of 39%(2d) and 51%(7d). Similar trends in the data were seen when lesion number was examined. The study was not powered to detect differences in stroke and neurological and neurocognitive assessments were not standardized/blinded.

8.5 SENTINEL-H (EU Postmarket Registry, Claret Sponsored)

The SENTINEL-H study was a 217-patient, 6-center, multi-operator, multi-valve registry assessing primarily embolic debris. A total of 420 filters were assessed and debris was captured in 99% of patients. Acute thrombus associated with tissue or foreign material was the most common debris.

The sponsor also provided a comprehensive comparison (Table 3) of key elements of the U.S. pivotal SENTINEL study to the OUS MISTRAL-C and CLEAN-TAVI studies.

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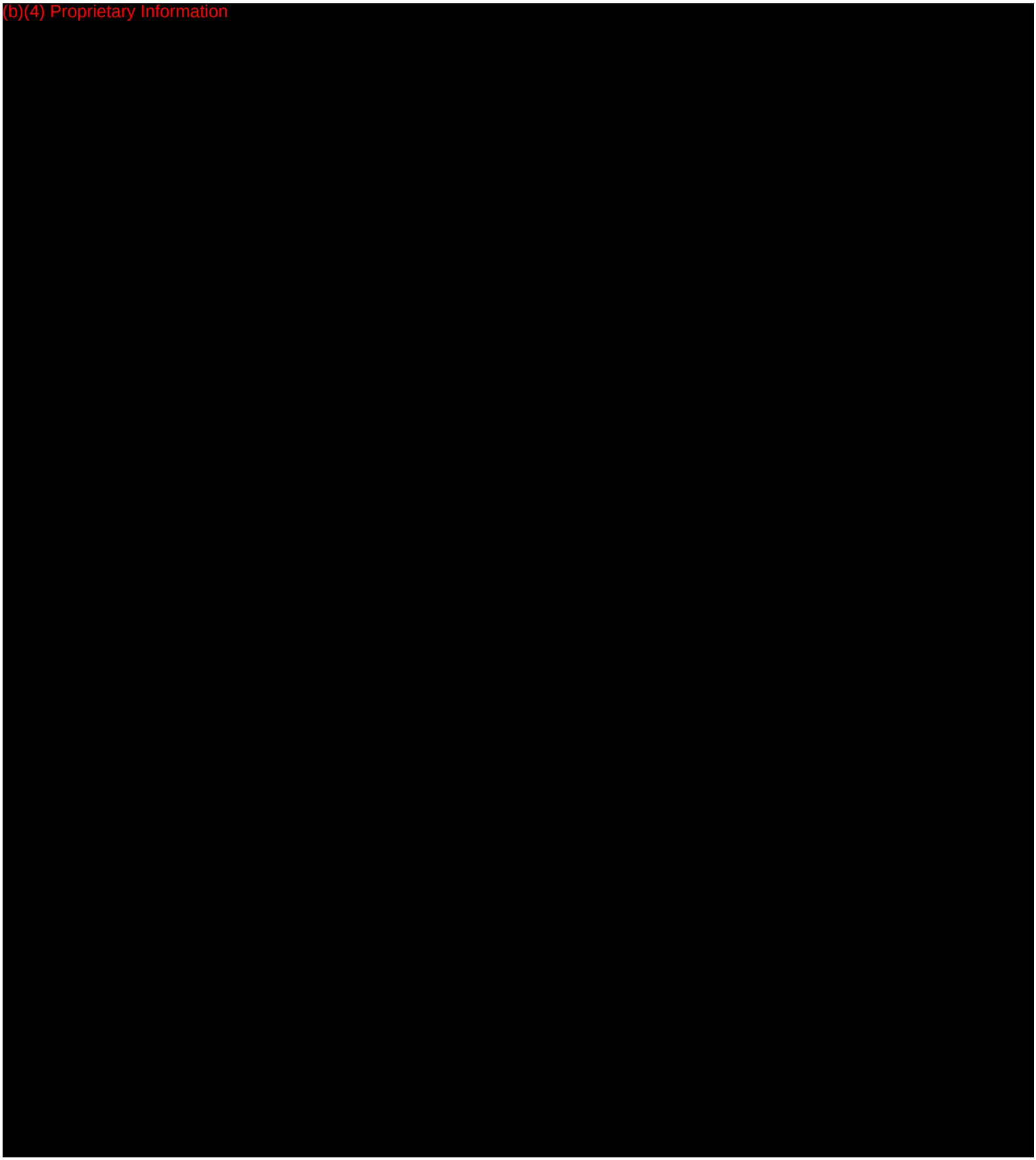
(b)(4) Proprietary Information



(b)(4) Proprietary Information

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(b) (4)

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9 SENTINEL Study Design

The primary pivotal study provided to support the De Novo request is "Cerebral Protection in Transcatheter Aortic Valve Replacement – The SENTINEL Study." The objective of the study was to assess the safety and effectiveness of the Claret Medical Sentinel Cerebral Protection System used for cerebral protection during Transcatheter Aortic Valve Replacement (TAVR) compared to TAVR without cerebral protection. Details of the study design may be found below and selected clinical results are provided in Section 10.

The SENTINEL Study is a prospective, single blind, multi-center, randomized study using the Sentinel System in patients with severe symptomatic calcified native aortic valve stenosis indicated for TAVR. After successful computed tomography (CT) angiography screening evaluation, baseline study assessments and patient selection criteria eligibility, patients were randomized in a 1:1:1 fashion as follows (Figure 4):

- Safety Arm - Patients in this group received the Sentinel System prior to TAVR procedure. MRI and Neurocognitive Test Battery were not conducted for this group of patients.
- Test Arm - Patients in this group received Sentinel System prior to TAVR procedure. MRI at baseline, 2-7 days and 30-days and Neurocognitive Test Battery were performed at baseline, day 2-7, 30 and 90.
- Control Arm - Control patients underwent TAVR procedure without the Sentinel System. MRI and Neurocognitive assessment were conducted with the same schedule at that for the Test Arm.

Note that for patients randomized to either the Test or Control arms, patients were subsequently assessed for continued eligibility including contraindications to MR imaging.

Patients, core laboratories, Claret Medical, and the CEC were blinded to study arm assignment. The CEC was composed of two cardiologists, two neurologists, and a nephrologist.

9.1 Inclusion and Exclusion Criteria

9.1.1 Selected Inclusion Criteria

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.

9.1.2 Selected Exclusion Criteria

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. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment.
4. Aortic valve was a congenital unicuspid or bicuspid valve; or is non-calcified.
5. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
6. Any therapeutic invasive cardiac procedure resulting in a permanent implant that was performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease).
7. Severe ventricular dysfunction with LVEF ≤20%.
8. Echocardiographic evidence of intracardiac or aortic mass, thrombus, or vegetation.
9. Recent (within 6 months) CVA or a TIA.
10. Renal insufficiency (creatinine > 3.0 mg/dL or GFR < 30) and/or renal replacement therapy at the time of screening.
11. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure.

9.1.3 Selected Exclusion Criteria for Randomized Patients Only

1. Patient Body Mass Index (BMI) precluding imaging in scanner.
2. Contraindications to MRI (patients 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 the TAVR procedure).
3. Planned implantation of a pacemaker or defibrillator implantation after TAVR.
4. Patients with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.
5. Patients whose brachiocephalic or left carotid artery revealed significant stenosis, calcification, ectasia, dissection, or aneurysm at the ostium or within 3 cm of the ostium.

FDA Comment 6: Patients were assessed initially for general eligibility and consented. CT was then performed to ensure that the patients met the anatomic criteria. If anatomic criteria were met, the patients were randomized to one of the three study arms (i.e., Safety, Test, or Control). Note that for patients randomized to either the Test or Control arms, patients were subsequently assessed for continued eligibility including contraindications to MR imaging. A total of 599 patients were screened for the study. Sixty-eight (68) patients (11%) screen-failed due to anatomical criteria, and 103 patients (17%) screen-failed based on not meeting one or more of the eligibility requirements and/or withdrew consent prior to randomization. See Figure 4 below.

9.2 Statistical Analysis Populations

Several analysis populations were defined to include Intent to Treat (ITT), ITT with Imputation, Per Protocol (PP) and As Treated (AT). The primary analyzable cohort for the primary endpoints was the ITT with Imputation population. ITT with Imputation includes patients as randomized and imputation to account for missing data (i.e., clinical, DW-MRI) since only 189 of the 240 patients randomized to the Imaging Cohort had analyzable data to assess effectiveness. In addition, a supporting ITT (without imputation) analysis was performed. Of note, the ITT patient population excludes those patients without paired DW-MRI imaging, and the PP population further excludes patients with DW-MRI imaging or neurocognitive testing performed outside of the follow-up window. The AT population reflects results based on treatment actually received regardless of the treatment assignment during randomization. Note that the Sentinel device was not used in 9 patients who were assigned to have the device. The PP and AT populations were used for secondary endpoints and supporting analyses. The analysis populations were defined as follows:

9.2.1 Intent-To-Treat (ITT) with Imputation ("As Randomized")

Patients enrolled and randomized to a treatment arm, with missing values imputed for patients that had missing clinical and/or MRI follow-up assessments. The model for multiple imputation of the missing primary safety endpoint data included covariates (b) (4) [redacted]. The model for multiple imputation of missing primary effectiveness endpoint data included (b) (4) [redacted] ITT with Imputation was pre-specified as the primary analyzable cohort for the primary endpoints.

9.2.2 ITT (without Imputation; "All Completers")

Patients enrolled and randomized to a treatment arm who had available follow-up data regardless of completion within protocol defined follow-up windows. Effectiveness and neurocognitive analyses required paired baseline and follow-up assessment data. Analyses based on the ITT cohort were used as supporting analyses.

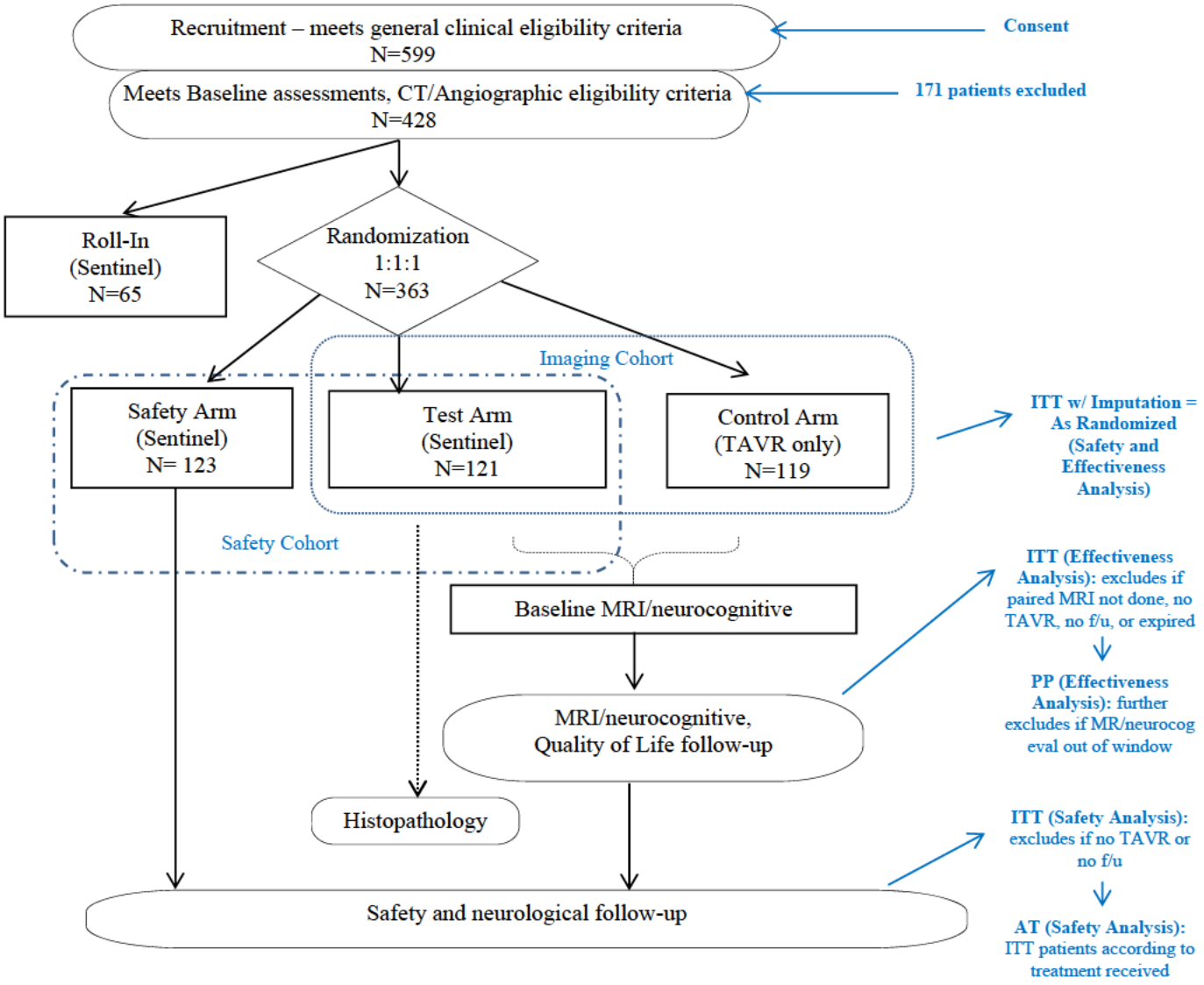
9.2.3 As Treated (AT)

Patients grouped in the analysis according to the treatment received, regardless of treatment assigned, e.g. a patient randomized to the Safety or Test Arm, but who did not receive the Sentinel System, was analyzed as a Control Arm patient in the "As Treated" analysis. This analysis population was used only for secondary and supporting safety analyses.

9.2.4 Per Protocol (PP)

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, i.e., MR: Baseline (within 14 days prior to TAVR); 2-7 days; 30 day (+/-7 days); and Neurocognitive Test Battery: Baseline (within 14 days prior to TAVR); 30 day (23-45 days); 90 day (+/- 10 days). The PP cohort was used for secondary effectiveness endpoints and additional supporting analyses of the primary endpoints.

Figure 4: Randomization and Study Flow Chart



FDA Comment 7: Note that the ITT with Imputation population includes all patients randomized to the Test or Control Arm, and missing Day 2-7 post procedure MRI data were imputed. ITT (without imputation) population consists of all patients who were randomized to the Test and Control arms, and had evaluable paired baseline and Day 2-7 post procedure MRI data. Therefore it is an analysis population of "All Completers."

The four analysis populations reflect different aspects of the data and no single population is considered alone for regulatory decision-making.

All enrolled subjects were required to receive follow-up assessments according to the schedule outlined in Table 4.

Table 4: Schedule of Evaluations

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

9.3 Statistical Analysis

9.3.1 Study Success Criteria

The study would be considered as a success if it met all three of the following criteria (See Sections 1.2 and 2.4 of the Statistical Analysis Plan in Appendix I):

1. Primary safety endpoint: The study needs to demonstrate that the 30-Day MACCE rate for the Safety Cohort (Safety Arm and Test Arm) is below the Performance Goal of 18.3%.

2. Superiority with respect to the primary effectiveness endpoint (FDA will refer to this as Primary Effectiveness Criterion #1): The Test Arm needs to demonstrate superiority over the Control Arm with respect to the total new lesion volume in protected territories at Day 2-7 post-procedure.

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

Each of these success criteria are described in more detail below.

FDA Comment 8: The primary effectiveness endpoint was total new lesion volume in *protected territories* at Day 2-7 post-procedure as assessed by DW-MRI. There were two study success criteria (2 and 3 listed above) based on this endpoint. One was hypothesis test based to show superiority (FDA will refer to this as Primary Effectiveness Criterion #1) and the other was the observed treatment difference (FDA will refer to this as Primary Effectiveness Criterion #2).

9.3.2 Primary Safety (Non-Inferiority) – Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 Days

The primary safety endpoint was Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 Days. MACCE was defined as All Death, All Stroke, Acute Kidney Injury (class 3 at discharge or 72 hours post index procedure, whichever occurs first) as adjudicated by a Clinical Events Committee (CEC) using VARC-2 definitions. The CEC was blinded to treatment arm and composed of two cardiologists, a vascular neurologist, a stroke neurologist, and a nephrologist. A list of definitions from the SENTINEL Study Investigational Plan is provided in Appendix V.

For the primary safety endpoint, the null and alternative hypotheses are:

H_0: $p \geq 18.3\%$
H_A: $p < 18.3\%$

where p = 30-day MACCE rate (primary safety endpoint).

The hypotheses were to be tested using one-sided 95% exact binomial confidence interval. The upper bound of the one-sided 95% confidence interval

for the primary endpoint event rate needed to be less than the pre-specified performance goal of 18.3% for the null hypothesis to be rejected.

The performance goal of 18.3% was determined based on reported MACCE rates for different valve types in the literature and expected distribution of valve types to be used in the trial. The proposed performance goal of 18.3% is the weighted MACCE rates (13.3%) plus a 5% margin.

9.3.3 Primary Effectiveness Criterion #1 (Superiority) – Total New Lesion Volume in Protected Territories as assessed by DW-MRI at 2-7 Days

The primary effectiveness endpoint was total new lesion volume in *protected territories* between the Imaging Cohort Arms (Test and Control Arms) as assessed by DW-MRI at Day 2-7 post-procedure. Total new lesion volume is 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* are 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.

For Primary Effectiveness Criterion #1, the null and alternative hypotheses are:

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

where, μ_{test} = Day 2-7 DW-MRI median total new lesion volume based on *protected territories* from the Test arm,
and $\mu_{Control}$ = Day 2-7 DW-MRI median total new lesion volume based on *protected territories* from the Control Arm.

The hypothesis was planned to be tested using Wilcoxon test at a significance level of 0.05 due to expected skewness in the distribution of the total new lesion volume.

9.3.4 Primary Effectiveness Criterion #2 (Observed Clinical Treatment Effect) – Total New Lesion Volume in Protected Territories as assessed by DW-MRI at 2-7 Days

As noted above, study success also required a third criteria to demonstrate that the observed reduction in the median total new lesion volumes in *protected territories* is ≥ 30% in the Test Arm compared to the Control Arm ((i.e., (Control-Test)/Control ≥ 30%)). This was also assessed by DW-MRI at Day 2-7 post-procedure. There is no hypothesis test associated with this criterion as it is based

on the point estimate of the ratio of observed median total new lesion volumes in *protected territories*.

FDA Comment 9: Note that the primary effectiveness endpoint was written by the sponsor to reflect the function of the device in protecting the cerebral territories supplied by the carotid arteries bilaterally and the right vertebral artery. The left vertebral artery was unprotected given the device design and function; therefore, the sponsor did not "count" new DW-MRI lesions in the distribution of the left vertebral artery in their primary analysis. FDA raised this issue as a significant study design limitation because, conceptually, the overall clinical impact of embolic protection during TAVR procedures relates to the goal of protecting the whole patient/brain. FDA believes it is important to consider defects in "all territories" when considering the totality of the data to support a marketing decision. Some additional analyses have been provided to also assess DW-MRI defects in all cerebral territories. The Panel will be asked to comment on the effectiveness results for both the Protected Territories and All Territories Analyses. The Panel will also be asked to comment on the appropriateness of reporting results for Protected Territories versus All Territories in the labeling, if the De Novo request were to be granted.

FDA Comment 10: Study success required that all three criteria (i.e., non-inferior safety, superior effectiveness, and observed treatment effect) be met. Two of the criteria included hypothesis testing and the third was a requirement on the magnitude of the observed treatment difference. Again note that the primary effectiveness endpoint included only assessment of DW-MRI infarcts in *protected territories* and infarcts in the left vertebral distribution were excluded. Note that FDA's intent of the additional criterion on observed treatment effect (Criterion #2) was to add assurance in the event that simple superiority were statistically established that there was an amount of lesion volume reduction that may approach clinical meaning. Note that evidence is evolving in this space and there is no established data to suggest that a margin of 30% in lesion volume reduction correlates with clinical benefit. The Panel will be asked to comment on the appropriateness of using DW-MRI as a surrogate endpoint for clinical stroke.

9.4 Secondary Endpoints

Numerous secondary endpoints were prospectively established as follows:

9.4.1 Secondary Safety Endpoints

1. Incidence of in-hospital MACCE [Safety Cohort]
2. MACCE rate [Test and Control Arms] – at 30 days post-procedure
3. Incidence of major vascular complications [Safety Cohort] during index procedure and within 30 days
4. Incidence of Serious Adverse Events [all study arms] within 30 days of index procedure

9.4.2 Secondary Effectiveness Endpoints

1. Difference in Day 2-7 DW-MRI median number of new lesions based on *protected territories*
2. Difference in Day 2-7 DW-MRI median total new lesion volume based on *all territories*
3. Difference in Day 2-7 DW-MRI median number of new lesions based on *all territories*
4. Difference in change in neurocognitive battery composite z-score from baseline to 30 days
5. Difference in Day 30 T2/FLAIR MRI median total new lesion volume based on the *protected territories*
6. Observe at least a 30% reduction in median total lesion volume in *protected territories* between the Test and Control Arms at Day 2-7 DW-MRI post procedure = Effectiveness Criterion #2
7. Difference in Day 30 T2/FLAIR MRI median number of lesions based on the *protected territories* and based on all territories
8. Difference in Day 2-7 DW-MRI maximum (and average) single new lesion volume per patient based on *protected territories* (and *all territories*)
9. Difference in Day 30 T2/FLAIR MRI maximum (and average) single new lesion volume per patient based on *protected territories* (and *all territories*)
10. Captured debris histopathology (observational) [Test Arm] – post-procedure
11. Correlation of Day 2-7 DW-MRI lesion volume metrics with change in 2-7 day, 30-day and 90 day neurocognitive battery composite z-score [Test and Control Arms]
12. Correlation of Day 30 T2/FLAIR MRI lesion volume metrics with change in 2-7 day, 30-day and 90 day neurocognitive battery composite z-score [Test and Control Arms]
13. Difference in Day 30 T2/FLAIR MRI total new lesion volume based on *all territories*
14. Difference in change in neurocognitive battery composite z-score from baseline to 2-7d and 90 days
15. Sentinel System acute delivery and retrieval success [Safety Cohort]

10 SENTINEL Study Results

10.1 Subject Enrollment

A total of three hundred and sixty-three (363) patients were enrolled in the study at 19 sites in the United States (17) and Germany (2). Based on study randomization, enrollment in each study arm was as follows: 119 Control, 121 Test and 123 Safety. As illustrated in Figure 4 above, 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 primary effectiveness endpoint analysis. The first patient was enrolled on October 2,

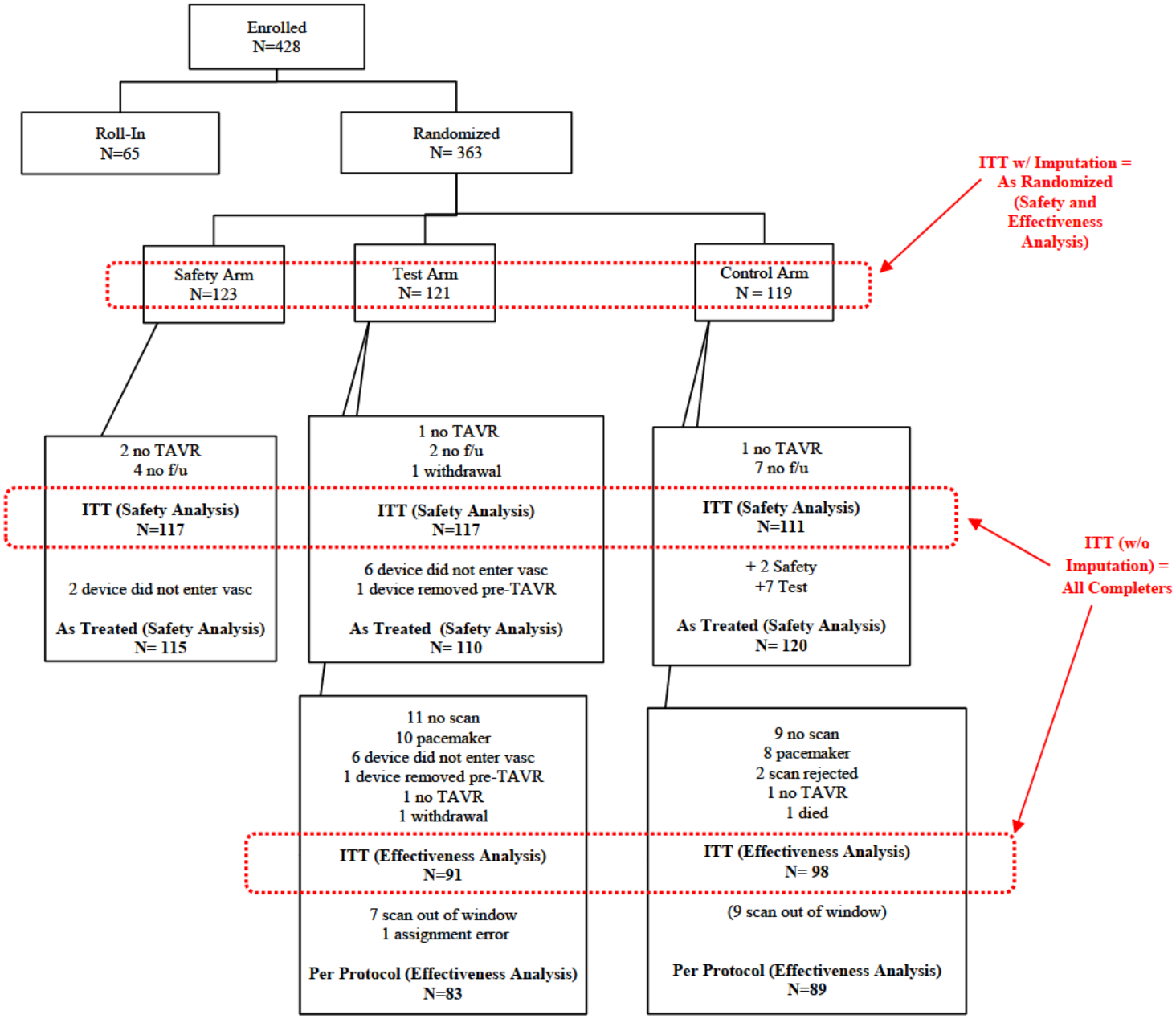
2014 and the final patient was enrolled on March 10, 2016. (b) (4) [redacted]

(b) (4) [redacted]

10.2 Patient Accountability and Follow-Up

Of the 363 patients randomized in the study, 1.1% (4/363) did not undergo the TAVR procedure, and 3.7% (9/244) of the patients randomized to receive the Sentinel System (Safety Arm and Test Arm) did not receive the device (device did not enter the vasculature) or had the device removed pre-TAVR procedure. See Figure 6 below. Overall, study clinical follow-up visit completion was 97.8% (355/363) for the 2-7 Day visit, 90.4% (328/363) for the 30-day visit, and 79.9% (290/363) for the 90-day visit. Refer to Figure 4 above for patient accountability categorized by analysis population. Refer to Appendix III for Study Flow diagrams provided by the sponsor.

Figure 6: SENTINEL Patient Accountability



10.3 Baseline and Procedural Characteristics

Baseline and procedural characteristics were assessed regarding demographics, medical history, clinical characteristics, medications and baseline imaging data. Details of these data will not be repeated. Overall, baseline characteristics were generally balanced between groups except for the following:

- The Control Arm had a higher STS PROM (predicted risk of operative mortality) score (7.5) compared to both the Safety Arm (6.2) and Test Arm (6.4) which would tend to favor outcomes for the Sentinel System.
- The Safety Arm had an increased incidence of prior clinical stroke (8.1%) compared to the Test Arm (4.1%) and Control Arm (5.0%).
- The diastolic pressures in the Safety (70.4 mmHg) and Test Arms (68.3 mmHg) trended higher than the Control Arm (66.3 mmHg).
- Assessments of patients with missing MR data compared to those who completed the exam showed that patients who did not have the MR follow-up had higher weight/BMI and incidence of CABG. They also had less severe valve characteristics (e.g., valve area index, gradient and velocity).

With regard to procedural characteristics, the Control Arm had a reduced procedure time and patients had a greater brachiocephalic diameter.

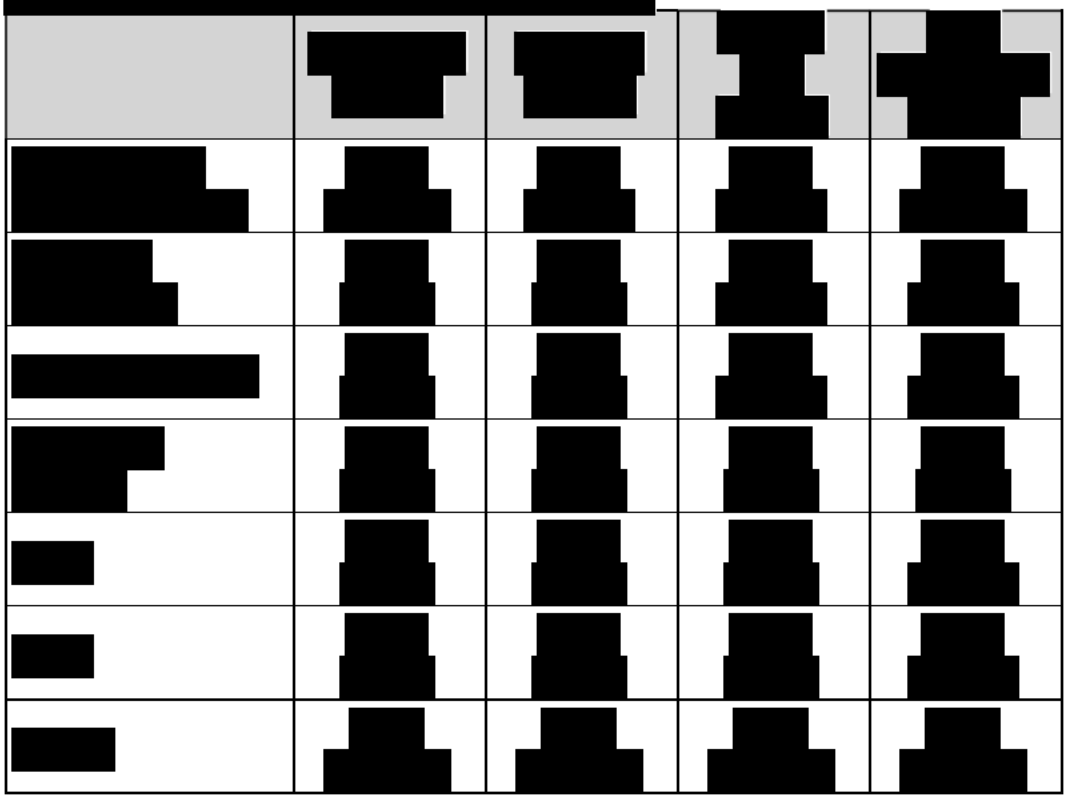
10.4 Protocol Deviations

Protocol deviations include issues related to informed consent and protocol eligibility as well as noncompliance with follow-up assessments. If issues related to informed consent and protocol eligibility are considered separately, there were only 9 randomized patients with deviations (2.5% (9/363)). Deviations associated with follow-up are reported separately in Section 10.5 below.

10.5 Follow-Up Compliance

At study completion, 78.5% (285/363) patients finished the study as planned, 5.23% of study patients (19/363) withdrew, and 7.44% (27/363) were lost to follow-up (LTF). The remaining 32 patients exited the study for other reasons (see Table 5 below). Following study exit for completion of the study, patients continued to receive the standard medical care for their condition as determined necessary and appropriate by their physician.

(b) (4)



10.5.1 Clinical Assessments

Compliance with all baseline clinical assessments, irrespective of study time windows, across all study arms exceeded 95%. Overall completion of neurological assessments (NIHSS and mRS, both administered by a neurologist) was greater than 85% at discharge and 78% at the 30 day visit. Neurological assessments were only required at the 90-day time point for those patients who were suspected of experiencing a stroke (physician discretion) prior to the visit.

10.5.2 MRI AND Neurocognitive Assessments

Only the Imaging Cohort (Test and Control Arms) underwent MRI and neurocognitive assessments. The neurocognitive test battery included assessment of the following seven (7) domains: Attention, Executive Function, Processing Speed, Verbal Memory, Visual Memory, Mental Status, and Depression and were administered by a neuropsychologist (blinded) or personnel trained and certified in administration of these tests. See Table 6 below.

At baseline, both DW-MRI and T2/FLAIR MRI were conducted. DW-MRI was repeated at the 2-7 day study time point. Baseline compliance was 95% (228/240), and 2-7 day compliance was 75.2% (91/121) in the Test Arm, and 82.4% (98/119) in the Control Arm for an overall rate of 78.8% (189/240). At baseline, 97.5% (234/240) of patients received a neurocognitive assessment.

The 2-7 day neurocognitive assessment was optional, and therefore only 55% (132/240) of patients received the exam.

At the 30 Day follow-up, only T2/FLAIR MRI imaging was conducted. Compliance for the Test Arm was 64.5% (78/121), and the Control Arm compliance was 67.2% (80/119), for an overall Imaging Cohort compliance of 65.8% (158/240). Neurocognitive assessment completion was 77.1% (185/240) for the Imaging Cohort: Test Arm 76.9% (93/121), and 77.3% (92/119) for the Control Arm.

No MRI assessments were performed at the 90-day follow-up visit. Neurocognitive assessment completion was 63.8% (153/240) for the Imaging Cohort: Test Arm 63.6% (77/121) and 63.9% (76/119) for the Control Arm.

Table 6: Imaging and Neurocognitive Follow-Up
Visit-Specific Imaging Cohort Exam Completion (All Evaluable Data)

	Safety Arm %, (n/N)	Test Arm %, (n/N)	Control Arm %, (n/N)	Total %, (n/N)
Baseline Assessments				
DW and T2/FLAIR MRI	N/A	94.2% (114/121)	95.8% (114/119)	95.0% (228/240)
Neurocognitive Test Battery	N/A	96.7% (117/121)	98.3% (117/119)	97.5% (234/240)
2-7 Day				
DW-MRI	N/A	75.2% (91/121)	82.4% (98/119)	78.8% (189/240)
Neurocognitive Test Battery	N/A	54.5% (66/121)	55.5% (66/119)	55.0% (132/240)
30-Day				
T2/FLAIR MRI	N/A	64.5% (78/121)	67.2% (80/119)	65.8% (158/240)
Neurocognitive Test Battery	N/A	76.9% (93/121)	77.3% (92/119)	77.1% (185/240)
90-Day				
Neurocognitive Test Battery	N/A	63.6% (77/121)	63.9% (76/119)	63.8% (153/240)

FDA Comment 11: Of the 240 patients randomized for the effectiveness analysis (Imaging Cohort consisting of 119 Control Arm and 121 Test Arm), 21.3% (51/240) were excluded from the ITT analysis. Of those 51 excluded patients, the main reason for exclusion was that 40 patients did not have paired MR imaging for assessment. Similarly, of the 240 patient randomized in the Test and Control arms, 23.3% (56/240) were excluded from the ITT neurocognitive analysis. Of those 56 excluded patients, 41 patients did not have the neurocognitive tests completed. Refer to Figure 6 above and Appendix III for flow diagrams.

10.6 Primary Safety and Effectiveness Results

10.6.1 Primary Safety Results

The Sponsor's primary safety analysis included comparison of the 30-day MACCE (i.e., All Death, All Stroke, Acute Kidney Injury) rate to a literature-based perform goal of 18.3% (i.e., 13.3% literature rate plus 5% margin). See Table 7. The Roll-In patient 30-day MACCE rate of 6.8% is also similar to that observed in the randomized cohort. A summary of the results for the MACCE components is included in Table 8.

Table 7: Primary Safety Results: MACCE at 30-Days

	Safety Cohort (Safety Arm + Test Arm)				
Population	**Total Events**	**Patients w/ Events** n/N, (%)	**Performance Goal**	**Upper Limit of 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%)		10.7%	<.0001
AT	17	17/225 (7.6%)		11.1%	<.0001

[1]Upper limit of 95% confidence interval and p-value based on exact one-sided test for alternative hypothesis: rate <PG with 0.05 alpha level
[2]Binary outcome based on imputation analysis, number of events does not apply

A sensitivity/tipping point analysis on missing data using the ITT population was performed. If the 10 subjects with missing 30-day MACCE data were all assumed to have a MACCE event (worst-case scenario), the MACCE rate would be 11.1% (27/244) with an upper 95% confidence bound of 14.9%, which still meets the performance goal of 18.3%.

FDA Comment 12: The ITT with Imputation population is the primary analysis population. The sponsor also provided analysis results for the ITT (without Imputation) and AT patient populations (Table 7 above). For all analysis populations, the overall MACCE rate was ~7.5% (with 95% CI upper bound ~11%) which meets the pre-specified performance goal of 18.3%. Note that the safety analysis included clinical neurological assessments; therefore, the clinical impact of all cerebral territories was automatically included.

Table 8: Components of the Safety Results: MACCE at 30-Days (Combined Safety and Test Arms) – ITT Population

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

Note: Data presented as: % of subjects with event (number of subjects with event/subjects per arm evaluable at 30 days or experienced an event) [number of events] (exact 95% CI)

[1]Stroke was defined as a duration of a focal or global neurological deficit ≥24 h; OR, <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.

[2]Disabling Stroke was defined as a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline.

[3]Non-disabling Stroke was defined as a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline

*Safety Cohort – Control Arm

**Note that event rates were low for Disabling Stroke and AKI, making confidence intervals difficult to calculate reliably.

FDA Comment 13: Of the 17 MACCE events reported for patients who received the Sentinel System, the majority of events were stroke (13). Of those stroke events, the majority were non-disabling (11). There were also three Deaths and one Acute Kidney Injury. No deaths were adjudicated to be related to the Sentinel System.

Note that the primary safety assessment is MACCE rate compared to a Performance Goal and not to the active control arm (given considerations related to power and sample size). Nonetheless, a secondary qualitative comparison of the patients in the Test Arm (treated with the Sentinel System) to the Control Arm showed no signal of differences with regard to type and frequency of events. This is discussed in more detail in Section 10.7.1 below.

10.6.2 Primary Effectiveness Results

The sponsor's primary effectiveness analysis included two assessments designed to evaluate DW-MRI infarct lesion volume between patients with and without protection. The first hypothesis-driven criterion was to show that there was statistically significant reduction in median total new DW-MRI lesion volume in *protected territories* for patients with protection with the Sentinel System compared to those without protection (Criterion #1). The second criterion was intended to show that there was an observed reduction of at least 30% in median new lesion volume (Criterion #2) in *protected territories* in the Test Arm comparing to the Control Arm. Note that total new lesion volume is 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* are 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. The ITT with Imputation analysis population was pre-specified as the primary analysis population.

Results for Effectiveness Criterion #1 and Effectiveness Criterion #2 are depicted in Tables 9 and 10, respectively.

Table 9: Primary Effectiveness Results - Criterion #1 - *Superiority*: 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.

Population	Test Arm (mm^3)	Control Arm (mm^3)	Observed Treatment Difference (Test - Control)	p-value[1]
ITT with Imputation[2]	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	0.2354
ITT	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	0.3345
PP	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	0.5715

Note: Data presented as: median, (25^{th} percentile, 75^{th} percentile), n, min, max.
[1] Based on two-sided Wilcoxon test
[2] Missing lesion volume was imputed using Multiple Imputation

FDA Comment 14: Superiority was not demonstrated for the pre-specified endpoint (Effectiveness Criterion #1). The sponsor was unable to demonstrate that the median total new DW-MRI lesion volume was statistically significantly lower in patients that had protection with the Sentinel System (Test Arm) compared to those who had no protection (Control Arm). For all analysis populations, lesion volume reductions of ~65-75 mm^3 were observed between groups. Note that this assessment included a comparison of *protected territories* only and all lesions in the left vertebral artery distribution were not counted.

Table 10: Primary Effectiveness Results - Criterion #2 - *Observed Treatment Effect*: 30% Reduction in 2-7 Day DW-MRI Median Total Lesion Volume (*Protected Territories*) in the Test Arm comparing to the Control Arm

Population	Test Arm (mm^3)	Control Arm (mm^3)	Target	Observed % Reduction* (95% CI)
ITT	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)
PP	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		34.8 (-8.1, 60.6)

Note: Data presented as: median, (25^{th} percentile, 75^{th} percentile), n, min, max.
* [(Control-Test)/Control]%. Confidence Interval calculated using Price et al method.

FDA Comment 15: There was an observed reduction of approximately 35-40% in median new DW-MRI lesion volume in patients who had protection with the Sentinel System (Test Arm) compared to those who did not have protection (Control Arm). This was simply an observed relative reduction among randomized subjects with available new lesion volume data (ITT without imputation) and no hypothesis testing was performed. Again, note that this analysis only included a comparison of *protected territories*.

FDA Comment 16: Two of the three study success criteria were met; however, the study did not show that patients with protection using the Sentinel System had a statistically significant reduction in new DW-MRI lesions in *protected territories* after TAVR. Although nominal/observed trends favored the Sentinel System, the clinical significance of the observed lesion volume reduction in the territories described remains uncertain.

10.7 Secondary Endpoint Analyses

In addition to the primary analyses, there were four secondary safety endpoints and fifteen secondary effectiveness endpoints. Five of these secondary effectiveness endpoints were planned for hypothesis testing for possible labeling claims if the primary endpoints were met. However, the hypothesis testing was not conducted because superiority was not established with the primary effectiveness endpoint.

10.7.1 Safety

Additional endpoints were assessed with regard to MACCE, vascular complications and Serious Adverse Events. Results are summarized in Tables 11-13 below.

As previously noted, the primary safety assessment is MACCE rate compared to a Performance Goal and not to the active control arm (given considerations related to power and sample size). However, a secondary qualitative comparison of the patients in the Test Arm (treated with the Sentinel System) to the Control Arm showed no signal of differences with regard to type and frequency of events.

Table 11: 30-Day MACCE and Component Rates (Test vs. Control) – Secondary Safety Endpoint 2

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

Note: Data presented as: % of subjects with event (number of subjects with event/subjects per arm evaluable at 30 days or experienced an event) [number of events] (exact 95% CI)

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

Table 11: 30-Day MACCE and Component Rates (Test vs. Control) – Secondary Safety Endpoint 2 - Continued from previous page

	Test Arm	Control Arm	p-value*
As Treated			
Any MACCE	6.4% (7/110) [7] (2.6%,12.7%)	9.9% (11/111) [12] (5.1%,17.0%)	0.6168
Death	0.9% (1/110) [1] (0.0%,5.0%)	1.8% (2/111) [2] (0.2%,6.4%)	1.0000
Stroke (all)	4.6% (5/109) [5] (1.5%,10.4%)	9.1% (10/110) [10] (4.4%,16.1%)	0.5702
Disabling Stroke	0% (0.0%,3.3%)	0.9% (1/109) [1] (0.0%,5.0%)	0.4979
Non-disabling Stroke	4.6% (5/109) [5] (1.5%,10.4%)	8.2% (9/110) [9] (3.8%,15.0%)	1.0000
AKI (Class 3)	0.9% (1/109) [1] (0.0%,5.0%)	0% (0.0%,3.3%)	0.4910

Note: Data presented as: % of subjects with event (number of subjects with event/subjects per arm evaluable at 30 days or experienced an event) [number of events] (exact 95% CI)

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

Table 12: Incidence of Major Vascular Complications – Secondary Safety Endpoint 3

	Safety Cohort (Safety + Test Arms)	Control Arm
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%)
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

Data presented as: % of subjects with event (number of subjects with event/subjects per arm evaluable at 30 days or experienced an event) [number of events] (exact 95% CI)

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)

Table 13: Incidence of Serious Adverse Events within 30 Days – Secondary Safety Endpoint 4

	Safety Cohort (Safety Arm + Test Arm)			Control Arm		
	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%)
AT	162	42.9% (99/231)	(36.4%, 49.5%)	97	43.8% (56/128)	(35.0%, 52.8%)

FDA Comment 17: The following are general conclusions that may be made from the secondary safety analyses:

a. The In-hospital (Secondary Safety Endpoint 1; not shown) and 30-day (Secondary Safety Endpoint 2; Table 11 above) MACCE rates were numerically lower for patients with protection compared to those without protection. The clinical trends also held for MACCE components with minor exceptions. The low event rates preclude any robust conclusions.

b. Vascular complications (Secondary Safety Endpoint 3; Table 12 above) were rare with the Sentinel System. One brachial artery event was reported.

c. The incidence of serious adverse events comparing groups with and without protection was numerically comparable and reported to be approximately 43% (Secondary Safety Endpoint 4; Table 13 above).

Overall, there were no concerning major safety trends with the data reported.

10.7.2 Effectiveness

Numerous secondary effectiveness endpoints were pre-specified and analyzed. One of the more important assessments compared lesion volumes for patients with and without protection for *all* cerebral vascular territories rather than restricted to only those territories that the device is designed to protect (Secondary Effectiveness Endpoint 2). See Table 14 below.

Table 14: 2-7 Day DW-MRI Median Total New Lesion Volume (*All Territories*) - Secondary Effectiveness Endpoint 2

Population	Test Arm (mm^3)	Control Arm (mm^3)	Observed Treatment Difference (Test - Control) (mm^3)	p-value*
ITT with Imputation[1]	247.2 (97.6, 572.2), n=121 0 min, 14179 max	311.1 (110.7, 848.4), n=119 0 min, 24300 max	-63.9	0.5794
ITT	294 (69.2, 786.4) n=91 0 min, 14179 max	309.8 (105.5, 859.6) n=98 0 min, 24300 max	-15.8	0.8076
PP	(b) (4) [redacted]			

Note: Data presented as: median, (25^{th} percentile, 75^{th} percentile), n, min, max.

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

[1] Although not pre-specified for this secondary analysis, missing lesion volume was imputed using Multiple Imputation and results for the ITT with Imputation population are presented for reference.

FDA Comment 18: The primary effectiveness endpoint discussed in the above section included only *protected territories* and any new lesions detected by DW-MRI in the left vertebral distribution were not counted. If the technical limitations of the device were not accounted for and one were to include all new lesions regardless of their location within the brain, the effectiveness of the device is less apparent when observing new median DW-MRI lesion volumes after TAVR. In fact, if one were to observe the median new lesion volume in the Per Protocol Population (i.e., those patients with DW-MRI conducted within the assessment window), patients who received protection with the Sentinel System had a non-statistically significant but numerically higher lesion volume difference (10.6 mm^3). It's unclear if this small difference is clinically meaningful or simply attributed to random variation.

The above assessment (Table 14) includes Effectiveness Criterion #1 modified to assess *all territories* instead of only *protected territories*. If one were to similarly consider Effectiveness Criterion #2 modified to assess *all territories* instead of only *protected territories*, a similar trend in reduced effect is noted. See Table 15 below.

Table 15: Percent Reduction in the Test Arm comparing to the Control Arm in Median 2-7 Day DW-MRI Total New Lesion Volume (*Protected Territories* and *All Territories*)

Population	Test Arm (mm^3)	Control Arm (mm^3)	% Reduction*
Protected Territories			
ITT	102.8 (36.9, 423.2) n=91 0 min, 5175.9 max	178 (34.3, 482.5) n=98 0 min, 24300 max	42.2
PP	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	34.8
All Territories			
ITT	294 (69.2, 786.4) n=91 0 min, 14179 max	309.8 (105.5, 859.6) n=98 0 min, 24300 max	5.1
PP	(b) (4) [redacted]		

Note: Data pres

* (Test-Control)/Control

FDA Comment 19: Similar to the trend seen with the hypothesis driven effectiveness endpoint (Criterion #1), the observed difference in lesion volume (Criterion #2) shows little if any differences between patients who were treated with the Sentinel System if all cerebral lesions are included (rather than just those in the *protected territories*). Specifically, the percent reduction in median total lesion volume is substantially diminished from ~35-40% reduction in new lesions (*protected territories* only) to a best case scenario of ~5% reduction in new lesions (*all territories*). The PP analysis shows a worst case increased median new lesion volume (*all territories*) in patients with protection. It is important to note that these are observed treatment differences and no statistical hypotheses were tested.

There were several additional analyses performed by the sponsor to assess effectiveness of the device as it relates to neurocognitive testing, additional imaging findings (MRI T2/FLAIR assessments, lesion number), mechanism of action (i.e., histopathological analysis), and device utility (see list in Section 9.4). A summary of the results is provided in the tables below.


(b) (4)

Table 17: Maximum single new lesion volume per patient (*Protected Territories* and *All Territories*) - Secondary Effectiveness Endpoints 8.1 and 8.2

Population	Test Arm (mm^3)	Control Arm (mm^3)	p-value*
Protected Territories			
ITT	63.3 (29, 199.7), n=91, 0 min, 1945.9 max	85.7 (31, 226.8), n=98, 0 min, 24244.6 max	0.5728
PP	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	0.9364
All Territories			
ITT	128.5 (56, 282.1), n=91, 0 min, 13563.9 max	116 (55.4, 302.6), n=98, 0 min, 24244.6 max	0.8397
PP	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	0.3468

Note: Data presented as: max (25th percentile, 75th percentile), n, min, max

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

Table 18: Average single new lesion volume per patient (*Protected Territories* and *All Territories*) - Secondary Effectiveness Endpoints 8.3 and 8.4

Population	Test Arm (mm^3)	Control Arm (mm^3)	p-value*
Protected Territories			
ITT	48.8 (25.7, 87) n=91 0 min, 386 max	49.2 (25.2, 79.1) n=98 0 min, 8100 max	0.9426
PP	52 (30.3, 87.9) n=83 0 min, 386 max	48.3 (30.1, 73.5) n=89 0 min, 8100 max	0.4931
All Territories			
ITT	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	0.2956
PP	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	0.0574

Note: Data presented as: average (25th percentile, 75th percentile), n, min, max

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

Table 19: Correlation of Day 2-7 DW-MRI Lesion Volume (log transformed) with Change in Neurocognitive Battery Composite Z-Score - Secondary Effectiveness Endpoint 11

	Test Arm	Control Arm
2 to 7 Days Post-TAVR	-0.53 (49) p=<0.0001	-0.25 (53) p=0.0768
30 Day Follow-Up (23-45 days)	-0.21 (74) p=0.0743	-0.20 (72) p=0.0899
90 Day Follow-Up (46-100 days)	-0.24 (54) p=0.0839	-0.10 (55) p=0.4524

Note: Data presented as: r (n); p-value*

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

Table 20: Correlation of Day 30 T2/FLAIR MRI Lesion Volume (log transformed) with Change in Neurocognitive Battery Composite Z-Score - Secondary Efficacy Endpoint 12

	Test Arm	Control Arm
30 Day Follow-Up (23-45 days)	-0.04 (68) p=0.7403	-0.16 (63) p=0.1965
90 Day Follow-Up (46-100 days)	-0.06 (50) p=0.7037	-0.07 (47) p=0.6377

Note: Data presented as: r (n); p-value*

* p-values here are for reference only and should not be used to make inference since no formal statistical tests were pre-specified.

FDA Comment 20:

a. Secondary effectiveness endpoints 1 and 3 assessed the median number of new lesions after TAVR (as opposed to the lesion volume). In general, the control group demonstrated a numerically increased number of lesions for patients without protection compared to those with protection in both *protected territories* and *all territories* (see Table 16 above).

b. Secondary effectiveness endpoints 5, 7, 9 and 13 included additional assessments of lesion volume and number using T2/FLAIR imaging at 30 days. No new lesions were detected in either the Control or Test arms. Note that previous reports suggest that ~10% of patients experience new lesions between the post-procedural MRI and the assessment at 30 days.[9]

c. Secondary effectiveness endpoints 4 and 14 included assessment of neurocognitive decline at 2-7 days, 30 days and 90 days. These assessments did not show any discernable difference between patients with protection with the Sentinel System and those patients without protection. This is discussed in more detail in section 10.8.2 below.

d. Secondary effectiveness endpoint 8 included comparisons with regard to maximum and average new lesion volumes per patient for both *protected* and *all territories*. The average single new lesion volume per patient in all territories was numerically lower for the Control Arm (56.4mm^3) compared to the Test Arm (65.2mm^3) (see Tables 17 and 18 above).

e. Correlation of 2-7 day DW-MRI lesion volume and 30-Day T2/FLAIR MR lesion volume with change in neurocognitive composite z-score at 2-7 Day, 30 Days, and 90 Days and by treatment arm was performed (secondary effectiveness endpoints 11 and 12). In all subgroups, the correlation was in the negative direction (i.e., increased lesion volume correlated to decreased z-score or neurocognitive function). All comparisons showed weak correlation (i.e., $r \leq -0.25$). The most correlative measure was decline in z-score in the Test Arm at 2 to 7 days post-TAVR (-0.53) (see Tables 19 and 20 above).

f. Secondary effectiveness endpoint 10 includes a histopathological analysis of captured debris. In 99% of cases debris was captured with acute thrombus with tissue and foreign material being the most commonly removed debris. Material such as valve tissue and myocardium clearly relate to embolized debris; however, the distinction of embolic capture versus possible filter generated debris (e.g., arterial wall, acute thrombus) is less clear.

g. Secondary effectiveness endpoint 15 showed that the device could be effectively delivered and retrieved in > 90% of cases.

[9] Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation. Eur Heart J. 2015;36(31):2070-2078.

10.8 Additional Analyses

10.8.1 Quality of Life

The sponsor performed SF-12 quality of life assessments at baseline, 30 days and 90 days and no obvious difference or meaningful clinical trend was observed between groups.

10.8.2 Neurocognitive Testing

As noted in the section above, there were no statistical differences in decline in neurocognitive z-score at 30 days. In a post-hoc analysis, the sponsor did note that neurocognitive decline was correlated with increasing lesion volume/number in all territories. Although the data show no meaningful difference in neurocognitive outcomes (from both a clinical and statistical perspective), the sponsor concludes from the correlation that a decrease in lesion volume is a predictor for neurocognitive decline.

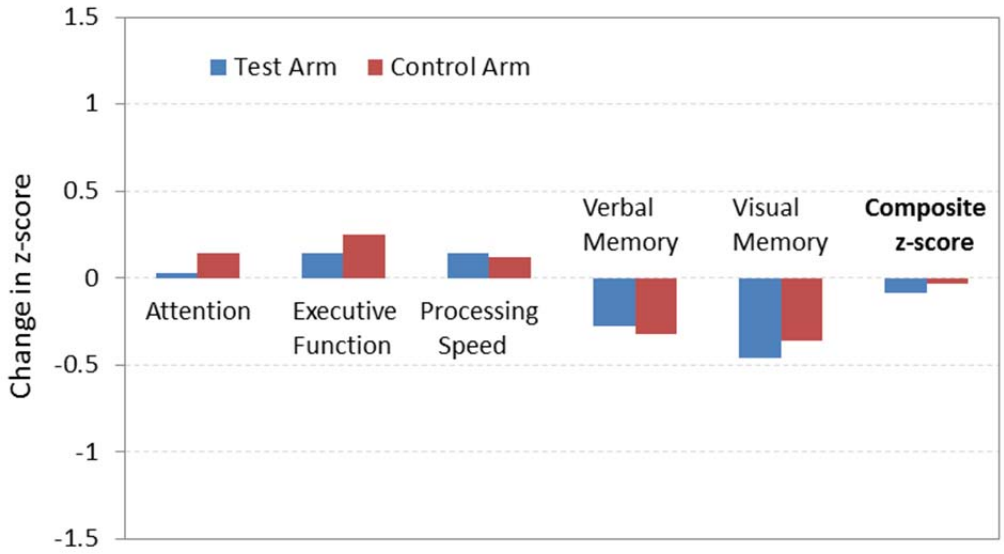
A Neurocognitive Battery was conducted at baseline, 30 days, and 90 days post index procedure to assess patient's neurocognitive status. Calculation of the composite z-score was based on five of the 7 domains: Attention, Executive Function, Processing Speed, Verbal Memory, Visual Memory. A z-score for each domain was calculated based on the normative means and standard deviations for each neurocognitive test that were supplied by the Neurocognitive Core Lab at Columbia. These norms were stratified by age at time of visit. When there was more than one test for a given domain, an average z-score was computed from the z-scores of the tests for that domain. Table 21 presents changes in Neurocognitive Battery Composite Z-Score for the Test and Control Arms. Note that a positive change in z-score indicates improvement.

Table 21: Change in Neurocognitive Battery Composite Z-Score from Baseline (Secondary Efficacy Endpoint 4, 14) (ITT Population)

	Test Arm Mean ± SD, n	**Control Arm** Mean ± SD, n
30 Days	-0.09 ± 0.44, 93	-0.03 ± 0.37, 92
90 Days	0.18 ± 0.38, 77	0.18 ± 0.35, 76

FDA Comment 21: Although it is observed that the Neurocognitive Battery Composite z-score decreased at 30-day follow-up and then increased at 90-Day follow-up (see Table 21 above), it is unclear whether the small change represents a clinically meaningful change in neurocognitive function or if it is merely due to random variation. No obvious difference between Test and Control Arms were noted with respect to changes in overall z-scores at both 30 days and 90 days follow-up, and this is also true for change in component z-scores for all five component domains at 30 Days (Figure 7) and 90 Days (not shown). The Panel will be asked to comment on the clinical significance of the neurocognitive outcomes.

Figure 7: Change in Neurocognitive Test Battery Z-Scores from Baseline to 30 Days



Note: Data used to generate this graph was taken from the Clinical Study Report. Table 44 of the Sponsor Executive Summary presents the same data in tabular form.

Mental Status and Depression were also assessed (data not shown here). Again, no noticeable difference between the two arms was observed.

10.8.3 Gender

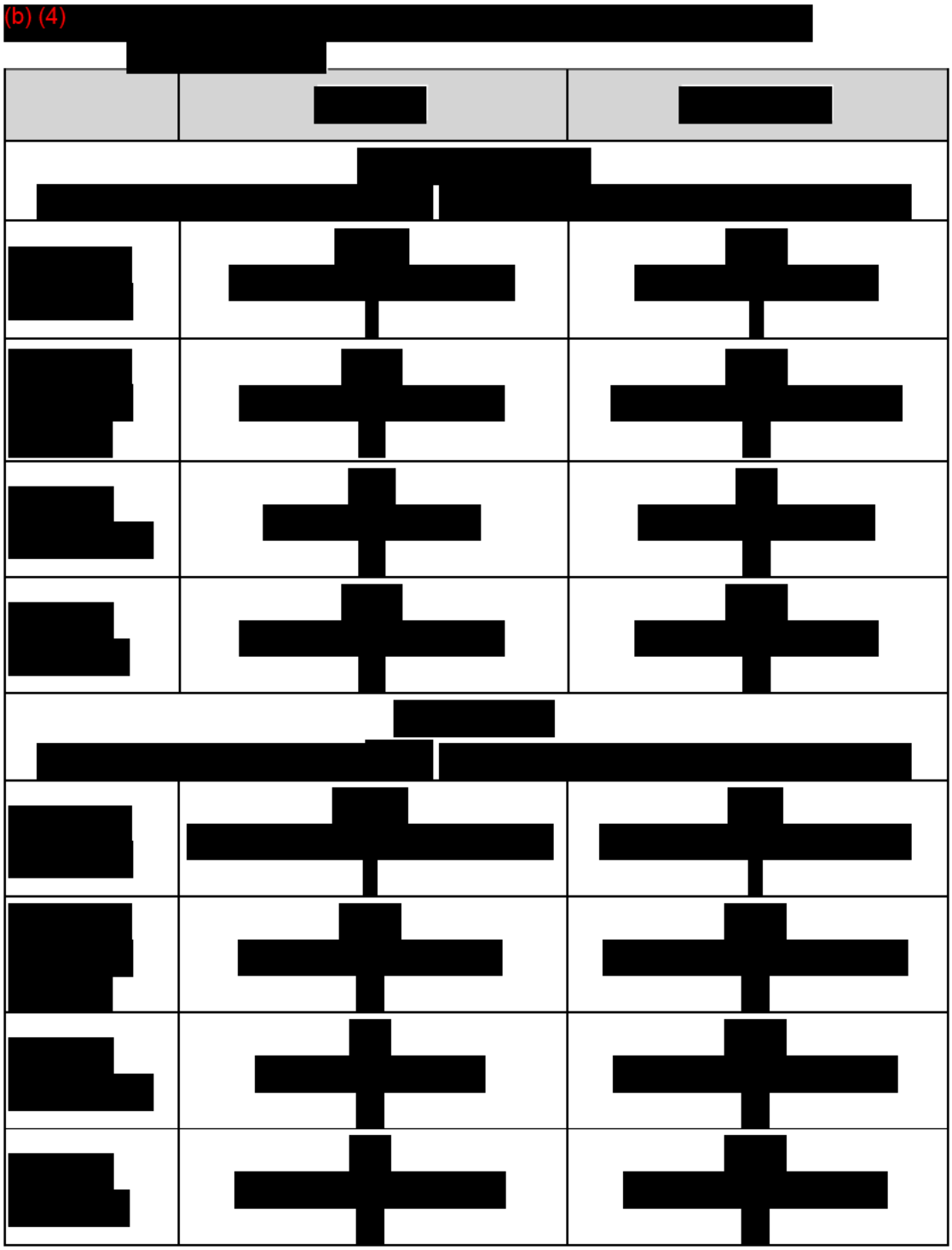
The sponsor provided data comparing 30-Day MACCE and new lesion volume between genders. No significant differences between groups were noted.

FDA Comment 22: Between the Test Arm and the Control Arm, there was no notable difference in quality of life measures. As noted above, there were no differences or clear clinical trend in the aggregate neurocognitive battery or its components. Gender differences were not noted for MACCE and new lesion volumes.

10.8.4 Valve Type

The trial allowed for the use of valves as they became introduced into the market. The median total new DW-MRI lesion volume was compared for the Test and Control Arms by valve type. See Table 22 below.

(b) (4)



FDA Comment 23: Valves were noted to be associated with different trends in total new lesion volume. Note that the study did not pre-specify stratification of results by valve type and statistical inference should not be made. Reliance on this data for any definitive conclusions is not warranted. FDA cautions that any conclusions about the superiority of one valve system over another would be misleading given the inability of the data to allow such comparisons.

10.8.5 Multi-Variable Analysis (Valve Type and baseline T2/ FLAIR lesion Volume)

The sponsor performed a post-hoc covariate analysis to assess the impact of possible between-group imbalance of the influential factors on outcomes. The sponsor identified white matter disease at baseline (baseline lesion volume as measured by T2/FLAIR) as the covariate (high vs. low) for adjustment since it is believed to be a predictor of poorer outcome. Valve type was another covariate. An analysis of variance was employed with log transformed lesion volume at Day 2-7 as the response variable, and baseline lesion volume and valve type as the covariates. (b) (4) [redacted]

10.9 Roll-in Patients

Each investigational site participated in a formal, documented training program prior to enrollment of the first 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.

Table 23: 30-day MACCE Rate (Roll-In Patients)

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

Data presented as: % patients with event (n patients with event/N patients evaluable at 30 days or who experienced an event within 30 days) [number of events] (exact 95% CI)

10.10 Highest Enrolling Sites vs. Remaining Sites

At FDA's request, the sponsor conducted a post-hoc analysis of the top four enrolling sites grouped and compared to the remaining sites to assess the physician learning curve. The data are based on patients with 30-day follow-up or who experienced an event within 30 days. No significant difference between the top 4 enrolling sites and remaining sites was observed.

Table 24: 30-day MACCE Rate (Site Comparison) (PP Population)

	Top 4 Sites	Remaining Sites
Any MACCE	8.3% (19/230) [20] (5.0%, 12.6%)	7.6% (9/119) [9] (3.5%, 13.9%)
Death	1.7% (4/230) [4] (0.5%, 4.4%)	0.8% (1/119) [1] (0.0%, 4.6%)
Stroke	7.0% (16/230) [16] (4.0%, 11.1%)	5.9% (7/119) [7] (2.4%, 11.7%)
Disabling	0.9% (2/230) [2] (0.1%, 3.1%)	0.8% (1/119) [1] (0.0%, 4.6%)
Non-disabling	6.1% (14/230) [14] (3.4%, 10.0%)	5.0% (6/119) [6] (1.9%, 10.7%)
AKI (Class 3)	0% (0.0%, 1.6%)	0.8% (1/119) [1] (0.0%, 4.6%)

10.11 Device Success, Utility & Malfunction

The sponsor noted 3.1% (9/296) device malfunctions, including problems with deployment (5), the guide wire (3) and failure to flush (1). The sponsor did not report any adverse events related to the malfunctions or failures.

11 FDA's Perspective and Considerations

When evaluating whether the results of the SENTINEL study support the safety and effectiveness of the Sentinel System for the proposed indications, the following points should be considered.

11.1 Clinical Background

A particular challenge with TAVR procedures is the uncontrolled release of embolic debris, some of which may enter the cerebral circulation and present as stroke. Clinical stroke rates of approximately 2-5% have been reported after TAVR which is generally higher than stroke rates traditionally reported in patients who undergo surgical valve placement. The goal of the subject device is to maintain the benefits of TAVR while reducing embolic cerebral ischemia. Because a clinical trial designed to focus on clinical stroke reduction alone would be overly burdensome given the anticipated large sample size and trial duration in this dynamic field, a surrogate was considered to evaluate effectiveness/benefit of the Sentinel System as measured by cerebral infarct volume on DW-MRI. DW-MRI lesions may be seen in >80% of patients after TAVR; however, most of these lesions are not apparent as clinical strokes and the clinical significance of these lesions remains an area of research and clinical debate. One aspect of this debate is whether these nonclinical infarcts contribute to more subtle neurological deficits that may be detected by neurocognitive testing.

11.2 Device Design & Function

The SENTINEL System is designed to protect territories of the cerebral vasculature supplied by the carotid and right vertebral arteries in patients undergoing TAVR. The left vertebral artery distribution is unprotected. The device intended for market is the one studied in the SENTINEL clinical trial with exception of planned minor design modifications not expected to impact the clinical use or function of the device.

11.3 SENTINEL Pivotal Study

The SENTINEL pivotal study was performed with a goal of demonstrating that patients who had protection with the Sentinel System had non-inferior safety (30-day MACCE) compared to a performance goal derived from historical data on patients without protection. It was also designed to show that the device had superior effectiveness with regard to reduction in cerebral ischemic events as measured by new lesion volumes in *protected territories* detected by DW-MRI after TAVR. (The study was not designed to show reduction in clinical stroke.) The effectiveness assessment included a statistically driven component and an observed treatment effect component. Study success required that all three primary assessments were met. Two of the three criteria were met (i.e., safety and observational treatment effect); however, statistical superiority with regard to DW-MRI lesion volume reduction was not met. Therefore, the study did not meet the pre-specified study success criterion.

11.4 Analysis Populations

Several analysis populations were defined to include ITT with imputation, ITT (without imputation), PP and AT. The sponsor pre-specified the ITT with Imputation population as the primary analyzable cohort. This analysis includes patients as randomized and imputation to account for missing data (i.e., clinical, DW-MRI) since only 189 of the 240 patients randomized to the Imaging Study Arm had analyzable data to assess effectiveness. In addition, an ITT (without imputation) analysis was performed. Of note, the ITT patient population excludes those patients without paired DW-MRI imaging, and the PP population further excludes patients with DW-MRI imaging or neurocognitive testing performed outside of the follow-up window. The AT population reflects results based on treatment actually received regardless of the treatment assignment during randomization. Note that the Sentinel device was not used in 9 patients who were assigned to have the device. The four analysis populations reflect different aspects of the data and no single population is considered alone for regulatory decision-making.

11.5 Primary Safety Analysis

For all analysis populations, the overall MACCE rate was ~7.5% (with 95% CI upper bound of ~11%) which meets the pre-specified performance goal of 18.3%. The pre-specified safety success criterion was met and no unusual safety problems were noted with device use.

11.6 Primary Effectiveness Analysis

Success for effectiveness required that two criteria were met:

Criterion #1: Hypothesis test-driven criterion to show that there was statistically significant reduction in median total new DW-MRI lesion volume in *protected territories* in patients who received the Sentinel System. For the sponsor's proposed primary analysis population (ITT with Imputation), there was a 64.9 mm^3 observed volume reduction between the Test Arm (median 109.1 mm^3) and the Control Arm (median 174 mm^3), yielding an p-value of 0.2354. Criterion #1 was not met. Note that this analysis included only *protected territories*.

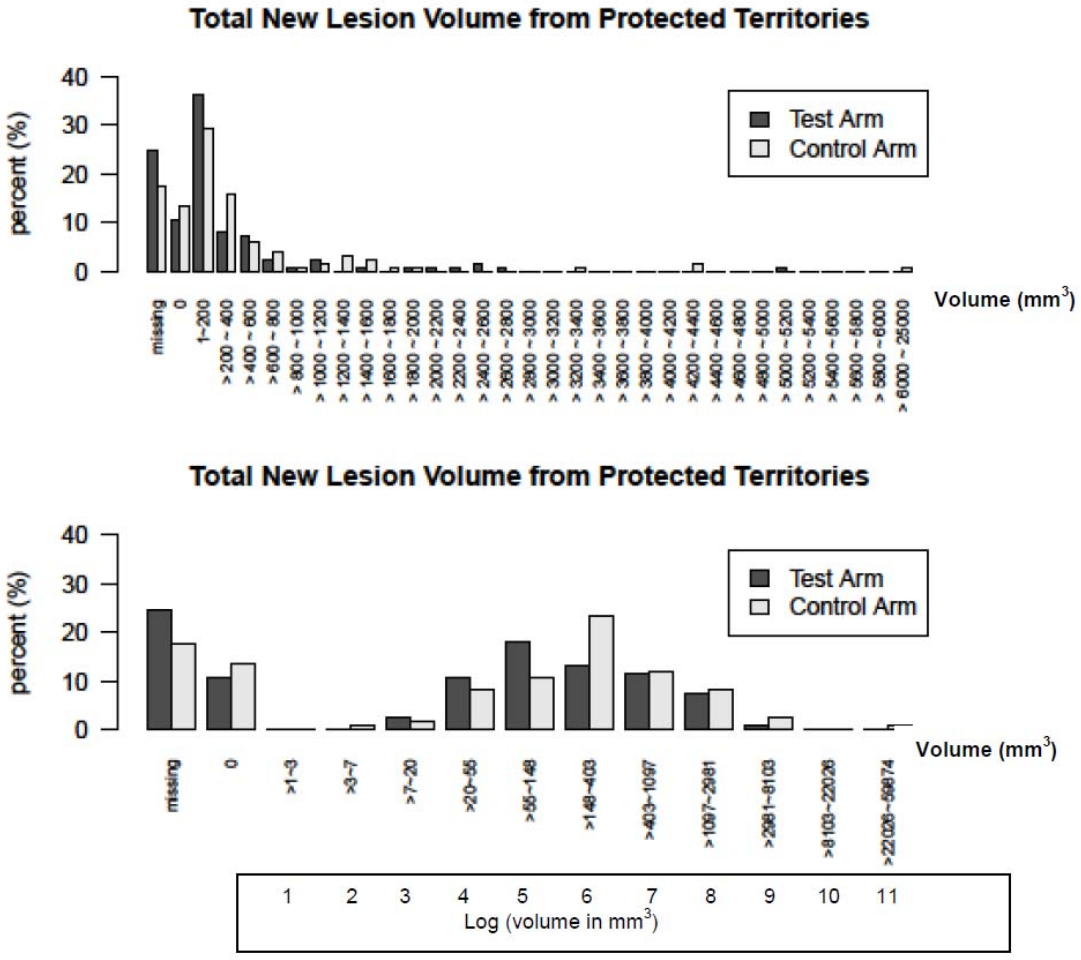
Criterion #2: Observed reduction of at least 30% in median new lesion volume in *protected territories* in patients who received the Sentinel System comparing to those who did not. For the sponsor's proposed analysis population (ITT), lesion volume reduction of 42.2% was observed which is above the 30% threshold. Criterion #2 was met. Again, this analysis only included *protected territories*.

The pre-specified effectiveness success criterion was not met.

Furthermore, because the overall clinical impact of the concept of embolic protection during TAVR procedures relates to the goal of protecting the whole patient/brain, FDA believes it is important to consider defects in all territories when considering the totality of the data to support a marketing decision.

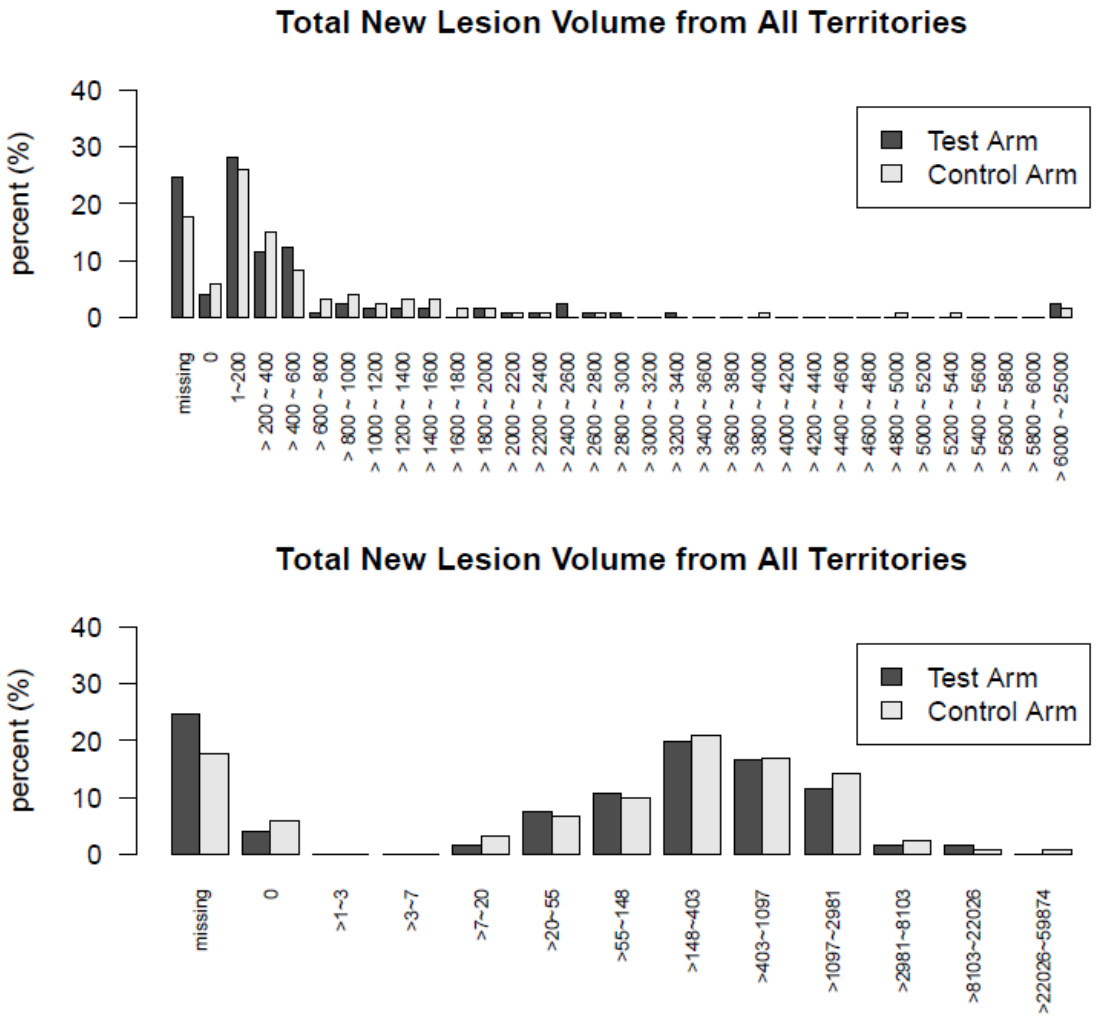
FDA plotted the frequency distribution of the observed total new lesion volume in protected territories for the Test and the Control Arms (see Figure 8 below). The two plots differ only in how the data are grouped: the top plot uses equal width intervals (in an increment of 200 mm3), while the bottom plot uses unequal width intervals but equal width intervals under log scale. The distribution of the observed total new lesion volume for the Test Arm shows a small shift to the left, suggesting a slightly lower total volume in the Test Arm as the results based on medians indicated. Note that "missing" is the percent of subjects with missing lesion volume measurements (Test: (121-91)/121 = 24.8%; Control: (119-98)/119 =17.6%) and "0" indicates the percentage of subjects with no new lesion volume (or new lesion volumes below a detectable level).

Figure 8: Frequency Distribution of Total New Lesion Volume – *Protected Territories*



Similarly, FDA plotted the frequency distribution of the observed total new lesion volume in all cerebral territories for the Test and the Control Arms (see Figure 9 below). The total new lesion volumes in all territories are similar for the Test Arm and the Control Arm, suggesting no difference between the two.

Figure 9: Frequency Distribution of Total New Lesion Volume – *All Territories*



11.7 Pre-Specified Secondary Safety Endpoints

There were four pre-specified secondary safety endpoints. Comparison of 30-day MACCE rates between the Test (6.0%) and Control Arms (9.9%) demonstrated a favorable trend for the device; however, no statistical conclusions may be drawn regarding the observed difference in stroke rate between the Test (4.3%) and Control Arms (9.1%) since the study was not designed to detect differences in

clinical stroke rates. Similar trends were noted for In-Hospital MACCE events. Vascular complications were rare with one brachial injury noted. An overall serious adverse event rate of ~43% was noted in the Test and Control Arms. Overall, no concerning safety trends were noted in patients treated with the Sentinel System.

11.8 Pre-Specified Secondary Effectiveness Endpoints

There were 15 pre-specified secondary safety endpoints. The most noteworthy endpoint is designated by the Sponsor as Secondary Endpoint #2. This is similar to the primary effectiveness endpoint except that it includes *all cerebral territories* and not just those that are protected by the Sentinel System. For the sponsor's proposed primary analysis population (ITT), there was a 15.8mm^3 observed volume reduction in the Test Arm (median 294mm^3) comparing to the Control Arm (median 309.8mm^3), yielding a p-value of 0.8076 and the observed reduction in terms of percent is 5.1% which is much smaller than that for *protected territories* only (42.2%).

Several additional secondary endpoints showed:

1) No clear clinical trends in the aggregate neurocognition battery or its component z-scores were noted.
2) Assessment of lesion number generally tracked lesion volume and was not uniquely informative.
3) In 99% of cases debris was captured with acute thrombus with tissue and foreign material being the most commonly removed debris. Differentiation of filter-generated material and captured material is not discernable for all cases.
4) The median number of patients with new T2/FLAIR lesions was zero in all study arms at 30-days.

11.9 Supplemental Post-Hoc Analyses

1) No differences in Quality of Life measure were noted between groups.
2) The Sponsor noted that for patients who suffered a clinical stroke, their total lesion volume was lower for patients who were protected by the Sentinel System. They also provided an analysis to show that neurocognitive decline is associated with an increase in both lesion volume and lesion number. However, as noted in Section 10.8.2 above, no trends were noted in the neurocognitive testing outcomes.

(b) (4)

[redacted]

11.10 Roll-In Patients

The 30-day MACCE rate for Roll-In Sentinel patients (6.8%) was similar to that of Randomized Sentinel patients (~7.5%).

11.11 Blinding & Bias

The sponsor included trial elements to minimize bias including: (1) randomization; (2) independent assessment of events (CEC); (3) independent assessment of imaging by blinded imaging core laboratories (MR, CT); (4) systematic neurocognition training; (5) neurological and neurocognitive assessment by a blinded neurologist or certified examiner; (6) patient blinded to treatment; and (7) independent assessment of debris (histopathological analysis by core pathology laboratory. In general, controls for this trial were in place to minimize bias, and the sponsor made reasonable efforts to minimize missing data. The main source of missing data in the effectiveness evaluation was that paired DW-MRI studies were not performed.

11.12 Device Success/Utility and Malfunction

There were a total of 9 device malfunctions reported, none of which were associated with adverse events. The device appears to technically function as intended.

12 Conclusions

The data presented in the subject De Novo request characterizes the safety and effectiveness of the Sentinel® Cerebral Protection System. The Panel will be asked to fully assess the significance of these results and comment on the benefit-to-risk ratio of using the Sentinel® Cerebral Protection System during TAVR procedures.

APPENDIX I:

SENTINEL Study Statistical Analysis Plan (SAP)

STATISTICAL ANALYSIS PLAN

Cerebral Protection in Transcatheter Aortic Valve Replacement
The SENTINEL Study

Revision B

Product Name:
Claret Medical™ Sentinel™ Cerebral Protection System

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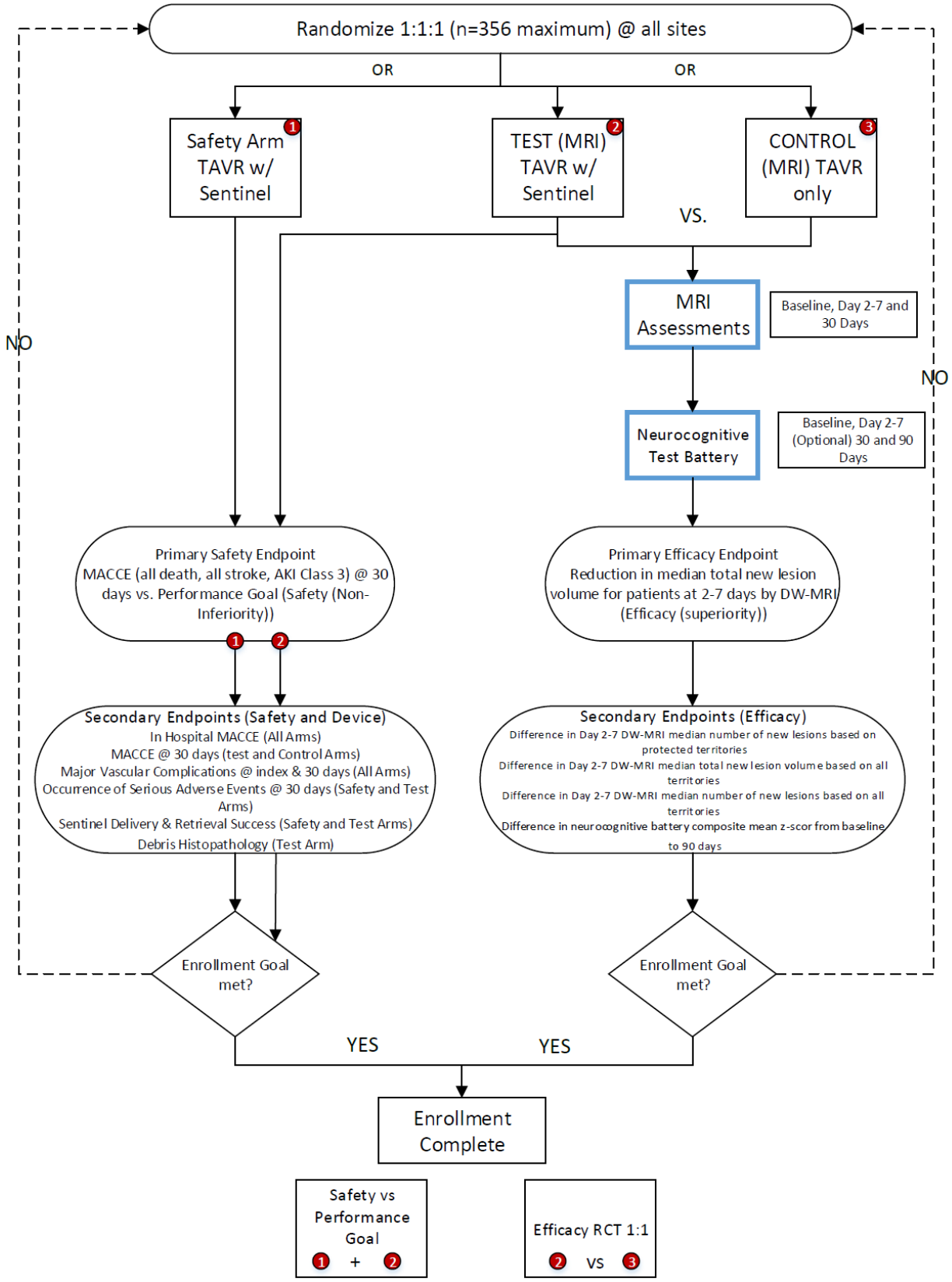
Table of Contents

1. Overview

The primary objective of this study is to characterize the safety and efficacy of the Sentinel Cerebral Protection System (Sentinel System) in subjects with severe symptomatic calcified native aortic valve stenosis undergoing a TAVR procedure with or without the Sentinel investigational device. The study will enroll up to 356 randomized patients with up to 150 roll in patients. The study design is a concurrent three-arm randomized trial that includes subjects who will be randomized to undergo TAVR with the test procedure without MRI (Safety Arm), and subjects randomized to either test or control (Imaging Arms) in a 1:1:1 ratio. The subjects randomized to the Imaging Arms will undergo MRI at baseline, 2-7 days, and 30 days following the study TAVR procedure with or without the Sentinel test device. In addition, this cohort will undergo baseline, 2-7 days (optional), 30 days and 90 days neurocognitive evaluation. See figure below for an overview of the SENTINEL study.


Randomize 1:1:1 (n=356 maximum) @ all sites
OR
OR
Safety Arm TAVR w/ Sentinel
1
TEST (MRI) TAVR w/ Sentinel
2
CONTROL (MRI) TAVR only
3
VS.
MRI Assessments
Baseline, Day 2-7 and 30 Days
NO
NO
Neurocognitive Test Battery
Baseline, Day 2-7 (Optional) 30 and 90 Days
Primary Safety Endpoint
MACCE (all death, all stroke, AKI Class 3) @ 30 days vs. Performance Goal (Safety (Non-Inferiority))
1
2
Primary Efficacy Endpoint
Reduction in median total new lesion volume for patients at 2-7 days by DW-MRI (Efficacy (superiority))
Secondary Endpoints (Safety and Device)
In Hospital MACCE (All Arms)
MACCE @ 30 days (test and Control Arms)
Major Vascular Complications @ index & 30 days (All Arms)
Occurrence of Serious Adverse Events @ 30 days (Safety and Test Arms)
Sentinel Delivery & Retrieval Success (Safety and Test Arms)
Debris Histopathology (Test Arm)
Secondary Endpoints (Efficacy)
Difference in Day 2-7 DW-MRI median number of new lesions based on protected territories
Difference in Day 2-7 DW-MRI median total new lesion volume based on all territories
Difference in Day 2-7 DW-MRI median number of new lesions based on all territories
Difference in neurocognitive battery composite mean z-scor from baseline to 90 days
Enrollment Goal met?
Enrollment Goal met?
YES
YES
Enrollment Complete
Safety vs Performance Goal
1 + 2
Efficacy RCT 1:1
2 vs 3

The primary superiority efficacy endpoint of Total Median New Lesion Volume in Protected Territories by DW-MRI will be solely based on the Imaging Arms (Test and Control Groups), where DW-MRI performed at 2-7 days following the study procedure.

The primary safety endpoint of MACCE (Major Adverse Cardiac and Cerebral Events) at 30 days will be based on the Imaging Arms Test subjects randomized to receive the test procedure **plus** the subjects randomized to the Safety Arm who will all undergo TAVR with the test procedure.

The statistical methods proposed for this study will determine if the 30 day MACCE rate is non ï inferior to the rate derived from the peer-reviewed literature (safety), and if the total median new lesion volume in the protected territories at 2-7 days post-procedure is significantly less in TAVR subjects randomized to receive the test procedure compared to control patients (efficacy).

Study Success

Study success is defined relative to the primary safety and efficacy endpoints. The following criteria must be met to achieve study success:

- The upper bound of the one-sided 95% confidence interval for the MACCE rate must be less than the pre-specified threshold of 18.3%
- and a significant difference ($p<0.05$) in the median new total lesion volume between the 2 randomized treatment groups where the treatment arm has a lower median new total lesion volume from the protected territories compared to the Control Group study endpoints.
- To demonstrate the observed ratio of the median total new lesion volumes Ó30% in favor of the Test group having a lower median total new lesion volume in the protected territories as compared to the Control group in order to demonstrate a meaningful clinical success criteria,. There is no hypothesis test associated with this criteria as it is based on the point estimate of the ratio of observed median total new lesion volumes.

A detailed discussion of the main study endpoints and their derivation is included in the following sections.

1.1 Primary Efficacy Endpoint and Derivation (Superiority)

The primary efficacy endpoint for the study is to show a reduction in median total new lesion volume in protected territories between the test and control cohorts assessed by DW-MRI at day 2-7 post-procedure.

- Total new lesion volume is defined as the sum of all diffusion-positive new cerebral lesions in post-procedural DW-MRI relative to the pre-TAVR DW-MRI scans.
- Protected territories are 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

Background

The use of magnetic resonance imaging (MRI) is a well-established tool for quantifying ischemic lesions in the brain. Diffusion weighted MRI (DW-MRI) is a powerful tool used to characterize ischemic lesions that have occurred within the first several days of an embolic event. The use of DW-MRI has been established historically in assessing the outcomes for acute stroke in carotid artery stenting (CAS)[1,2,3] and TAVR[4,5,6,7,8,9]. Total lesion volume and likelihood of neurological deficit are strongly associated[2,8]. The occurrence of a single or few small lesions may result in large total lesion volumes. Therefore, the number of lesions may not correlate well to the total volume or clinical

outcome and will not be of primary interest. Similarly, single lesion volume analysis may not translate well to being predictive of effectiveness or clinical relevance.

DW-MRI Total Lesion Volume

The use of DW-MRI as a surrogate endpoint for risk of sub-clinical stroke has been proposed. TAVR DW-MRI publications have been reviewed. Reports of new cerebral lesions in TAVR subjects ranges from 68-91%. A summary of the reported data is described in the table below.

Table 1: DW-MRI Findings in TAVR Subjects

	Rodes-Cabau 2011		Ghanem 2010*	Arnold 2010	Kahlert 2010		Fairbaim 2011	Astarci 2011	
	TF-TAVI	TA-TAVI	TF-TAVI	TA-TAVI, SAPIEN	Sapien	CoreValve	CoreValve	TF-TAVI, Sapien	TA-TAVI, Sapien
Sample size (with MRI), n	29	31	22	25	22	10	31	21	14
Number of lesions									
Mean	n/r	n/r	3.4	n/r	4	2.6	4.2	6	6.6
Median	3	4	1.5	n/r	n/r	n/r	2	4	4.5
S.D. (95%CI); IQR	IQR 1-7	IQR 2-9	5.1	n/r	(2.1-6.0)	(0.3-4.9)	6.5 (IQR 1-5)	6.8	7.1
% w/ new lesions	66.0%	71.0%	72.7%	68.0%	86.4%	80.0%	77.0%	90.0%	93.0%
Volume, per lesion (mm^3)									
Mean lesion volume	n/r	n/r	1022	n/r	81	61	n/r	n/r	n/r
Median lesion volume	n/r	n/r	175	n/r	n/r	n/r	n/r	n/r	n/r
Lesion S.D. (95%CI); IQR	n/r	n/r	2872	n/r	(60-103)	(37-86)	n/r	n/r	n/r
Volume, total (mm^3)									
Mean total patient volume	n/r	n/r	5564	n/r	n/r	n/r	2050	475	2170.5
Median total patient volume	n/r	n/r	400	n/r	n/r	n/r	n/r	n/r	n/r
Total volume S.D. (95%CI)	n/r	n/r	16826	n/r	n/r	n/r	3500	n/r	n/r
Periprocedural neuro deficits, n (%)	n/r	n/r	>1	20%	0	0	6.0%	0	0

n/r = not reported; n/a = not applicable
*Ghanem: 1 patient w/ 70,000 mm^3

A number of parameters contribute to the MRI output. Machine settings, magnetic field strength, timing of the scan relative to the intervention, and treatment and interpretation of the scans may all contribute to inter-study and inter-site variability. Rigorous management of all aspects of the Imaging Study Arm is required including investigational site equipment and staff qualifications, site staff contacts and training, management of imaging status by subject, ensuring accuracy and quality of MRI sequence acquisition (slice thickness, FOV, echo repetition time, matrix size, etc.) image sharing and handling, and communication with the MRI Core Laboratory. All these factors will be documented in a formal, revision controlled MRI manual of operations.

Presence of lesions, number of lesions, location of lesions, intensity of lesions, and volume of lesions are extracted from each subject and are available for analysis.

Consistent with the clinical outcomes, most of the subjects have ischemic lesions, but they remain clinically silent. Only Ghanem, et. al[5] provided raw data allowing a probability density function to be plotted as shown in the figure below.

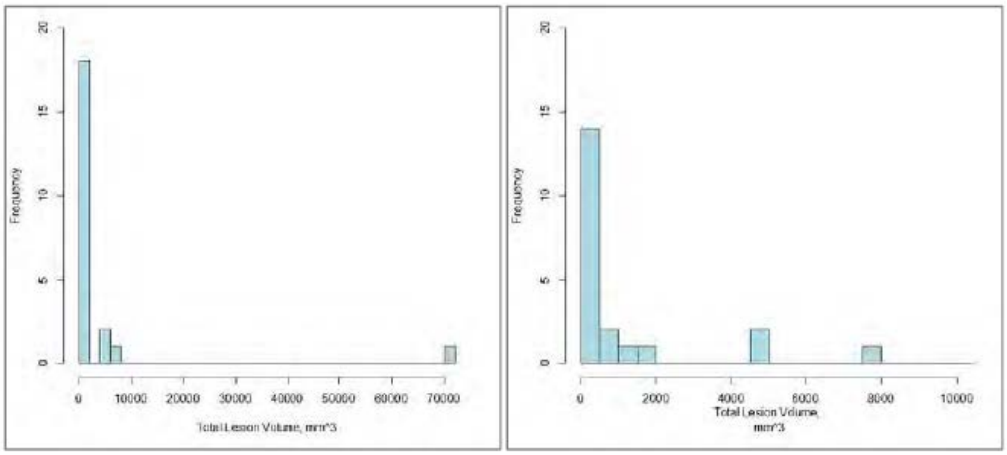


Figure 1: Total lesion volume among subjects, Ghanem, et. al., n = 22. (Left: all subjects; Right: truncated)

The distribution is demonstrably non-normal, requiring non-parametric methods for analyzing data or transformation to stabilize the data.

(b) (4)

[redacted]

DW-MRI Field Strength and Timing

The available TAVR DW-MRI literature[4,5,6,7,8,9] utilizes a mix of 1.5 T and 3.0 T field strengths. The peak DW-MRI signal intensity is two to four days, as shown in the graphic below. The signal is sufficient at both two and seven days to produce a meaningful comparable lesion volume.

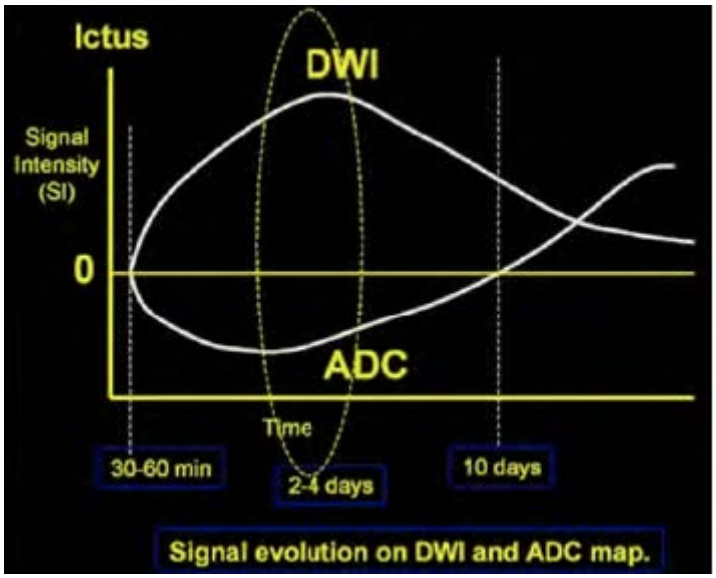


Figure 2: Signal evolution on DW-MRI

Other practical considerations include TAVR post-op care and discharge practices and maintaining data integrity/consistency across study sites. In order to align with the signal intensity window and management of subject care, the specified DW-MRI window is 2-7 days.

These volumes are in line with the 73% parenchymal brain volume estimate and constitute more than 60% of the total lesion burden in these subjects.

REFERENCES:

[1] Stojanov et al, New Ischemic Brain Lesions on Diffusion-Weighted MRI after Carotid Artery Stenting with Filter Protection: Frequency and Relationship with Plaque Morphology. AJNR 2012; 33:708-714.

[2] Bonati LH, Jongen LM, Haller S, et al. New ischemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol* 2010;9:353ï 62

[3] Flach et al, Cerebral Ischemia After Carotid Intervention. J Endovasc Ther 2044; 11:251-257.

[4] Rodes-Cabau J, et al. Cerebral Embolism Following Transcatheter Aortic Valve Implantation. Comparison of Transfemoral and Transapical Approaches. J Am Coll Cardiol 2011;57:18ï 28

[5] Ghanem A, Muller A, Nahle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G, Thomas D. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol 2010;55:1427-1432.

[6] Arnold M, et al. Embolic Cerebral Insults After Transapical Aortic Valve Implantation Detected by Magnetic Resonance Imaging. J Am Coll Cardiol Intv 2010;3:1126ï 32

[7] Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation 2010;121:870-878.

[8] Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, Blackman DJ, Plein S, Greenwood JP. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. Heart. 2012 Jan;98(1):18-23

[9] Astarci P, et al. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve. European Journal of Cardio-thoracic Surgery 40 (2011) 475ð 479

[10] Moeller, T. B., and E. Reif. "Pocket Atlas of Sectional Anatomy. Computed Tomography and Magnetic Resonance Imaging. Volume I." Head and Neck. 3rd ed, Germany (2007).

[11] Grabner, G¿nther, et al. "Symmetric atlasing and model based segmentation: an application to the hippocampus in older adults." Medical Image Computing and Computer-Assisted Interventionï MICCAI 2006. Springer Berlin Heidelberg, 2006. 58-66.

[12] Jenkinson, Mark, et al. "Improved optimization for the robust and accurate linear registration and motion correction of brain images." Neuroimage 17.2 (2002): 825-841.

[13] Avants, Brian B., et al. "Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain." Medical image analysis 12.1 (2008): 26-41.

1.2 Primary Safety Endpoint and Derivation (Non-Inferiority)

The primary safety endpoint for the study is to evaluate the rate of adjudicated Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days compared to a historical performance goal. MACCE events are adjudicated by a Clinical Events Committee blinded to the treatment arms and composed of two cardiologists, a vascular neurologist, a stroke neurologist, and a nephrologist.

- MACCE is defined as All Death, All Stroke, Acute Kidney Injury (Class 3)*

*Adjudicated by the CEC ï AKI-class 3 at discharge or 72 hours post index procedure, whichever occurs first

Safety Endpoint Derivation

The point estimate for the historical performance goal for the safety endpoint of MACCE (all death, all stroke, acute kidney injury) at 30 days for the TAVR population has been derived from published FDA documents.

(b) (4)

[redacted]

(b) (4) [redacted]

2. Statistical Methods and Analyses

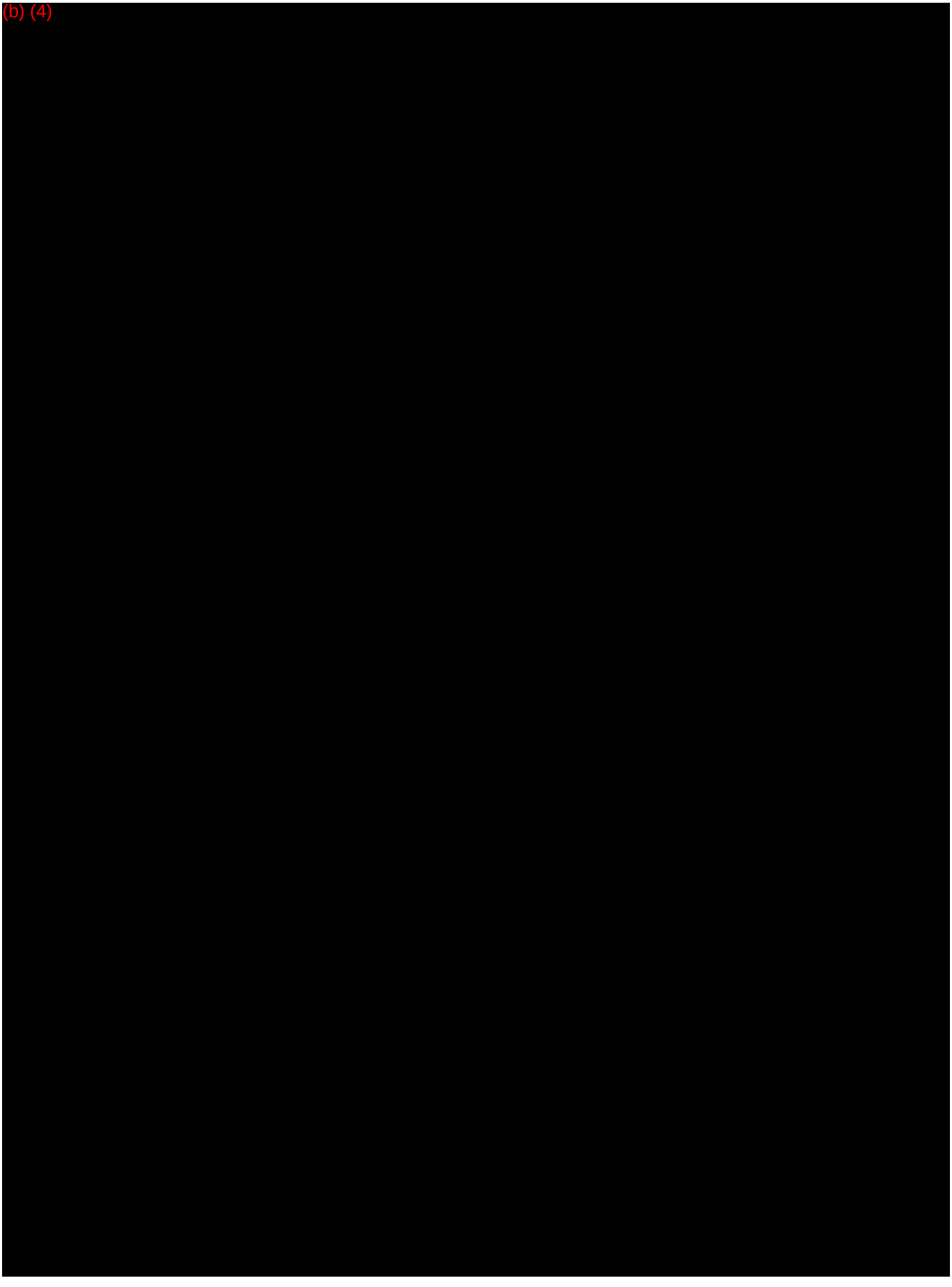
2.1 Determination of Sample Size (Primary Efficacy)

Sample size estimates for comparing the total new lesion volume from the protected territories between the 2 randomized imaging arms were obtained based on a Wilcoxon-Mann-Whitney test, assuming data with a lognormal distribution. Sample size was calculated using SAS Version 9.3. The observed means and lognormal means used to obtain sample size are presented in the table below.

(b) (4) [redacted]

[redacted]

2.2 (b) (4) [redacted]


(b) (4)

2.3 Populations for Analysis

The primary safety, efficacy, and sensitivity analyses will be predicated on the intention-to-treat (ITT) population, composed of all randomized subjects, irrespective of whether they undergo the study procedure.

Due to the nature of the study design and randomization process, there may be subjects that are randomized but no study procedure is attempted due to Imaging (Angiographic and/or CT and/or DW-MRI) exclusion criteria or an extenuating circumstance such as deterioration in subject health or withdrawal of consent between the time of randomization and scheduled study procedure. Thus, the following supportive analyses will be performed:

- Per Protocol (referred to as modified intention-to-treat in the protocol): Consists of all randomized subjects in whom the investigational study procedure is attempted as prescribed by their treatment arm and whose follow-up assessments are in the pre-specified windows. The ñper protocolò population will be used for secondary endpoints and as a supportive analysis population for the primary safety and efficacy endpoints.
- As Treated: Consists of randomized subjects placed into an analysis arm 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 device would be analyzed as a control patient in the ñAs Treatedò analysis.

2.4 Primary Efficacy Analyses

The primary efficacy analysis will be based on median total new lesion volume in protected territories within the ITT population and utilizes imputation for missing or out of window data (referred to as ITT with imputation). This population consists of:

- Data from patients in the imaging arms who received a DW-MRI scan in the pre-specified 2-7 day window
- Imputed data for the following patients:
    - Imaging arm patients who received neither the assigned treatment nor a post-procedure DW-MRI scan
    - Imaging arm patients who did not receive a post-procedure DW-MRI scan
    - Imaging arm patients who received a DW-MRI scan outside the pre-specified 2-7 day window

Primary efficacy success is predicated on detecting a significant difference ($p<0.05$) in median total new lesion volume in favor of the test group 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.

- Total new lesion volume from the protected territories volume is defined as the sum of all diffusion-positive new cerebral lesions from the protected territories in post-procedural DW-MRI relative to the pre-TAVR DW-MRI scans.
- Protected territories are 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.

The null and alternative hypotheses for determining if there is a significant difference is presented below

H_0: $\tilde{O}_{test} = \tilde{O}_{control}$
H_A: $\tilde{O}_{test} \neq \tilde{O}_{control}$

where,
$\check{\imath}\ \tilde{O}_{test}$ = Day 2-7 DW-MRI median total new lesion volume based on protected territories from the test group
$\check{\imath}\ \tilde{O}_{control}$ = Day 2-7 DW-MRI median total new lesion volume based on protected territories from the control group

(b) (4)

The primary efficacy endpoint will also be evaluated using a Two-Part model. The point estimate used in SENTINEL was predicated on the CLEAN-TAVI trial which solely used Medtronic CoreValve. During SENTINEL enrollment, additional valves were introduced to the U.S. market and used in the study. A review of the complete, aggregate, blinded SENTINEL dataset shows these new valves exhibit a different lesion volume distribution than observed in CLEAN-TAVI with a much higher occurrence of zero lesion volumes. These zero volumes may confound the Wilcoxon-Mann-Whitney analysis; therefore, Claret also intends to utilize a Two-Part analysis. In this Two-Part analysis the first part compares the occurrence of zero volumes, and the second part compares the non-zero values using the Wilcoxon-Mann-Whitney U test. Since these are two independent evaluations, the chi-squares for two tests are summed and evaluated as a chi-square with 2 degrees of freedom[3]. The impact of using the Two-Part model will also be evaluated by comparing the data from the Wilcoxon-Mann-Whitney U test.

Bootstrapped estimates of the treatment difference and 95% confidence interval will also be obtained. One thousand (1000) datasets will be created by sampling with replacement from the imputed dataset. The number sampled for test and control subjects will depend on the number

[3] Lachenbruch, P. A. (2001). Power and sample size requirements for two-part models. *Statistics in Medicine, 20*, 1235-1238.

randomized to each cohort after enrollment is complete. For each dataset, the 2-7 Day median total new lesion volume based on protected territories will be calculated for each group, and a difference between the median values obtained (test minus control). A 95% confidence interval based on the percentile bootstrap will be constructed from the sampling distribution, and will be presented along with the observed treatment difference. The observed treatment difference will be calculated from the imputed dataset as the median total new lesion volume in the treatment group minus that in the control group.

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

Best case: Treatment arm subjects with missing data will have 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 will have their 2-7 Day total new lesion volume imputed with the highest value observed among all randomized imaging subjects with data available.

Worst case: Treatment arm subjects with missing data will have 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 will have their 2-7 Day total new lesion volume imputed with the lowest value observed among all randomized imaging subjects with data available.

For the best and worst case analysis, the median total new lesion volume will be presented by group, along with the standard deviation and range. The differences between the test and control will be evaluated on the imputed dataset using the Hodges-Lehmann estimate of location shift, and a 95% confidence interval about the shift.

A summary of the DW-MRI analyses to be performed using median lesion volumes in protected territories is provided below:

(b) (4)

2.5 Secondary Efficacy Analyses

All secondary endpoints will be evaluated using the per protocol population and used for labeling. All median lesion volume secondary endpoints will be evaluated using both the Wilcoxon and Two-Part methods. Secondary efficacy endpoints No. 1, 2, 3, 4 and 5 will be tested for statistical

significance. The statistical tests will only be performed if the primary efficacy and primary safety endpoints are met. To preserve overall Type I error, the Hochberg method will be employed for testing secondary efficacy endpoints 1, 2, 3, 4 and 5 (see below). See Appendix A for explanation of z-score normative data and analysis.

For secondary efficacy endpoints 1, 2, 3, and 5 the median, IQR, and range will be summarized for each group. The differences between the test and control will be summarized using the Hodges-Lehmann estimate of location shift, and a 95% confidence interval about the shift. The null hypothesis will be tested using a Wilcoxon test. A supportive Poisson Regression analysis will also be performed for endpoints 1 and 3.

For secondary efficacy endpoint 4, the mean, standard deviation, and range will be summarized by group. The difference between test and control will be summarized and tested using the point estimate and corresponding p-value from a linear regression model with change in z-score as the outcome and adjusting for baseline Geriatric Depression Scale and Mini Mental State Exam scores.

Secondary Endpoint No. 10 Detail: A histopathology core laboratory will provide independent analysis and data processing for the study. The histopathology will be performed on the debris captured during the procedure with the Sentinel System. Results will be summarized and presented using counts and percentages for multinomial categories and univariate statistics for all data collected on a continuous scale.

Secondary Endpoint No. 11 & 12 Detail: To evaluate the potential effects of cerebral lesions on neurocognitive outcomes, lesion volume and lesion metrics will be correlated with the neurocognitive test scores. The correlation will be performed independent of treatment assignment. The neurological assessments to be collected and analyzed have been tailored to TAVR and the deployment of the Sentinel System cerebral protection device.

Secondary Efficacy Endpoint No. 1

Difference in Day 2-7 DW-MRI *median* number of new lesions based on protected territories

The null and alternative hypotheses for evaluating this secondary endpoint is presented below:
H_o: Õtest = Õcontrol
H_a: Õtest Í Õcontrol
where

ǐ Õtest = *median* number of Day 2-7 DW-MRI lesions based on protected territories from the test group
ǐ Õcontrol= *median* number of Day 2-7 DW-MRI lesions based on protected territories from the control group

Secondary Efficacy Endpoint No. 2

Difference in Day 2-7 DW-MRI *median* total new lesion volume based on all territories

The null and alternative hypotheses for evaluating this secondary endpoint is presented below:
H_o: Õtest = Õcontrol
H_a: Õtest Í Õcontrol
where

ǐ Õtest = *median* Day 2-7 DW-MRI total new lesion volume based on all territories from the test group

ĭ Õcontrol = *median* Day 2-7 DW-MRI total new lesion volume based on all territories from the control group

Note: Per Protocol and As Treated co-variate adjusted analyses (similar to the ones described for the primary efficacy endpoint) will also be conducted for Secondary Efficacy Endpoint No. 2.

Secondary Efficacy Endpoint No. 3

Difference in Day 2-7 DW-MRI *median* number of new lesions based on all territories

The null and alternative hypotheses for evaluating this secondary endpoint is presented below:
H_o: Õtest = Õcontrol
H_a: Õtest Í Õcontrol
where
ĭ Õtest = *median* number of Day 2-7 DW-MRI new lesions based on all territories from the test group
ĭ Õcontrol= *median* number of Day 2-7 DW-MRI new lesions based on all territories from the control group

Secondary Efficacy Endpoint No. 4

Difference in change in neurocognitive battery composite z-score from baseline to 30 days[4], adjusting for baseline Geriatric Depression Scale and Mini Mental State Exam scores.

The null and alternative hypotheses for evaluating this secondary endpoint is presented below:
H_o: $ß_1$= 0
H_a: $ß_1$ Í 0
where
ĭ $ß_1$ = the randomization arm parameter coefficient

Secondary Efficacy Endpoint No. 5

Difference in Day 30 FLAIR-MRI *median* total new lesion volume based on the protected territories

The null and alternative hypotheses for evaluating this secondary endpoint is presented below:
H_o: Õtest = Õcontrol
H_a: Õtest Í Õcontrol
where
ĭ Õtest = *median* Day 30 FLAIR-MRI total new lesion volume based on protected territories for the from the test group
ĭ Õcontrol = *median* Day 30 FLAIR-MRI total new lesion volume based on protected territories for the from the control group

The following Secondary Efficacy Endpoints will be presented using descriptive statistics only.

Secondary Efficacy Endpoint No. 6

Observe at least a 30% reduction in *median* total lesion volume in protected territories between the test and control groups at Day 2-7 DW-MRI post procedure

[4] Note: (As discussed during the Q130419/S003 Pre-Submission meeting on 26 February 2016 the window for all 30 day Neurocognitive assessments will be 23 ï 45 days.)

Secondary Efficacy Endpoint No. 7

7.1 Difference in Day 30 FLAIR-MRI *median* number of lesions based on the protected territories

7.2 Difference in Day 30 FLAIR-MRI *median* number of lesions based on all territories

Secondary Efficacy Endpoint No. 8

8.1 Difference in Day 2-7 DW-MRI *maximum* single new lesion volume per subject based on protected territories

8.2 Difference in Day 2-7 DW-MRI *maximum* single new lesion volume per subject based on all territories

8.3 Difference in Day 2-7 DW-MRI *median* average single new lesion volume per subject based on protected territories

8.4 Difference in Day 2-7 DW-MRI *median* average single new lesion volume per subject based on all territories

Secondary Efficacy Endpoint No. 9

9.1 Difference in Day 30 FLAIR-MRI *maximum* single new lesion volume per subject based on the protected territories

9.2 Difference in Day 30 FLAIR-MRI *maximum* single new lesion volume per subject based on all territories

9.3 Difference in Day 30 FLAIR-MRI *median* average single new lesion volume per subject based on protected territories

9.4 Difference in Day FLAIR-MRI *median* average single new lesion volume per subject based on all territories

Secondary Efficacy Endpoint No. 10

Captured debris histopathology (observational) [Test arm] - post-procedure

Secondary Efficacy Endpoint No. 11

11.1 Correlation of Day 2-7 DW-MRI lesion volume metrics with change in 90 day neurocognitive battery composite *z*-score [Test and Control arms]

11.2 Correlation of Day 2-7 DW-MRI lesion volume metrics with change in 30 day neurocognitive battery composite *z*-score [Test and Control arms]

11.3 Correlation of Day 2-7 DW-MRI lesion volume metrics with change in 2-7 day neurocognitive battery composite *z*-score [Test and Control arms]

Secondary Efficacy Endpoint No. 12

12.1 Correlation of Day 30 FLAIR-MRI lesion volume metrics with change in 90 day neurocognitive battery composite *z*-score [Test and Control arms]

12.2 Correlation of Day 30 FLAIR-MRI lesion volume metrics with change in 30 day neurocognitive battery composite *z*-score [Test and Control arms]

Secondary Efficacy Endpoint No. 13

Difference in Day 30 FLAIR-MRI total new lesion volume based on all territories

Secondary Efficacy Endpoint No. 14

14.1 Difference in change in neurocognitive battery composite *z*-score from baseline to 90 days

14.2 Difference in change in neurocognitive battery composite *z*-score from baseline to 2-7 days[5]

Secondary Efficacy Endpoint No. 15

Sentinel System acute delivery and retrieval success [Safety and Imaging Test arms]

Secondary Efficacy Endpoint No. 16*

Change in individual neurocognitive domain scores from Baseline to 2-7, 30 & 90 days between test & control, and the relationship among these domain scores to Baseline FLAIR, DWI & 30 day FLAIR imaging variables.

- Attention
- Depression
- Executive Function
- Mental Status
- Processing Speed
- Verbal Memory
- Visual Memory

*As presented in Q130419/S003 on February 26, 2016.

2.6 Primary Safety Analyses

The primary safety analysis will be based on the ITT population derived from the combination of the Safety and Test arms. This analysis will be performed using imputation where the binary outcome for subjects who withdraw prematurely will be based on the Markov Chain Monte Carlo (MCMC) algorithm specifying missing at random (MAR). The dependent variable used in the primary analysis will be dichotomous and set to Yes if the subject experiences a MACCE, and No if they do not experience an MACCE within 30 days of the procedure. Results from the analysis of the primary endpoint will be based on a 1-sided binomial test, compared to an *a priori* threshold of 18.3%. The 1-sided 95% exact binomial confidence interval will also be presented.

The null and alternative hypotheses are presented below.

Ho: p Ó 18.3%
Ha: p < 18.3%

Where p equals the 30-day primary safety endpoint based on CEC adjudication: MACCE rate defined as all death, all stroke, within 30 days of the procedure or acute kidney injury (AKI- Class 3) through discharge or 72 hours, whichever comes first.

[5] Note: The 2-7 day neurocognitive assessment was made optional per G130276/S015

The upper bound of the one-sided 95% confidence interval for the primary endpoint event rate must be less than the pre-specified threshold of 18.3% for the null hypothesis to be rejected in favor of the alternative.

The following additional analyses will also be performed on the primary safety endpoint:

- **Per Protocol:** An analysis using the Per Protocol population will be performed, considering all subjects without the endpoint data as missing data. Therefore, the point estimate and confidence interval will not include these subjects in the calculation because the data is missing.
- **As Treated:** An analysis using the As Treated population will be performed, considering all subjects without the endpoint data as missing data. Therefore, the point estimate and confidence interval will not include these subjects in the calculation because the data is missing.
- **Sensitivity/Tipping Point:** A sensitivity/tipping analysis using the ITT population will also be performed to determine how many more subjects would need to have a MACCE event for the upper 1-sided 95% exact binomial confidence interval to exceed 18.3%.
- **18.8% Rate Analysis:** Three additional analysis will be performed using the ITT, Per Protocol and As Treated populations in the same manner as the primary analysis with the performance goal of 18.8%.
- **Superiority:** If the primary safety null hypothesis is rejected, a superiority analysis will be performed against the weighted MACCE rate of 13.3%.

2.7 Secondary Safety Analyses

There are 5 secondary safety analyses that will be performed and described for labeling purposes using descriptive statistics. Each endpoint will be evaluated using the Per Protocol and As Treated populations within the safety cohort:

Secondary Safety Endpoint No. 1

1.0 Incidence of in-hospital MACCE [Safety and Test arms, combined] - through discharge

Secondary Safety Endpoint No. 2

2.0 MACCE rate [Test and Control arms] ï at 30 days post procedure

Secondary Safety Endpoint No. 3

3.1 Incidence of major vascular complications (radial and brachial) of the test device [Safety and Test arms, combined] during the index procedure

3.2 Incidence of major vascular complications of the test device [Safety and Test arms, combined] within 30 days of the index procedure

Secondary Safety Endpoint No. 4

4.0 Incidence of Serious Adverse Events [Control arm and Safety and Test arms, combined] within 30 days of the index procedure

2.8 Poolability

Poolability analyses by site, gender, and valve type will be performed for both primary efficacy and primary safety endpoints using the framework of interaction tests using the ITT population. Poolability for the primary safety endpoint will be assessed via the Breslow-Day test of homogeneity of treatment effect by subgroup, while for the primary efficacy endpoint a two-factor analysis of

variance with treatment as one factor and site or gender as the other will be performed on the ranks of the protected lesion volume, and the interaction term between treatment and subgroup assessed. Poolability analyses will be performed separately by site, gender, valve type; sites enrolling fewer than five (5) subjects may be combined into a ñmeta-siteò if necessary for stable analysis. In each case, poolability will be declared if the relevant p-value is found to be greater than 0.15.

2.9 General Considerations for Analysis

With the general exception of the tests comparing the response to an a priori threshold, all statistical tests will be 2-sided. Baseline is defined as the last observation recorded before the subject undergoes the study procedure.

Continuous demographic parameters, such as the subjectôs age at the time of enrollment, will be summarized for both the per protocol (i.e. all randomized subjects in whom the study procedure is attempted) and ITT populations using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value, and 95% 2-sided confidence limits). Categorical demographic parameters, such as gender, will be summarized as a proportion of both the per protocol and ITT populations. Co-morbid risk factors will be summarized for both the per protocol and ITT populations by sub-population and according to the type of variable (categorical, continuous).

Subject Disposition

Subject disposition will be presented as the number of subjects:

- Consented and enrolled
- Who were anatomical screen failures
- In the roll-in group (Baseline, Discharge & 30 Day Safety)
- Randomized (ITT cohort) by arm and overall
- Randomized and had the study procedure attempted by arm and overall
- In the per protocol cohort by arm and overall
- Who complete each visit, including percentage of subjects, by arm and overall
- Who exited early by discontinuation reason, including percentage of subjects, by arm and overall

In the event that time-to-event analyses are performed, Kaplan-Meier estimates will be obtained for the ITT population. For time-to-event analyses, the subjects that are randomized and the study procedure was not attempted will be censored at day zero.

The number and proportion of subjects who experience a specific event of interest will be tabulated and summarized using exact 95% binomial confidence limits. The 1-sided 95% confidence limit of the difference will be calculated and compared to the a priori threshold using a binomial test. Separate tables containing subject counts, percentages, and 95% exact binomial confidence limits will be prepared based on individual risk factors.

Univariate analyses will be prepared for each laboratory parameter. The proportion of subjects found to have abnormal values considered clinically significant will be summarized using counts, percentages, and 95% confidence limits. Laboratory shift tables from baseline containing subject counts and percentages will be prepared by laboratory parameter and time.

2.10 Un-Blinding Plan

The Sponsor, Core Lab, and personnel performing follow-up assessments (Neurocognitive, MRI, etc.) will remain blinded until the final subject has completed their 30-day visit or reached the end of

the 30-day follow-up window. The Clinical Events Committee will remain blinded until the last MACCE event has been adjudicated.

3. Protocol Deviations

Protocol deviations will be summarized by type and treatment arm as well as overall. The number of deviations and percentage of subjects with deviations will be provided.

4. Additional Analyses

Additional exploratory analyses may be performed and will be designated as post-hoc. These analyses include, but may not be limited to:

- Valve Type (i.e. SAPIEN XT, SAPIEN 3, CoreValve, Evolut R, etc.)
- Valve Access (Transfemoral, Transapical, Transaortic, Subclavian)
- Pre/Post Dilatation during TAVR procedure
- DW-MRI lesion volume threshold sensitivity analysis
- DW-MRI temporal signal decay sensitivity analysis
- Patients with previous Atrial Fibrillation
- DAPT (preload and procedural)
- Low gradient/Low flow population
- Device/procedure failures (one or no filter deployed)
- Quality of Life (SF-12)

5. Statistical Analysis Software

All tables, listings, and figures will be produced using SAS Version 9.3 (SAS Institute, Cary, NC.) or later.

Appendix A. Neurocognitive Data Analysis Plan

Doris and Stanley Tananbaum Stroke Center
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SENTINEL TRIAL
Neurocognitive Data Analysis

Ronald M. Lazar, PhD, FAHA, FAAN, Professor
Marykay Pavol, PhD, ABPP, Assistant Professor
Co-Principal Investigators
Version 1.1
March 18, 2016

Cerebrovascular Disease Division
Department of Neurology
Columbia University Medical Center

Test Battery:

Neurocognitive Test	Domain
Trails A	Attention
Trails B	Executive Function
Digit Span	Attention
Digit Symbol	Processing Speed
Letter Number Sequencing	Attention
Controlled Oral Word Association	Processing Speed
Hopkins Verbal Learning Test	Verbal Memory
Rey Complex Figure (Copy)	Executive Function
Brief Visual Memory Test	Visual Memory
Mini Mental State Exam	Mental Status
Geriatric Depression Scale	Depression

Primary Neurocognitive Analysis: Comparison of the change in composite neurocognitive z-scores from Baseline to 30-days post-TAVR between the group in whom the Sentinel device was used and the group that did not receive distal protection, controlling for MMSE, education, and the depression scores.

Composite Score Calculation: A z-score for each domain will be calculated based on the normative means and standard deviations for each neurocognitive test that will be supplied by the Neurocognitive Core Lab at Columbia. These norms will be stratified by age at time of visit. When there is more than one test for a given domain (e.g., Trails A and Digit Span for "Attention"), an average will be computed from the z-scores comprising of the tests for that domain. When there is more than one outcome for a given test (e.g., Total Recall, Delayed Recall and Recognition for "Verbal Memory"), a mean z-score will be derived from

these outcomes. The composite neurocognitive z-score for each treatment group will the average z-score from all domains (Attention, Executive Function, Processing Speed, Verbal Memory, Visual Memory). Change scores will be calculated (by domain) by subtracting baseline scores from the 30-day post-surgical exam scores. Change scores for a visit will be averaged. This approach will produce for each treatment group an average z-score for the Baseline and 30-day visits (average of domain z-scores) and an average change score (average of domain change scores) for the 30-day visit.

Secondary Neurocognitive Analyses:

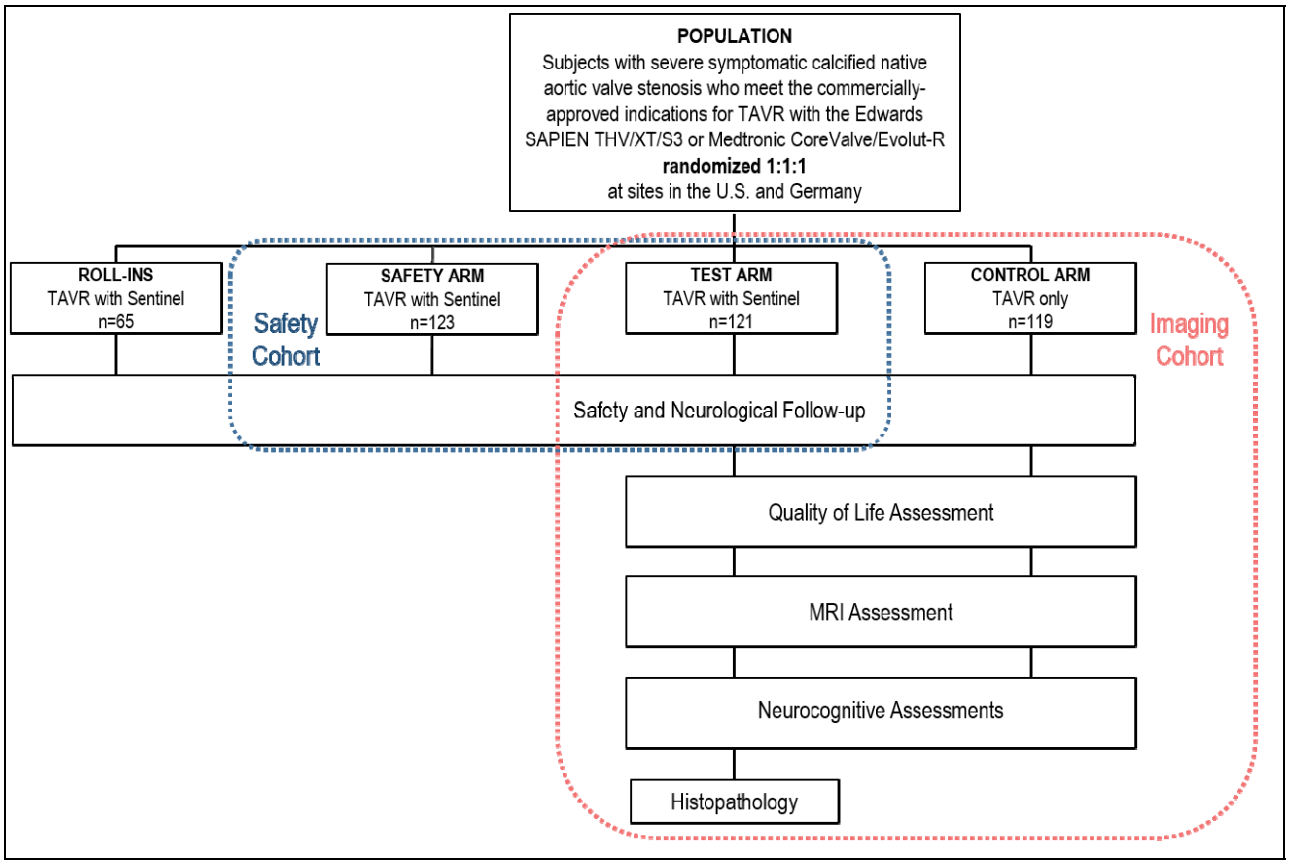
1. The interaction of the 30-day composite neurocognitive change score for each treatment group with lesion outcomes from post-TAVR DWI, 30-Day FLAIR, and Baseline FLAIR.
2. Change in neurocognitive composite scores from baseline to 3-7-days and baseline to 90-days post-TAVR for each treatment group.
3. Baseline composite neurocognitive scores for all study participants to characterize pre-TAVR cognitive function and correlations between these baseline composite scores and baseline FLAIR imaging variables.

Change in individual domain scores from Baseline to 3-7-days, 30-days and 90-days post-TAVR between the group in whom the Sentinel device was used and the group that did not receive distal protection, and the relationships among these domain scores to Baseline FLAIR, post-TAVR DWI and 30-Day FLAIR imaging variables.

APPENDIX II:

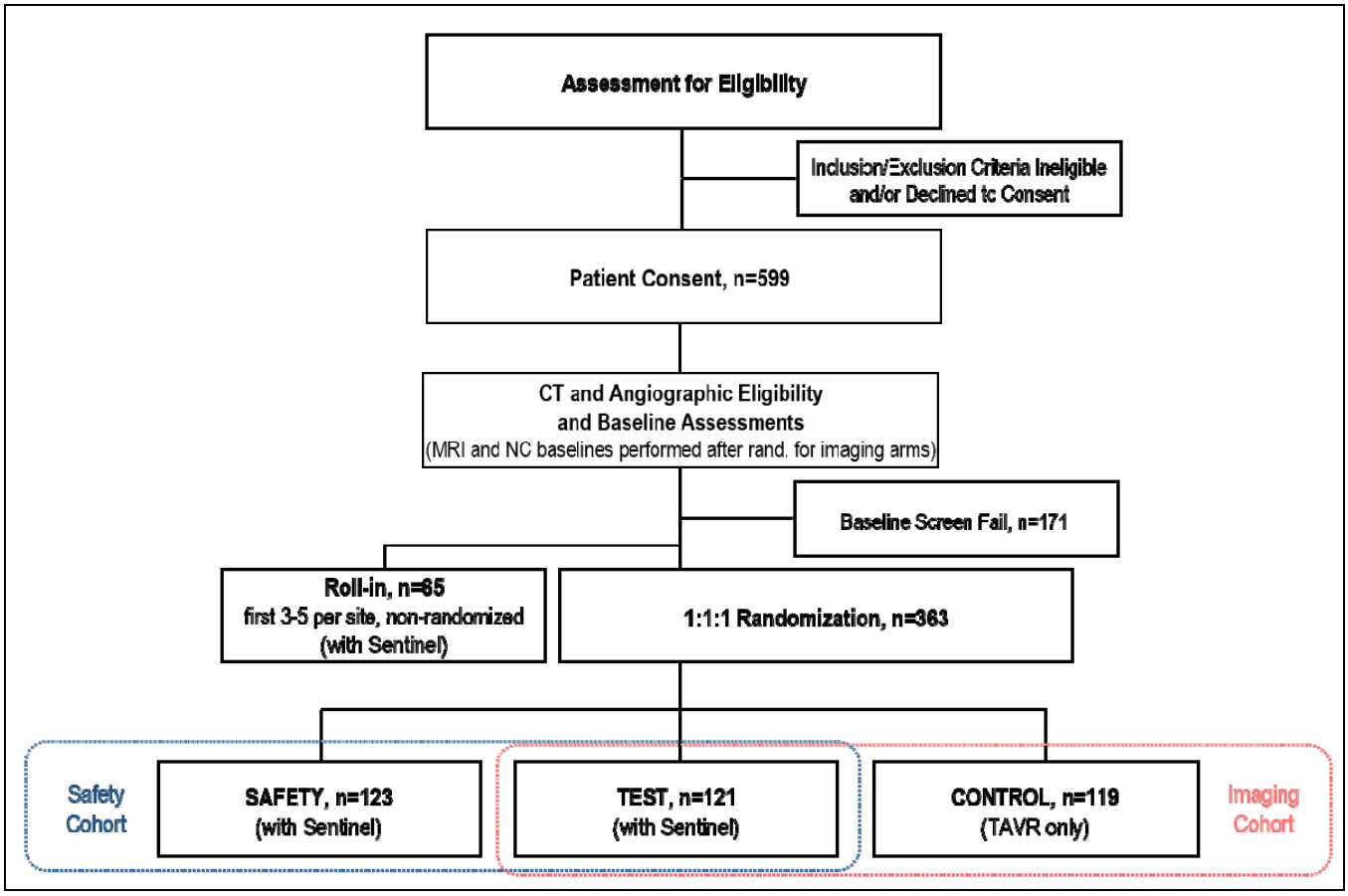
Study Flow Diagrams

Study Overview:



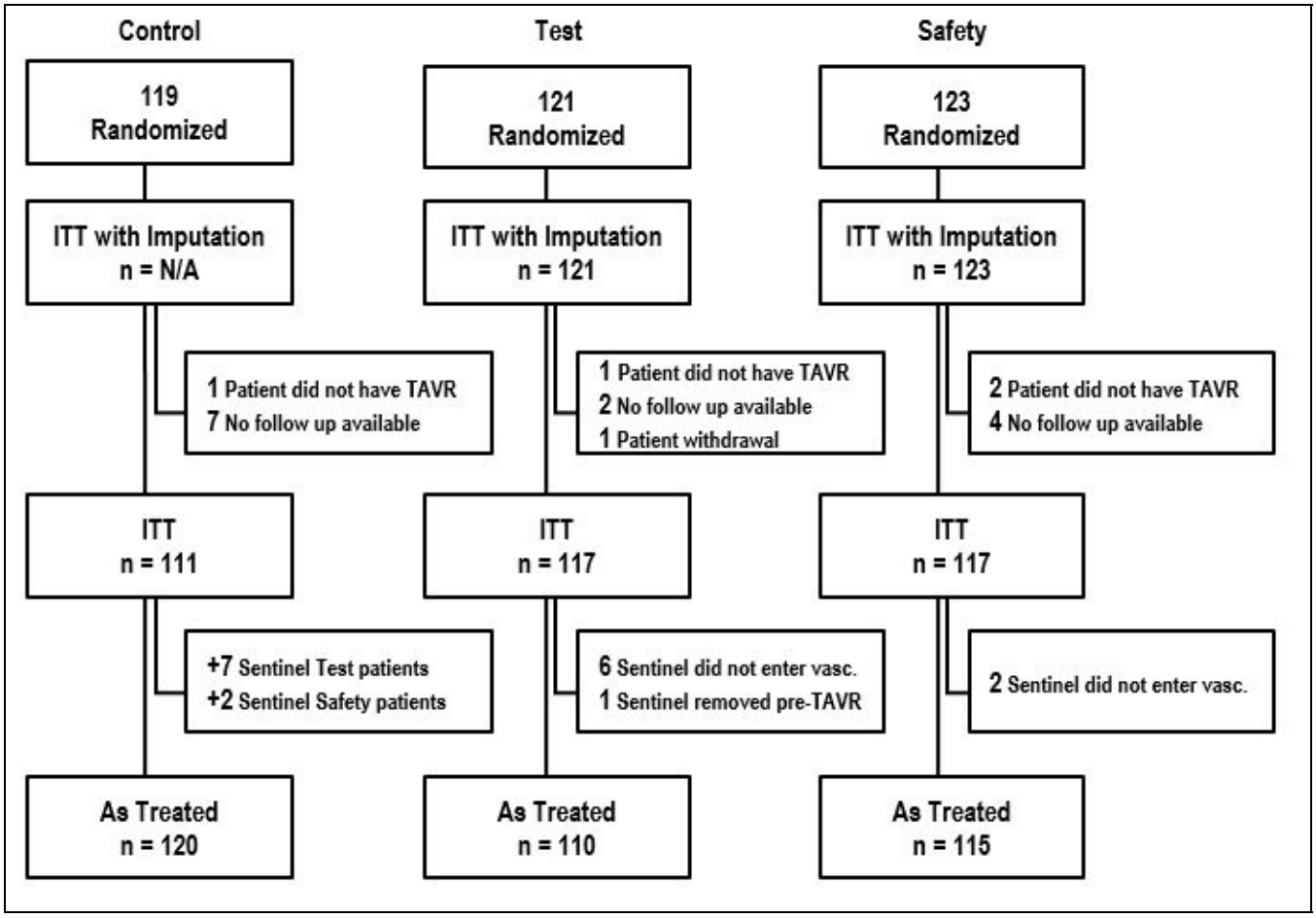
Source: Claret SENTINEL Clinical Study Report

Enrollment Scheme:



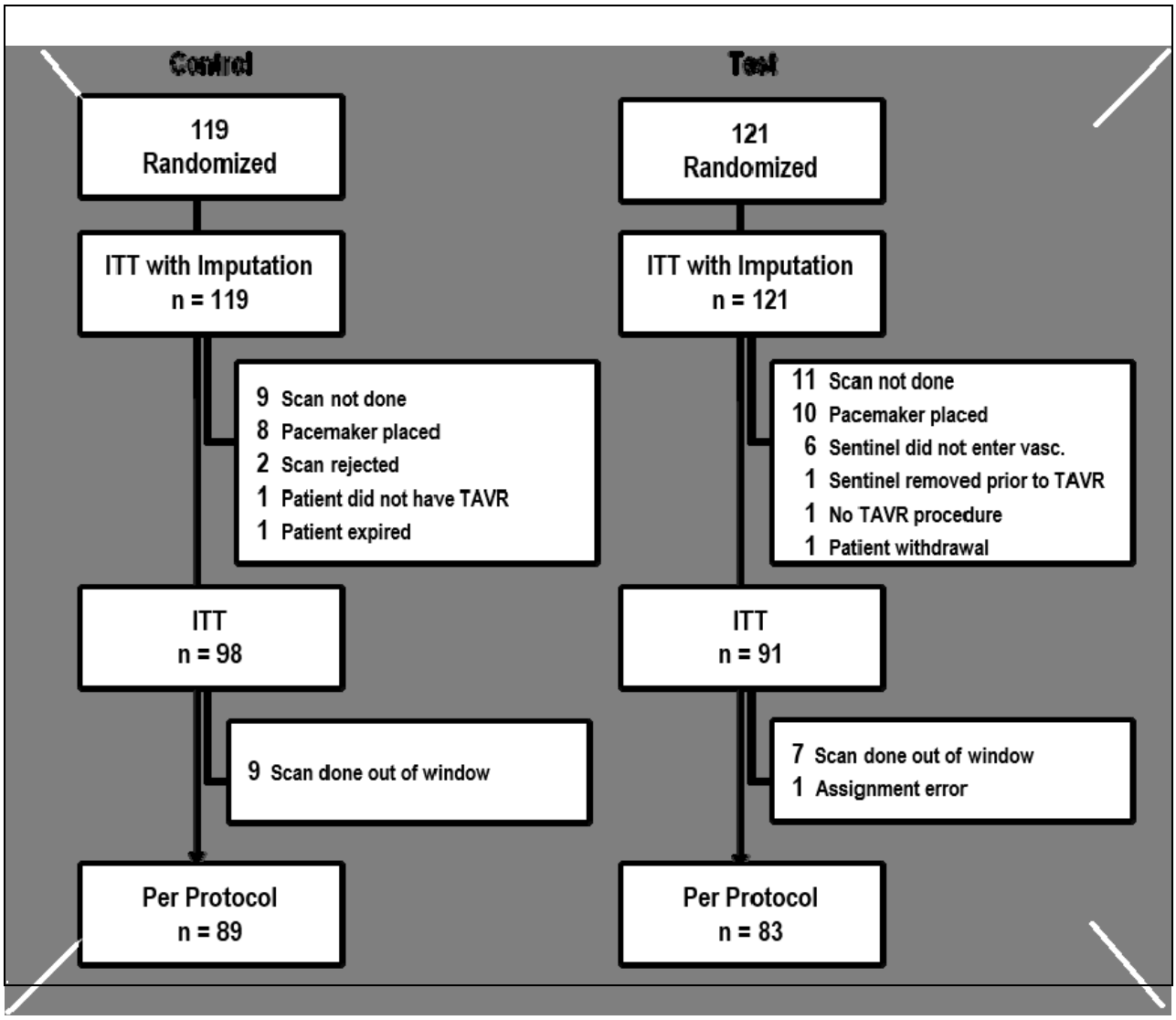
Source: Claret SENTINEL Clinical Study Report

Safety Analyses:



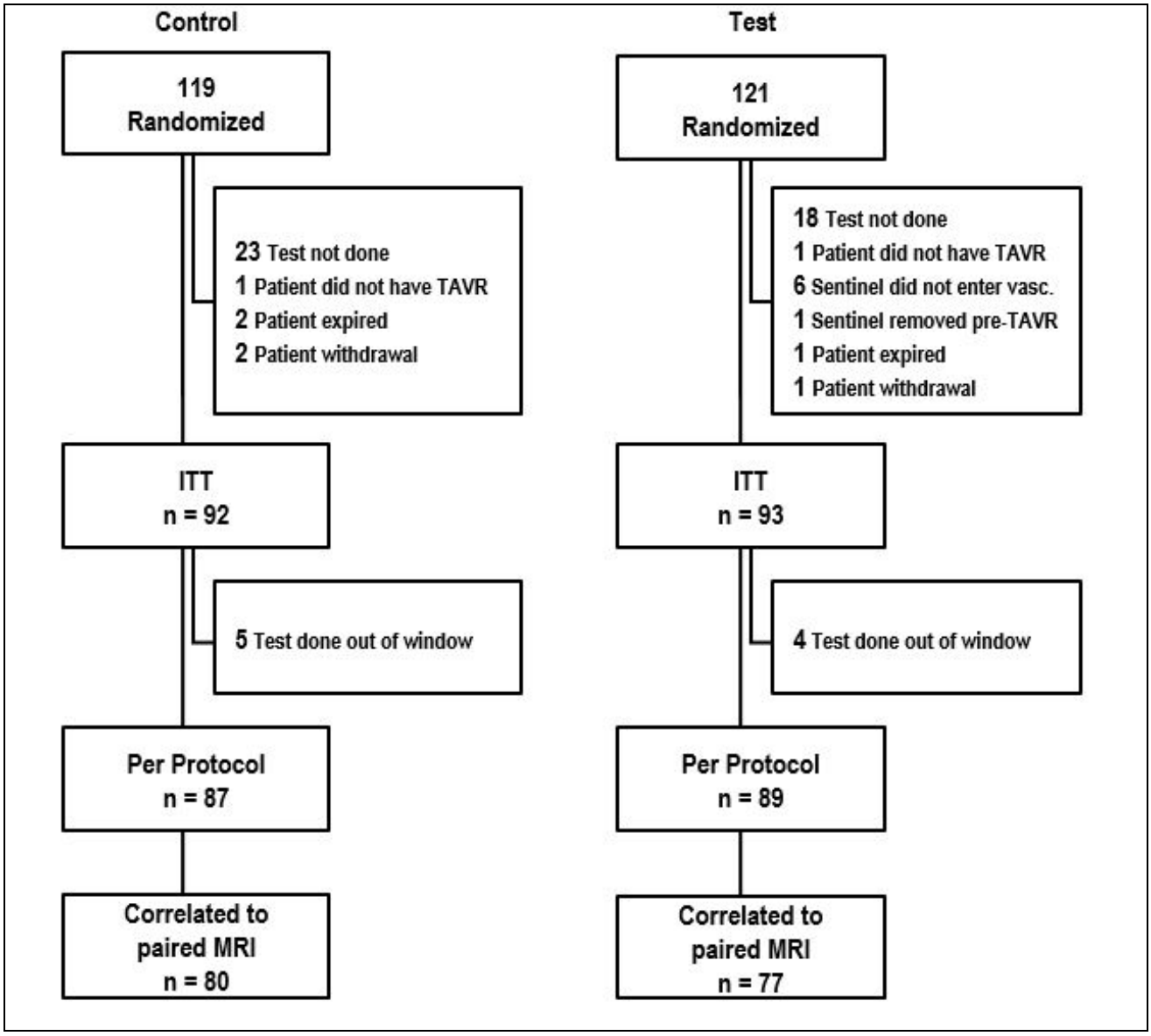
Source: Claret SENTINEL Clinical Study Report

Effectiveness Analyses:



Source: Claret SENTINEL Clinical Study Report

Neurocognitive Analyses:



Source: Claret SENTINEL Clinical Study Report

APPENDIX III:

Benefit-Risk Guidance

Guidance for Industry and Food and Drug Administration Staff

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

Document issued on: March 28, 2012

The draft of this document was issued on August 15, 2011.

For questions about this document concerning devices regulated by CDRH, contact Ruth Fischer at 301-796-5735 or by electronic mail at Ruth.Fischer@fda.hhs.gov. For questions about this document concerning devices regulated by CBER, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 301-827-1800.

Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number 1772 to identify the guidance you are requesting.

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Guidance for Industry and Food and Drug Administration Staff

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

FDA has developed this guidance document to provide greater clarity for FDA reviewers and industry regarding the principal factors FDA considers when making benefit-risk determinations during the premarket review process for certain medical devices. FDA believes that the uniform application of the factors listed in this guidance document will improve the predictability, consistency, and transparency of the premarket review process.

FDA's guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

2. Scope

This guidance document explains the principal factors that FDA considers when making benefit-risk determinations in the premarket review of certain medical devices. The processes discussed in this guidance are applicable to devices subject to premarket

approval (PMA) applications or *de novo* classification petitions. This guidance applies to both diagnostic and therapeutic devices. The concepts discussed in this guidance are applicable to the medical device development process from design to market. As such, the benefit-risk factors set out herein should be considered during the design, non-clinical testing, pre-Investigational Device Exemption (IDE), and IDE phases as well as in assembling and assessing PMA applications or *de novo* petitions. Although guidance is not binding, the concepts and factors described herein generally explain how benefit-risk determinations are made by FDA during the premarket review process. The intersection of this Guidance with ISO 14971 is discussed in Appendix A.

3. Background

3.1 The Statutory Standard for Safety and Effectiveness

Under section 513(a) of the Federal Food, Drug & Cosmetic Act (the "FD&C Act"), FDA determines whether PMA applications provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.[1] To aid in this process, PMA applicants submit valid scientific evidence, including one or more clinical investigations where appropriate, which FDA reviews to determine whether "the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device."[2] FDA staff review the data submitted as part of the PMA application and determine – based on a number of factors – if the data support the claims made by the sponsor concerning clinically significant results from the device, i.e., intended use and

[1] In addition to section 513(a), the criteria for establishing safety and effectiveness of a device are set forth in 21 CFR 860.7. Subsection (b)(1) notes, "In determining the safety and effectiveness of a device … the Commissioner and the classification panels will consider the following, among other relevant factors …The probable benefit to health from the use of the device weighed against any probable injury or illness from such use." (21 CFR 860.7(b)).
To make this determination, "the agency relies upon only valid scientific evidence." (21 CFR 860.7(c)(1)). Valid scientific evidence is defined as "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use." (21 CFR 860.7(c)(2)).
A reasonable assurance of safety occurs when "it can be determined, based upon valid scientific evidence, that the probable benefits … outweigh any probable risks," and can be demonstrated by establishing "the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use." (21 CFR 860.7(d)(1)).
Similarly, a reasonable assurance of effectiveness occurs when "it can be determined, based upon valid scientific evidence … the use of the device for its intended uses … will provide clinically significant results." (21 CFR 860.7(e)(1)). The evidence of which is demonstrated principally through "well-controlled investigations" (see 21 CFR 860.7(e)(2)), as defined in 21 CFR 860.7(f).

[2] Section 513(a)(3)(A) of the FD&C Act.

indications for use, and if the data analysis demonstrates that the probable[3] benefits of the device outweigh its probable risks. A balanced consideration of probable benefits and probable risks is an essential part of FDA's determination that there are reasonable assurances of safety and effectiveness.[4] Other considerations include that the device is being manufactured in accordance with FDA's quality system requirements.[5]

Similarly, in accordance with section 513(f)(2) of the FD&C Act, sponsors of devices that have been determined to be not substantially equivalent (NSE) through the 510(k) program may be eligible to submit a *de novo* petition requesting FDA to make a risk-based classification determination for the device under section 513(a)(1) of the FD&C Act.[6] Because devices classified under this pathway (*de novo* devices) are low to moderate risk devices, they may not need to confer as substantial a benefit to patients[7] in order to have a favorable benefit-risk profile. Devices granted marketing authority under *de novo* petitions should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general and/or special controls to provide reasonable assurance of safety and effectiveness. Further, devices classified under *de novo* petitions may serve as predicates for future devices which can be appropriately regulated through the 510(k) program; therefore, FDA carefully considers the benefit-risk profile of these devices in the determination that there is reasonable assurance of safety and effectiveness.

3.2 Types of Scientific Evidence

Medical devices can be evaluated using clinical and non-clinical testing methods. Clinical testing methods for medical devices can include, when appropriate, randomized clinical trials in the appropriate target population, well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, reports of significant human experience, and testing on clinically derived human specimens (DNA, tissue, organ and cadaver studies).[8] Non-clinical testing methods can encompass an array of methods including performance testing for product safety/reliability/characterization, human factors and usability engineering testing under simulated conditions of use, animal and

[3] In general, "probable" and "probability" in this guidance have the same connotation as in 21 CFR 860.7(b)(3), i.e. they refer to the likelihood of the patient experiencing a benefit or risk. Hypothesis testing, formal concepts of probability and predictive probability, likelihood, etc., typically are critical elements in the assessment of "probable" benefit and risk. FDA does not intend for the use of the term "probable benefit" in this guidance to refer to the regulatory context for Humanitarian Device Exemptions (HDE) under section 520(m) of the FD&C Act, and FDA's implementing HDE regulations.

[4] Equally important is FDA's determination of effectiveness. See footnote 1.

[5] See 21 CFR Part 820.

[6] See Draft Guidance for Industry and Food and Drug Administration Staff - De Novo Classification Process (Evaluation of Automatic Class III Designation).

[7] In general, for the purposes of this guidance, the use of the term "patient" refers to an individual who is under medical care or treatment and is not a subject, and the use of the term "subject" refers to an individual who participates in a clinical investigation.

[8] See 21 CFR 860.7.

cell-based studies, and computer simulations. These tests characterize mechanical, electrical and chemical properties of the devices including but not limited to wear, tensile strength, compression, flow rate, burst pressure, biocompatibility, toxicity, electromagnetic compatibility (EMC), sterility, stability/shelf life data, software validation, and testing of synthetic samples, including cell lines. The information obtained from any clinical and/or non-clinical testing is taken into account during the premarket review process and FDA's benefit-risk determination.

Although a great deal of emphasis is placed on the importance of clinical data in demonstrating the safety and effectiveness of a medical device, non-clinical data also can be critical to understanding a device's safety and effectiveness. Medical devices often have attributes that cannot be tested using clinical methods alone and that play a major role in the safety or effectiveness of the device.

Both clinical and non-clinical testing methods may be used to assess the probability or severity of a given risk, and/or the success of risk mitigation. For example, in the case of some implants, the most robust long-term evidence comes from engineering tests that are able to challenge the device under worst-case conditions, test the device to failure, and simulate many years of use. In contrast, clinical studies are usually limited in duration of follow-up, and, as a result, may be less informative with respect to the long-term performance of the device. In this case, the results of engineering testing may significantly influence FDA's benefit-risk determination independent of the clinical findings.

Both clinical and non-clinical data can play a role in FDA's benefit-risk determinations, and the factors discussed in this guidance are informed by both types of data.

FDA relies on valid scientific evidence in making risk and benefit determinations, including the critical issue of identifying 'probable risks' and 'probable benefits' in the first place. In general, a 'probable risk' and a 'probable benefit' do not include theoretical risks and benefits, and instead are ones whose existence and characteristics are supported by valid scientific evidence. Generally, isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. However, such information may be considered in identifying a device that has questionable safety and effectiveness.[9]

3.3 Benefit-Risk Determinations

The factors FDA considers as part of the benefit-risk determination are explained in detail below. We also give examples of how the factors interrelate and how they may affect FDA's decisions. By providing greater clarity about FDA's decision-making process, we

[9] 21 CFR 860.7(c)(2).

hope to improve the predictability, consistency, and transparency of the review process for applicable devices.

We have also included a worksheet that reviewers will use in making benefit-risk determinations as part of the premarket review process. The worksheet is attached as Appendix B to this guidance, and examples of how reviewers might use the worksheet are attached as Appendix C. By documenting reviewers' thought processes as part of the administrative record and, in certain cases, the publicly available summary of our decision,[10] sponsors will have a better idea of the basis for FDA's favorable decisions and gain a greater understanding of what factors were considered as part of an approval or a down-classification decision through the *de novo* process. However, because the weighting of the factors for a type of device may change over time – such as a device no longer being a first-of-a-kind or the only available treatment as new therapies are approved – the benefit-risk determination for a specific device at one point in time may no longer represent the proper weighting of the factors for the same or similar type of device in the future.

4. Factors FDA Considers in Making Benefit-Risk Determinations

The factors described below are considered within the intended use of the device, including the target population. These sections are not intended to provide device-specific data requirements for the assessment of the factors or methods by which inferences will be drawn from the data.

4.1 Assessment of the Benefits of Devices

Extent of the probable benefit(s): FDA assesses information provided in a PMA application or *de novo* petition concerning the extent of the probable benefit(s) by taking into account the following factors individually and in the aggregate:

- The **type of benefit(s)** – examples include but are not limited to the device's impact on clinical management, patient health, and patient satisfaction in the target population, such as significantly improving patient management and quality of life, reducing the probability of death, aiding improvement of patient function, reducing the probability of loss of function, and providing relief from symptoms. These endpoints denoting clinical benefit are usually measured directly, but in some cases may be demonstrated by use of validated surrogate endpoints. For diagnostics, a benefit may be assessed according to the public health impact of a particular device, due to its ability to identify a specific disease and therefore prevent its spread, predict future disease onset, provide earlier diagnosis of diseases, or identify patients more likely to respond to a given therapy.

[10] See http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma/cfm.

- The **magnitude of the benefit(s)** – we often assess benefit along a scale or according to specific endpoints or criteria (types of benefits), or by evaluating whether a pre-identified health threshold was achieved. The change in subjects' condition or clinical management as measured on that scale, or as determined by an improvement or worsening of the endpoint, is what allows us to determine the magnitude of the benefit in subjects. Variation in the magnitude of the benefit across a population may also be considered.

- The **probability of the patient experiencing one or more benefit(s)** – based on the data provided, it is sometimes possible to predict which patients may experience a benefit, whereas other times this cannot be well predicted. The data may show that a benefit may be experienced only by a small portion of patients in the target population, or, on the other hand, that a benefit may occur frequently in patients throughout the target population. It is also possible that the data will show that different patient subgroups are likely to experience different benefits or different levels of the same benefit. If the subgroups can be identified, the device may be indicated for those subgroups. In some cases, however, the subgroups may not be identifiable. In addition, we consider magnitude and probability together when weighing benefits against risks. That is, a large benefit experienced by a small proportion of subjects may raise different considerations than does a small benefit experienced by a large proportion of subjects. For example, a large benefit, even if experienced by a small population, may be significant enough to outweigh risks, whereas a small benefit may not, unless experienced by a large population of subjects.

- The **duration of effect(s)** (i.e., how long the benefit can be expected to last for the patient) – some treatments are curative, whereas, some may need to be repeated frequently over the patient's lifetime. To the extent that it is known, the duration of a treatment's effect may directly influence how its benefit is defined. Treatments that must be repeated over time may introduce greater risk, or the benefit experienced may diminish each time the treatment is repeated.

4.2 Assessment of the Risks of Devices

Extent of the probable risk(s)/harm(s): FDA assesses the extent of the probable risk(s)/harm(s) by taking into account the following factors individually and in the aggregate:

- **Severity, types, number and rates[11] of harmful events associated with the use of the device:[12]**

[11] For purposes of this guidance, "rates" means the number of harmful events per patient or number of harmful events per unit of time.

[12] We have listed each type of harm individually for the purpose of clarifying which of the more commonly recognized harms FDA would consider in benefit-risk assessments. In making benefit-risk assessments,

- **Device-related serious adverse events** – those events that may have been or were attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.[13]

- **Device-related non-serious adverse events** – those events that may have been or were attributed to the use of the device and that do not meet the criteria for classification as a device-related serious adverse event.

- **Procedure-related complications** – harms to the patient that would not be included under serious or non-serious adverse events, and that do not directly result from use of the device. For example, anesthetic-related complications associated with the implantation of a device. Similarly, FDA would factor risks associated with the collection of human biological materials into the benefit-risk determination.[14]

- **Probability of a harmful event** – the proportion of the intended population that would be expected to experience a harmful event. FDA would factor whether an event occurs once or repeatedly into the measurement of probability.

- **Duration of harmful events** (i.e., how long the adverse consequences last) – some devices can cause temporary, minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent, debilitating injury. FDA would consider the severity of the harm along with its duration.

- **Risk from false-positive or false-negative results for diagnostics** – if a diagnostic device gives a false-positive result, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. If a diagnostic device gives a false-negative result, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition. The risks associated with false-positives and false-negatives can be multifold, but are considered by FDA in light of probable risks.

We also consider the number of different types of harmful events that can potentially result from using the device and the severity of their aggregate effect. When multiple harmful events occur at once, they have a greater aggregate effect. For example, there may be a harmful event that is considered minor when it occurs on its own, but, when it

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FDA does not consider each type of harm individually, but rather looks at the totality of the harmful events associated with the device.

[13] See 21 CFR 803.3.

[14] These considerations affect the risk profile of in vitro diagnostic devices when the biological material is collected via an invasive procedure for the purpose of performing the diagnostic test.

occurs along with other harmful events, the aggregate effect on the patient can be substantial.

4.3 Additional Factors in the Assessment of the Probable Benefits and Risks of Devices

Uncertainty – there is never 100% certainty when determining reasonable assurance of safety and effectiveness of a device. However, the degree of certainty of the benefits and risks of a device is a factor we consider when making benefit-risk determinations. Factors such as poor design or poor conduct of clinical trials, or inadequate analysis of data, can render the outcomes of the study unreliable. Additionally, for certain device types, it is sometimes difficult to distinguish between a real effect and a placebo effect in the absence of a trial design that is capable of blinding investigators and subjects. Furthermore, the repeatability of the study results, the validation of the analytical approach, and the results of other similar studies and whether the study is the first of its kind or a standalone investigation can all influence the level of certainty. In addition, the generalizability of the trial results to the intended treatment and user population is important. For example, if the device requires in-depth user training or specialization, the results of the clinical study may not be generalizable to a wider physician population. Likewise, if the device is intended to diagnose a disease in a subpopulation, it may not be useful in the general population. In general, it is important to consider the degree to which a clinical trial population is representative of the intended marketing or target population.

Characterization of the disease – the treated or diagnosed condition, its clinical manifestation, how it affects the patients who have it, how and whether a diagnosed condition is treated, and the condition's natural history and progression (i.e., does it get progressively better or worse for the patient and at what expected rate) are all important factors that FDA considers when characterizing disease and determining benefits and risks.

Patient tolerance for risk and perspective on benefit – if the risks are identifiable and definable, risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable[15] in exchange for a probable benefit. When making a benefit-risk determination at the time of approval or *de novo* classification, FDA recognizes that patient tolerance for risk and a patient-centric assessment of risk may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life. How data concerning patient risk tolerance and other patient-centered metrics are developed will vary depending on a number of factors, including the nature of the disease or condition and the availability of existing treatments, as well as the risks and benefits they present. FDA encourages any sponsor that is

[15] 21 CFR 860.7(d)(1) states that "The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

considering developing such data to have early interaction with the appropriate FDA review division.

When assessing such data in a PMA application or *de novo* petition, FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse. Therefore, FDA would consider evidence relating to patients' perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others. It should also be noted that if, for a certain device, the probable risks outweigh the probable benefits for all reasonable patients, FDA would consider use of such a device to be inherently unreasonable.[16]

Different factors can influence patient risk tolerance, including:

- **Severity of disease or condition** – patients suffering from very severe diseases (i.e., those that are life-threatening) may tolerate more risk for devices used in treatment. For diagnostic devices, individuals might be more averse to the risk of a false negative result concerning a severe disease.
- **Disease chronicity** – some patients with chronic diseases who have adapted to their illness and minimized its interference with their daily lives may tolerate less risk and require risky devices to deliver a greater treatment benefit, whereas other patients who have suffered from a debilitating chronic illness over a long period of time may tolerate higher risk to gain less benefit.
- Availability of **alternative treatment/diagnostic options** (also see below) – if there are no other treatment/diagnostic options available, patients may tolerate more risk for even a small amount of benefit.

We recognize that patient-centric metrics such as validated quality of life measures can be helpful for health care practitioners when discussing treatment decisions with their patients, and may be used to demonstrate benefit for purposes of product approval. These types of metrics allow the physician to better quantify the impact of the device on the patient's well-being and help the patient make a more informed decision. Moreover, it may be appropriate to approve a device where only a minority of the intended patient population would accept the risks as weighed against the benefits if the information necessary for patients and health care practitioners to make well-informed decisions is available and can be presented in a manner that can be understood by the practitioners and patients. Patient-centric assessments should take into account both the patient's willingness and unwillingness to use a device or tolerate risk. Both preferences are informative and helpful in determining patient tolerance for risk and benefit and the benefit-risk profile of a device.

Availability of alternative treatments or diagnostics – when making benefit-risk determinations, FDA considers whether other treatments or diagnostics, including non-

[16] For the purpose of this guidance the concept of "unreasonable risk" should be construed to mean a risk that no set of reasonable patients would be willing to endure to achieve a probable benefit.

device therapies, have been approved or cleared for the intended condition and patient population. When considering other therapies, FDA takes into account how effective they are; what known risks they pose; how they are used in current medical practice; their benefit-risk profiles; and how well available alternatives address the needs of patients and providers. For a device with a known benefit and a probability of high risk that treats a condition for which no alternative treatments are available, FDA would consider the risk to the patient of having no treatment if a device were not approved. For example, if a new device has a very small significant benefit and there is significant uncertainty about that benefit, we may still approve the product if there are no available alternative treatments and the probable benefits outweigh the probable risks.

Risk mitigation – the use of mitigations, when appropriate, can minimize the probability of a harmful event occurring and improve the benefit-risk profile. The most common form of risk mitigation is to include appropriate information within labeling (e.g., warnings, precautions, etc.), or to restrict the indication to a more limited use. Some harms can be mitigated through other forms of risk communication, including training and patient labeling. For in vitro diagnostics, risks may be mitigated by the use of complementary diagnostic tests.

Postmarket data – the use of devices in a real world setting can provide a greater understanding of their risks and benefits. FDA may consider the collection of postmarket data as a way to clarify the magnitude and effect of mitigations or as a way to develop additional information regarding benefits or risks for certain device types or in specific patient populations when making a benefit-risk determination. FDA has the authority to require post-approval studies for PMA devices and postmarket surveillance for PMA and *de novo* devices.[17] In addition, pursuant to section 513(a)(3)(C) of the FD&C Act, in certain cases, such as if a device is likely to be denied approval due to uncertainty about its effectiveness, FDA will consider whether postmarket data collection or other conditions might be structured so as to permit approval subject to those conditions. These types of studies or other data that come to light after the device is used in the real-world setting may alter the benefit-risk profiles of certain devices, especially if new risks are identified, or if the information can be used to confirm that certain risks have been mitigated, to identify which patients are most likely to suffer adverse events, or to identify more specifically how different groups of patients will respond.

Novel technology addressing unmet medical need – in assessing benefit and risk, FDA considers whether a device represents or incorporates breakthrough technologies and addresses an unmet medical need. A device may address unmet medical need by providing a clinically meaningful advantage over existing technologies, providing a greater clinically meaningful benefit than existing therapy, posing less risk than existing therapy, or providing a treatment or means of diagnosis where no alternative is available.

[17] 21 CFR 814.82 states that "FDA may impose postapproval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval." In addition, under section 522 of the FD&C Act, and FDA's implementing regulations at 21 CFR Part 822, FDA may order postmarket surveillance for certain Class II or Class III devices.

It is not unusual for novel devices that address an unmet medical need to have relatively small probable benefits, and FDA may determine the novel device to be reasonably safe and effective even though the applicant demonstrates a relatively small probable benefit. In addition, the development of innovative technology may provide additional future benefits to patients. With subsequent iterations of the device its benefit-risk profile may change (e.g., the benefits may increase or the risks may be reduced), the expected level of safety and effectiveness may change, and later versions may offer significant advantages over the initial device. In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, we may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available.

5. Examples of Benefit-Risk Determinations

The examples below are hypothetical or simplified and are only offered for illustrative purposes. The decisions described in these examples are not predictive of future FDA decisions, rather they are hypothetical outcomes and are only intended to demonstrate how FDA considers the factors described in this guidance when making benefit-risk determinations. Similar scenarios or devices may result in different approval outcomes depending on the individual performance characteristics of a particular device and the population for which it is indicated.

A description of how FDA would consider these examples in the context of the reviewer worksheet is included in Appendix C.

5.1 Hypothetical Examples

Example 1

An implantable device is developed to treat a severe, chronic condition for patients who have failed all other treatment options.

The device is studied in a pivotal clinical trial with a design where all subjects are implanted with the device, but the device is only turned on in half of them. After completion of the trial, inactive devices can be turned on. The primary endpoint for the trial is the magnitude of the benefit, i.e., the trial is designed to measure how well the device reduces the subject's symptoms as compared to the current standard of care.

The results of the pivotal clinical trial revealed the following:

Benefits: Based on the clinical study, it is inferred that the probability that a patient will experience a substantial benefit when the device is implanted is 75%. The trial was considered to have met its primary endpoint. As a general matter, patients with this disease who are able to maintain good mobility tend to have a longer life expectancy.

However, the duration of the benefit cannot be determined because the subjects in the study were only followed for one year.

Risks: The study showed that there is a very low probability of occurrence (less than 3%) of harmful events after device implantation. However, all implanted devices that require a surgical procedure carry with them their own set of risks. In this case it is known from the literature that the implantation of this device is not routine and there is a 1% chance of death from surgery. In addition, permanent implants pose additional risks, namely, they typically remain with the patient for life and may be difficult to remove. Even in cases where the device is deactivated, it remains implanted and a risk of device fracture, mechanical failure, or an adverse biological response to the device remains (the probability is less than 3%).

Additional Factors

Uncertainty: It is difficult to discern the mechanism of action by which subjects' symptoms improved and whether the surgery may have contributed to such improvement. Because the trial ended after one year, it is difficult to determine the duration of the benefit beyond one year. There is only a 75% chance that a patient will experience total success when implanted with the device.

Patient Tolerance for Risk and Perspective on Benefit: The sponsor provided data showing that patients are willing to take the risk of having the device implanted even for a 75% probability of benefit because the alternative treatment options do not work for them and their symptoms are severe.

Risk Mitigation: The surgery to implant and explant (if necessary) the device is risky, but the risks can be mitigated by requiring the device to be implanted by a specially trained surgeon.

Approval/Non-Approval Considerations: The probability that a patient will experience a benefit is relatively high (approximately 75%, if the clinical trial results hold for the intended use population). In this particular case, FDA does not have the option to limit the use of the device to only those patients who are most likely to experience a benefit because the covariates that determine the subgroup of patients who would definitely experience the benefit are unknown. In addition, this type of permanently implantable device poses significant risks and there is some remaining uncertainty associated with the trial results. However, for those patients in the target population who will experience a benefit, symptom relief and improvement in quality of life is impressive and some patients have expressed a willingness to tolerate the risks for the potential of obtaining such benefits. In addition, the risks, although substantial, could be somewhat mitigated through limiting the device use to clinicians with specialized training. Finally, the device treats a severe and chronic disease for which there are few, if any, alternative treatments. Therefore, FDA is likely to approve the device.

Example 2

A revolutionary device that replaces a patient's memory is developed to treat Alzheimer's disease, dementia, and other memory disorders. The device is designed to be permanently implanted and the patient must undergo a brain resection for the device to work properly. The device functions by downloading all of a patient's memories onto a computer chip. Once the device is implanted, any residual memory the patient retained is no longer accessible to the patient.

Benefits: A clinical trial of the device showed significant improvement in subjects who were in the early stages of dementia and minimal improvement in subjects who were in more advanced stages. Subjects who received implanted devices when the majority of their memory was intact experienced the greatest benefit and their overall quality of life was enhanced. Since the trial design accounted for two subgroups, subjects at the early stage of the disease and subjects at advanced stages of the disease, it can be inferred that, if the device is marketed, the patient population in early stages of the disease is likely to experience significant improvement, whereas the patient population in advanced stages is likely to experience only minimal improvement.

Risks: The surgery to implant the device is highly risky and is usually only performed by specially trained neurosurgeons. Even with these procedural restrictions, it is known from previous studies and literature that there is an 8% risk of mortality from the surgery alone. In addition, the clinical study showed that adverse events include partial paralysis, loss of vision, loss of motor skills, vertigo, and insomnia (predictive probability of 1%). Non-serious adverse events include temporary personality shifts, mood swings, and slurred speech (predictive probability shown in the study was 5%).

Additional Factors

Uncertainty: The number of subjects eligible and willing to enroll in the trial was small, but the data were robust and the trial was well-designed and conducted. The results of the trial are generalizable. The study showed that the subjects likely to experience the best results are the ones at early stages of memory loss.

Patient Tolerance for Risk and Perspective on Benefit: Because of the serious effect on patients' quality of life from diseases like Alzheimer's, other forms of dementia, and other conditions that are associated with severe memory loss, patients suffering from these diseases often have a very high tolerance for risk in exchange for a potential improvement of the disease symptoms, and for potentially alleviating the burden that they anticipate they will place on family members during the later stages of the disease. Patients who are at more advanced stages of their illness and experiencing more severe symptoms are less likely to benefit from the device. However, their tolerance for risk is difficult to assess due to their advanced disease.

Availability of Alternative Treatments or Diagnostics: There are currently no alternative treatments available.

Risk Mitigation: The risks associated with this device are great. The risks associated with implantation and explantation (if necessary) can be somewhat mitigated by limiting use to surgeons who have undergone special training, but the risks associated with personality changes cannot be mitigated or predicted. The risks can also be mitigated by indicating the device for patients at earlier stages of the disease who are more likely to benefit, and explaining in the labeling using data from the clinical trial that individuals experiencing more severe symptoms are less likely to benefit from the device.

Novel Technology Addressing Unmet Medical Need: There is no other similar technology available. It is possible that future improvements of the device may allow treatment of many other conditions that affect cognitive function. Moreover, there are no other treatments that provide the level of benefit that this device confers on the target population.

Approval/Non-Approval Considerations: The device will confer a substantial benefit for a defined and predictable subgroup of patients and a minimal benefit for another defined and predictable subgroup. Even though the clinical trial was small, the quality of the data was good and the resulting confidence intervals are narrow. The uncertainty about results is the usual uncertainty resulting from drawing inferences from a sample in the study to the population in the market. The risks associated with the device are great and can be partially mitigated by training the physicians who implant/explant (if necessary) the device. And, because patients experience the greatest benefit when the device is implanted earlier, they must expose themselves to the risks for a longer period of time in order to reap the greatest benefit; therefore, the patients who stand to benefit most also take on the greatest amount of risk. The sponsor provided data showing that many patients who suffer from memory disorders are willing to try novel approaches that have significant risk, in order to preserve their memories and quality of life. The fact that there are no alternative treatments for this condition is another important consideration. Even though the device-related risks are high, they are tolerable to the patients because of the benefits they reap. Furthermore, the risks are known and quantifiable. Therefore, this device, although risky, may be approvable based on all of these considerations. The decision as to whether or not to implant the device is a matter of patient preference (perhaps with the involvement of a legally authorized representative) and medical opinion. After full consideration of the likelihood of, and timeframe for, progression of disease and the predictability of future impairment without intervention, FDA is likely to approve the device as long as the labeling prominently addresses the 8% mortality rate and would provide through conditions of approval that only a very small group of highly trained physicians will be able to implant the device.

Example 3

A sponsor claims that its new in vitro diagnostic device (IVD), a serum-based test, can differentiate patients with BI-RADS 4 mammography results into two groups, namely patients with a low probability of having cancer for whom the physician may recommend

waiting a few months for additional testing, thus avoiding the morbidity associated with a biopsy, and all other BI-RADS 4 patients for whom a biopsy would be recommended as currently occurs under standard of care. The proposed intended use is:

> The in vitro diagnostic test measures 10 peptide analytes and yields a single qualitative result. The test is intended for females 40 years or older following mammography of a breast lesion with a BI-RADS of 4 result to aid physicians in the decision to recommend a breast biopsy.
>
> Negative test result (Low Risk): immediate biopsy is not recommended, wait a few months for further tests.
>
> Positive test result (High Risk): immediate biopsy is recommended.

Results from a clinical study in the intended use population (with biopsy results for all subjects) are:

		Biopsy		
		Malignancy	Benign	
Test	Positive	97	75	172
	Negative	3	225	228
		100	300	400

Sensitivity=97% (97/100) with 95% two-sided CI: 91.5% to 99.0%
Specificity=75% (225/300) with 95% two-sided CI: 69.8% to 79.6%
Prevalence=25% (100/400)
NPV=98.7% (225/228)
PPV=56.4% (97/172)

Benefits: The main benefit from use of the device is avoiding morbidity associated with an immediate biopsy for the 57% (228/400) of subjects whose test results indicate a low probability of having breast cancer.

Risks: Among test-negative subjects, the observed (from immediate biopsy) prevalence of cancer is 1.3% (3/228 = 1-NPV). The main risk from use of the device is in failing to biopsy some BI-RADS 4 patients who have biopsy-detectible breast cancer, thus delaying their diagnosis and treatment. Concerning this risk, the sponsor asserts that a clinically acceptable prevalence for cancer among non-biopsied BI-RADS 4 subjects is 2% or lower, because: a) BI-RADS 3 patients are usually counseled not to have an immediate biopsy (waiting a few months, instead, for further evaluation), and b) the expected prevalence of breast cancer among BI-RADS 3 patients is 2%. The benefit-risk odds measurable from the clinical study is 75 (225/3), and the observed risk for non-biopsied BI-RADS 4 subjects is lower than the expected risk in BI-RADS 3 patients.

Additional factors:

Uncertainty: There are the usual uncertainties tied to statistical confidence intervals surrounding observed study results.

The benefit-risk odds are not weighted for the clinical impact of avoiding biopsy morbidity compared to the clinical impact of missing a biopsy-detectible cancer. That is, the type of benefit is not necessarily commensurate with the type of risk.

There is no assurance that the clinical impact of breast cancers missed among patients with BI-RADS 4 mammography results is equivalent to the clinical impact of breast cancers among patients who have BI-RADS 3 results. Hence, there is uncertainty about the extent of the probable risk(s)/harm(s).

Test-negative BI-RADS 4 patients, who do not undergo biopsy, will receive no histopathological assessment of benign disease that is present.

Patient Tolerance for Risk and Perspective on Benefit: Patients' tolerance for delayed diagnosis and treatment of breast cancer typically is low. This needs to be weighed against the value that patients place on avoiding biopsy-related morbidity.

Availability of alternative treatments or diagnostics: There are no other in vitro diagnostic devices cleared or approved for the new test's intended use.

Risk mitigation: All women with negative test results will have follow-up visits for further evaluation and testing.

Approval/Non-Approval Considerations: The kinds and probabilities of benefits and risks are reasonably defined. A clinical practice reference for acceptable risk is put forth, to which the test's performance characteristics are aligned. Weighting of the different kinds of benefits versus risks is not directly addressed, and additional information is needed to establish whether the trade-offs are acceptable. Given that the benefits are uncertain and the risk (for a very small number of patients) could be substantial, FDA might determine that this device is not approvable, but would likely take it to an advisory panel prior to making a decision.

Example 4 – *De Novo*

A new standalone therapeutic device is developed to provide enhanced stability for more invasive, higher-risk implanted devices, which could otherwise affix themselves without support. The device can be used to support a primary device at the time of implantation, or can be added to an already-implanted device that is malfunctioning.

The device is studied in a prospective, multi-center, single-arm clinical study of over 200 subjects. The primary endpoint for the trial is the magnitude of the benefit, i.e., the trial is designed to measure how well the device prevents movement and malfunction of the

primary device as compared to when it is implanted without the benefit of enhanced stability.

The results of the pivotal clinical trial revealed the following:

Benefits: Through one year of follow-up, no subject experienced device movement and only two subjects experienced complications related to the device malfunctioning. This is a significant improvement over primary device performance when implanted alone and gives a very high predictive probability that a patient receiving the device will not experience device movement.

Risks: Through one year of follow-up, there were no fractures of any primary device and only a handful of malfunctions of the support system, none of which lead to serious adverse events. The risks of the support system are not high because its potential failure is unlikely to lead to an overall failure of the primary device.

Even though all implanted devices that require a surgical procedure carry with them their own set of risks (e.g., 1% chance of death from surgery), this device is implanted along with the primary device and consequently does not require an additional surgery to implant. Or, if it is placed to enhance the performance of a malfunctioning primary device, it is put in during a surgery that would have otherwise been performed to fix the malfunctioning primary device. Therefore, the data suggest that adding the support device during surgery does not appear to increase the risk to the patient.

FDA determined that the support device poses low-to-moderate risk, the risks associated with its use are well-defined and understood, and the risks can be mitigated by general and special controls, which would provide reasonable assurance of the safety and effectiveness of the device. As a consequence, the support device is appropriate for the *de novo* pathway.

Additional Factors

Uncertainty: The results of the pivotal clinical trial are limited to one-year of follow-up. For a permanent, implantable device, longer follow-up times can reduce uncertainty regarding the long-term safety and effectiveness of the device.

Patient Tolerance for Risk and Perspective on Benefit: Patients who receive the support device either are already undergoing a surgery and implantation of the primary device or have had complications with an existing device that the support device can be used to correct non-surgically. The results of the pivotal clinical trial indicate that future patients stand to benefit from greater stability of the primary device as a result of the use of the support device; therefore, most patients feel that the benefits of the device greatly outweigh the risks.

Risk Mitigation: For this *de novo*, FDA established special controls to mitigate the risks associated with the device and make it appropriate to be classified under Class II. For

this device, FDA required demonstration of biocompatibility, sterility, safety and effectiveness data (including clinical performance data, durability, compatibility, migration, resistance, corrosion resistance, and delivery and deployment); evaluation of the MR-compatibility of the device; validation of electromagnetic compatibility of device; restriction of the device to prescription use; and clear instructions in the labeling regarding the safe and effective use of the device. Since this device does not require an additional surgery to be implanted, the surgical risk is not an issue.

Novel Technology Addressing Unmet Medical Need: This device is the first system that can access and repair a failed or problematic primary device, providing surgeons with a minimally-invasive option for re-affixing devices that are not properly positioned or that have migrated, or those that are at risk of such complications.

Approval/Non-Approval Considerations: The clinical trial results provide assurance of at least one year of clinical effectiveness of the device. Furthermore, it is important to consider that the device merely supports and supplements the effectiveness of another device and its failure would not significantly affect the performance of the primary device. The device does not pose risks that would rise to the level of a Class III device. Any safety concerns regarding device failure can be readily addressed through special controls related to appropriate testing and labeling. Given the device benefits, the ability to mitigate risks through special controls, and the fact that this device is not life-supporting or life-sustaining, FDA would be likely to grant a *de novo* petition to classify this device into Class II.

5.2 Examples Based on Actual FDA Benefit-Risk Determinations

- A device to treat a very rare cancer was tested in a clinical trial that demonstrated with some uncertainty that the device performed as well as standard treatment, but not better. However, use of the device did not have harmful effects as severe as those associated with the standard anti-cancer treatment, and neither treatment was curative. The cancer was rapidly progressive and terminal, so the subjects had very little time to live after they were diagnosed. FDA approved this device because it gave patients access to a treatment that appeared to be equivalent to the standard of care (with some uncertainty remaining), but that did not cause the same severity of side effects.
- A permanently implanted cardiovascular monitoring device is intended to diagnose heart failure. The device is studied and the study shows that its use reduces the number of days the subject is hospitalized for heart failure by about three. However, the implantation procedure for the device requires that the patient be hospitalized for two days. There are similar devices on the market that provide a similar level of benefit as this device that do not require an implantation procedure. FDA determined that the benefit of saving one day of hospitalization does not outweigh the risk of

complication from the surgery needed to implant the device and found the device to be not approvable.

- A permanent birth control device can be placed in a woman's reproductive system through the vagina using a specialized delivery catheter. This device is a permanent implant and is not intended to be removed. Explantation of the device would require surgery. Clinical data show that the device is effective in preventing pregnancy over a two-year period in women and the safety data show a low incidence of adverse clinical events. However, study results also show that there are several cases where the physician had difficulty correctly placing the device. In addition, the device was noted to be fractured on a follow-up x-ray in a few study subjects. Given the uncertainty of the long-term impact of the device, the possibility of device fracture (which was not predicted in any of the bench and animal testing), and the safety and effectiveness of alternative therapies, FDA deemed the device to be not approvable for the intended patient population.
- An implanted device offers a unique design feature in comparison to the standard of care used to treat similar conditions. While the current standard of care works very well, it has limitations associated with hindering the mobility of the patient; in contrast, the novel implanted device does not affect patient mobility. Based upon the effectiveness data from the clinical study, the device demonstrates that it has significantly improved functional outcomes in comparison to the current standardcare. However, from a safety perspective, the device did present different adverse events that were different from those of the current standard of care. The risks can be appropriately mitigated with training of surgical professionals as well as through proper labeling. In the event the implant was to fail over time, the clinician could also resort to the current standard of care. In this situation, despite the different adverse events, the probable benefits outweighed the risks and FDA approved the device.

Appendix A

Intersection of this Guidance with ISO 14971

ISO 14971 provides medical device manufacturers with a framework to systematically manage the risks to people, property and the environment associated with the use of medical devices. Specifically, the standard describes a process through which the medical device manufacturer can identify hazards associated with a medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of those controls throughout the product's lifecycle.[18] Implementing this standard requires the user to make decisions on the acceptability of individual risks, and overall residual risk for a medical device throughout its lifecycle.

ISO 14971 is an FDA-recognized standard, and assuring conformity with this standard may help device manufacturers meet the design validation requirements specified in the Design Controls section of Part 820 of FDA's regulations governing quality systems.[19] Part of the premarket review process is an evaluation (direct and/or indirect) of a medical device manufacturer's risk management decisions as they pertain to the requirements to market a device in the United States.[20] The medical device manufacturer's risk management decisions that are directly and/or indirectly evaluated include those pertaining to risk estimation, risk evaluation, risk acceptability, risk control measures, and overall residual risk. Good documentation of risk management decisions by manufacturers helps to streamline the premarket review process for both FDA and manufacturers. At some point, after the manufacturer has completed its risk management activities associated with the design phase of product development, the premarket submission process with FDA is initiated, and the benefit-risk assessment takes on a different shape, which is the primary focus of this guidance. This guidance discusses the considerations FDA makes when assessing the benefit-risk profile of a device that has been designed to deliver the most benefit for the least amount of risk and to provide a reasonable assurance of safety and effectiveness.

[18] ANSI/AAMI/ISO 14791:2007 *Medical devices – Application of risk management to medical devices*, p xi.

[19] Design controls are described in 21 CFR 820.30.

[20] Additionally, the manufacturer can engage FDA during the pre-submission stage regarding their proposed risk management decisions related to clinical study design, biocompatibility testing, preclinical animal testing, bench testing, etc, and receive preliminary feedback on the adequacy of the decisions probability for generating information that will establish whether the device meets the requirements to be marketed in the United States.

Appendix B

Worksheet for Benefit-Risk Determinations

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	

Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated:
	  o What was the magnitude of each treatment effect?
	- What scale is used to measure the benefit?
	  o How did the benefit rank on that scale?	

Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	

Availability of alternative treatments or diagnostics	- What other therapies are available for this condition?
	- How effective are the alternative treatments?
	  o How does their effectiveness vary by subpopulation?
	- How well-tolerated are the alternative therapies?
	  o How does their tolerance vary by subpopulation?
	- What risks are presented by any available alternative treatments?	

Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**

Conclusions Do the probable benefits outweigh the probable risks?

Appendix C

Worksheets for Hypothetical Examples

Worksheet for Hypothetical Example 1

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Reduction of symptoms. Improved mobility. Longer life expectancy.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Substantial reduction of the patient's symptoms.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	There is 75% probability (predictive probability) that a patient will experience the benefit once the device is on the market. The patients who experience the benefit value it substantially. Patients also value the potential to achieve the benefit.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Follow-up only to one year. Patients with improved mobility tend to have higher life expectancy. Patients value the benefit, even if it were only for one year.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	Known risks associated with permanent, implantable devices. Device fracture, mechanical failure or adverse biological response. If necessary, it would be difficult to remove the device.
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	N/A
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	Surgery is non-routine and carries high risks.
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	Low. 1% chance of death from surgery Less than 3% chance of occurrence of a harmful event after implantation. Less than 3% chance of device fracture, mechanical failure, and adverse biological response.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	The device-related adverse events last as long as the device remains implanted, but can be reversed by removing the device.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	N/A

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	Clinical study was well designed and conducted, but the follow up was only 1 year.
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Questionable – there were missing data.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	There were missing data, but sensitivity analyses were conducted and the results are relatively robust.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The device is more appropriate for use by surgeons with specialized training.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients are willing to take the risk of getting the device implanted for a potential benefit because there are no other treatment options and their symptoms are severe.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life and mobility.
• Disease chronicity	- Is the disease chronic? - How long do to patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic and incurable.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	This treatment is highly valued by patients because they failed all other treatment options and the treatment and potentially improve their overall quality of life.

Availability of alternative treatments or diagnostics	- What other therapies are available for this condition?
	- How effective are the alternative treatments?
	  o How does their effectiveness vary by subpopulation?
	- How well-tolerated are the alternative therapies?
	  o How does their tolerance vary by subpopulation?
	- What risks are presented by any available alternative treatments?
		There are alternatives available, but patients receiving this device have already failed alternative treatments.

Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Limit use to surgeons who have completed specialized training.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	There are similar devices in the market for different indications and that enhances the inference about long term adverse event rates, such as device fractures. Longer term device performance, such as duration of the benefit and long term adverse event rates (beyond 1 year) could be evaluated in the postmarket setting. As long as the device is implanted by specially trained surgeons, as required in the labeling, "real world" performance should be similar to premarket performance. Effectiveness of training could be assessed (and improved) as postmarket information becomes available.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	N/A
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
75% chance of improved patient mobility and quality of life.	Permanently implantable device that requires surgery. 25% chance that patient will experience no benefit. Serious adverse events include death, device fracture, mechanical failure or an adverse biological response.	Patients are willing to tolerate the risks because they have a high probability of receiving a substantial benefit. Risks can be mitigated by limiting to surgeons who have received specialized training.

Conclusions Do the probable benefits outweigh the probable risks?
Yes. There are no alternative treatments available for the intended population and the device treats a severe condition. Patients have a 75% chance of experiencing a significant improvement in quality of life. Patients are willing to take the risk even though it is uncertain that they will achieve the benefit, because if they benefit, the benefit is great. These patients have failed alternative treatments, so they are not foregoing an effective treatment for an uncertain benefit. Finally, the risks associated with this device, although serious, are not higher than those for similar treatments.

Worksheet for Hypothetical Example 2

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Memory preservation. Improvement of quality of life. Patients place an enormous value on the benefit.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Large for patients in early stages of the disease; smaller for patients in later stages of the disease.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	The trial was designed to study two subgroups, subjects at early stages of the disease and subjects at late stages of the disease. It can be inferred that benefits will be higher for patients in early stages of the disease and lower for patients in later stages of the disease.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Benefits should last as long as the device remains implanted.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	Partial paralysis, loss of vision, loss of motor skills, vertigo, and insomnia
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	Personality shifts, mood swings, and slurred speech
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	8% risk of mortality from surgery alone, even when done by highly trained neurosurgeon.
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	High – 8% risk of death from surgery; 1% chance of a serious adverse event; and 5% chance of a non-serious adverse event. When considered together, these present a high risk. Patients in the early stages of the disease will have higher risks due to longer permanence of the device. However, those patients experience the higher benefit.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Permanent for death and serious adverse events; possible reversal for non-serious adverse events.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	N/A

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	Good. The study was small, but the confidence intervals for the endpoints were reasonably narrow.
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Very good. Almost all subjects retuned for the follow up visits.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	Very robust. Subgroups for which the device worked the best were identifiable from the results. A subgroup analysis was pre-planned during the trial design.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	Generalizable because we know patients at an earlier stage of the disease respond better.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients are willing to take the risk of getting the device implanted because there are no other treatment options and their symptoms are extremely severe. Patients with this kind of disease are often willing to risk death in order to improve their prognosis.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life and memories.
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic and incurable.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	This treatment is highly valued by patients because they have no other treatment options and it could substantially improve their quality of life.

Availability of alternative treatments or diagnostics	- What other therapies are available for this condition?
	- How effective are the alternative treatments?
	  ○ How does their effectiveness vary by subpopulation?
	- How well-tolerated are the alternative therapies?
	  ○ How does their tolerance vary by subpopulation?
	- What risks are presented by any available alternative treatments?
		There are no alternative treatments available.

Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Provide training for surgeons. Note in the labeling that this device is most effective for patients in the early stages of the disease.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	The device is "first-of-a-kind" and there are no similar devices on the market. As a consequence, there is no prior information on other devices that could be used for inferences on the performance of this device. Therefore, longer term performance, including maintenance of effectiveness, long term adverse events, and device duration, should be assessed in the postmarket setting. A postmarket study will probably be recommended.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	Breakthrough technology. It is expected that future improvements will reduce the risks associated with the current version of the device.
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
High chance of benefit for patients in the early stages of the disease. Benefits include improved memory and quality of life. Benefits are extremely valued by patients and their families.	Permanently implantable device that requires surgery. 8% risk of death from surgery; 1% risk of serious adverse events; 5% risk of non-serious adverse events. For younger patients, the risk is higher because they will live with the device for a longer period of time.	Patients are willing to tolerate the risks because they receive a substantial benefit if the device works and there are no alternative treatments available. Risks can be mitigated by providing training and limitations in the labeling.

Conclusions Do the probable benefits outweigh the probable risks?
Yes. The benefits outweigh the risks for some patients and FDA would like to provide the opportunity for those patients who would like to take the risk to obtain the benefit. There are no alternative treatments available, the device treats a severe condition, and patients experience a significant improvement in quality of life and memory. Patients are willing to take the risk even though there is a high risk of death because the benefits that they receive are so significant and life-changing. The risks associated with this device are high; however, they can be mitigated through training and limitations in the labeling. Also, this treatment is novel and there are no other similar alternatives on the market. Therefore, even though the risks are high, due to the substantial benefit achieved and the mitigations available, the benefits outweigh the risks in this case. Finally, it is expected that the technology and surgical technique will improve with further iterations and the adverse event rates will decrease.

Worksheet for Hypothetical Example 3

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Avoidance of morbidity from breast biopsy procedures.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	Avoiding inconvenience, pain and potential complications associated with breast biopsy procedure.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	Approximately 57% (228/400), for the intended use population.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Variable. Might be long term (no biopsy needed, lifelong), or might last only until follow-up exam prompts a biopsy.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	Some patients with biopsy-detectible breast cancer will not have the cancer detected/treated until follow-up exam (assuming that follow-up exam occurs).
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	Failure to characterize non-malignant disease that would have been revealed by biopsy.
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	N/A
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	For the most serious harmful events, approximately 1% (3/400) in the intended use population. Slightly more than 1% (3/228) among test-negative subjects.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Potentially lifelong, if treatable/curable breast cancer is not detected.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	See above.

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	There is no assurance that the clinical impact of breast cancers missed among patients with BI-RADS 4 mammography results is equivalent to the clinical impact of breast cancers among patients who have BI-RADS 3 results. Hence, there is uncertainty about the extent of the probable risk(s)/harm(s).
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Good.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	Reasonably robust.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The relative value that patients place on avoiding biopsy morbidity, compared to the clinical impact of missing a biopsy-detectible cancer, is not known.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is very severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients' tolerance for delayed diagnosis and treatment of breast cancer typically is low. This needs to be weighed against the value that patients place on avoiding biopsy-related morbidity.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	Disease is very severe and affects patients' quality of life.
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic, potentially incurable and, in some cases, fatal.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	Patients weigh differently the value of the benefits and the risks. Information about patients who elect not to have biopsies after receiving a BI-RADS 3 result might be helpful.

Availability of alternative treatments or diagnostics	- What other therapies are available for this condition?
	- How effective are the alternative treatments?
	  o How does their effectiveness vary by subpopulation?
	- How well-tolerated are the alternative therapies?
	  o How does their tolerance vary by subpopulation?
	- What risks are presented by any available alternative treatments?
		None, for the proposed intended use.

Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Follow-up evaluation of patients might limit harms caused by erroneous test results. A plan is needed to handle circumstances with serially "BI-RADS 4" mammograms and negative test results.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	If it is determined that the device is approvable, then additional (postmarket) information that refines the understanding of the uncertainties and patient tolerance for risk and perspective on benefit might be in order.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	The technology is not novel.
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
The benefit in this case is to avoid biopsy-related morbidity in a substantial fraction of BI-RADS 4 patients.	Approximately 1% of tested patients (slightly more than 1% of test-negative patients) will have delay in detection/treatment of breast cancer.	In current practice, approximately 2% of patients with abnormal (i.e., BI-RADS 3) mammography results have breast cancer that (because of deferred biopsy) might not be detected until follow-up exam.

Conclusions Do the probable benefits outweigh the probable risks?
The kinds and probabilities of benefit and risk are reasonably defined. A clinical practice reference for acceptable risk is put forth, and the test's performance characteristics are aligned with that clinical practice reference. Weighting of the different kinds of benefit versus risk is not directly addressed. Additional information is needed to establish the overall acceptability of trade-offs between the different kinds of benefit and risk. Given that the benefits are uncertain and the downside risk (for a very small number of patients) could be substantial, this device could be not approvable, but FDA would be likely to take it to panel prior to making a decision.

Worksheet for Hypothetical Example 4

Factor	Questions to Consider	Notes
Assessment of Benefits of Devices		
Type of benefit(s)	- What primary endpoints or surrogate endpoints were evaluated? - What key secondary endpoints or surrogate endpoints were evaluated? - What value do patients place on the benefit?	Support the stability of the primary device (movement prevention) and reduction in primary device complications.
Magnitude of the benefit(s)	- For each primary and secondary endpoint or surrogate endpoints evaluated: o What was the magnitude of each treatment effect? - What scale is used to measure the benefit? o How did the benefit rank on that scale?	A very high probability (almost 100%) of reduction of primary device migration and substantial reduction of primary device complications.
Probability of the patient experiencing one or more benefit(s)	- Was the study able to predict which patients will experience a benefit? - What is the probability that a patient for whom the device is intended will experience a benefit? - How did the benefits evaluated vary across sub-populations? (If the study was sufficiently powered for subpopulations, note specific subpopulations, nature of difference and any known reasons for these differences.) - Was there a variation in public health benefit for different populations? - Even if the benefit is in a small portion of the population, do those patients who would experience the benefit value it?	A very high probability (almost 100%) of prevention of migration. A very high probability (almost 100%) of prevention of complications.
Duration of effect(s)	- Could the duration, if relevant, of each treatment effect, including primary and secondary endpoints be determined? If so, what was it? - Is the duration of the benefit achieved of value to patients?	Data up to one year of follow-up. However, the benefit is expected to last for as long as the device remains implanted.

Factor	Questions to Consider	Notes
Assessment of Risks of Devices		
Severity, types, number and rates of harmful events (events and consequences):		
• Device-related serious adverse events	- What are the device-related serious adverse events for this product?	None.
• Device-related non-serious adverse events	- What are the device-related non-serious adverse events for this product?	Complications related to movement.
• Procedure-related complications	- What other procedure-related complications may a patient be subject to?	None.
Probability of a harmful event	- What percent of the intended patient population would expect to experience a harmful event? - What is the incidence of each harmful event in the study population? - How much uncertainty is in that estimate? - How does the incidence of harmful events vary by subpopulation (if applicable)? - Are patients willing to accept the probable risk of the harmful event, given the probable benefits of the device?	Very low.
Duration of harmful events	- How long does the harmful event last? - Is the harmful event reversible? - What type of intervention is required to address the harmful event?	Harmful events are reversible.
Risk from false-positive or false-negative results for diagnostics	- What are the consequences of a false positive? - What are the consequences of a false negative? - Is this the only means of diagnosing the problem, or is it part of an overall diagnostic plan?	N/A

Factor	Questions to Consider	Notes
Additional Factors in Assessing Probable Benefits and Risks of Devices		
Uncertainty:		
• Quality of the study design	- How robust were the data?	The trial was designed to study an investigational system that included this device. The level of data collected was very good for a Class II device.
• Quality of the conduct of the study	- How was the trial designed, conducted and analyzed? - Are there missing data?	Very good.
• Robustness of the analysis of the study results	- Are the study results repeatable? - Is this study a first of a kind? - Are there other studies that achieved similar results?	The results are robust for up to one year of follow-up. Subjects will receive continual follow-up through five years, but only the one year data were required to evaluate the device.
• Generalizability of results	- Can the results of the study be applied to the population generally, or are they more intended for discrete, specific groups?	The device has been evaluated for use with all commercially-available primary devices in the U.S. Use with other devices used only outside the U.S. has not been evaluated.
Characterization of the Disease	- How does the disease affect the patients that have it? - Is the condition treatable? - How does the condition progress?	The disease is severe.
Patient tolerance for risk and perspective on benefit	- Did the sponsor present data regarding how patients tolerate the risks posed by the device? - Are the risks identifiable and definable?	Patients are willing to take the risk of getting the device implanted because they are already undergoing or have undergone surgery and the device has an excellent record of preventing migration and complications, which can be present without the use of the device.
• Disease severity	- Is the disease so severe that patients will tolerate a higher amount of risk for a smaller benefit?	In this case, because the device is lower-risk, the disease does not have to be as severe in order to achieve a favorable benefit-risk ratio.
• Disease chronicity	- Is the disease chronic? - How long do patients with the disease live? - If chronic, is the illness easily managed with less-invasive or difficult therapies?	The disease is chronic and treatable with either open surgery or minimally-invasive device placement. This device offers an additional method of improved treatment for those who use the minimally-invasive procedure.

Factor	Questions to Consider	Notes
• Patient-Centric Assessment	- How much do patients value this treatment? - Are patients willing to take the risk of this treatment to achieve the benefit? - Does the treatment improve overall quality of life? - How well are patients able to understand the benefits and risks of the treatment?	This treatment is highly valued by patients because it provides for a minimally-invasive solution to a problem that would otherwise have to be addressed by surgery, and the clinical trial results show that the device works, even if the follow-up is only one year in duration.

Availability of alternative treatments or diagnostics	- What other therapies are available for this condition?
	- How effective are the alternative treatments?
	  o How does their effectiveness vary by subpopulation?
	- How well-tolerated are the alternative therapies?
	  o How does their tolerance vary by subpopulation?
	- What risks are presented by any available alternative treatments?
		There are no alternative minimally-invasive treatments available to provide support for a primary device that could migrate or present complications. This device is first-of-a-kind.

Risk mitigation	- Could you identify ways to mitigate the risks such as using product labeling, establishing education programs, providing add-on therapy, etc? - What is the type of intervention proposed?	Special controls, which include demonstration of biocompatibility, sterility, safety and effectiveness (including durability, compatibility, migration, resistance, corrosion resistance, and delivery and deployment); evaluation of the MR-compatibility of the device; validation of electromagnetic compatibility of device; restriction of the device to prescription use; and clear instructions in the labeling regarding the safe and effective use of the device.

Factor	Questions to Consider	Notes
Postmarket data	- Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review? - Is postmarket data available that changes the risk/benefit evaluation from what was available when the previous devices were evaluated? - Is there reason to consider evaluation of any of the following elements further in the postmarket setting due to the risk/benefit evaluation as described above? o Longer-term device performance o Effectiveness of training programs or provider preferences in use of device o Sub-groups (e.g., pediatrics, women) o Rare adverse events - Is there reason to expect a significant difference between "real world" performance of the device and the performance found in premarket experience with the device? - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?	Patients were followed for one year during the clinical trial. Long term performance of the device may be assessed in the postmarket setting.
Novel technology addressing unmet medical need	- How well is the medical need this device addresses being met by currently available therapies? - How desirable is this device to patients?	This is a first-of-a-kind device.
Summary of the Benefit(s)	**Summary of the Risk(s)**	**Summary of Other Factors**
Highly probable improvement in treatment of failed or failing underlying device. How treatment will affect patient outcomes is highly variable on other cofactors.	Permanently implantable device that requires minimally-invasive surgery. Serious adverse events include death, device fracture, mechanical failure or an adverse biological response.	Patients are willing to tolerate the risks because they receive a substantial benefit.

Conclusions Do the probable benefits outweigh the probable risks?
Yes. The device provides substantial benefits and low risks. Moreover, given the ability to mitigate risks through special controls and the fact that this device is not life-supporting or life-sustaining, FDA would be likely to grant a *de novo* petition to classify this device into Class II. For lower-risk devices, less evidence may be necessary to tip the benefit-risk balance in favor of approval. In this case, even though the follow-up data are only one year in duration, the moderate-risk nature of the device, its non-invasive application method and the fact that the risks can be mitigated through special controls could lead to a *de novo* classification under Class II.

APPENDIX IV:

Referenced Literature

1. Athappan G, Gajulapalli RD, Sengodan P, Bhardwaj A, Ellis SG, Svensson L, Tuzcu EM, Kapadia SR. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. J Am Coll Cardiol. 2014;63:2101–2110.

2. Grabert S, Lange R, Bleiziffer S. Incidence and causes of silent and symptomatic stroke following surgical and transcatheter aortic valve replacement: a comprehensive review. Interact Cardiovasc Thorac Surg. 2016 Sep;23(3):469-76.

3. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, Calhoon JH, Carabello BA, Desai MY, Edwards FH, Francis GS, Gardner TJ, Kappetein AP, Linderbaum JA, Mukherjee C, Mukherjee D, Otto CM, Ruiz CE, Sacco RL, Smith D, Thomas JD. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol. 2012 Mar 27;59(13):1200-54.

4. Pagnesi M, Martino EA, Chiarito M, Mangieri A, Jabbour RJ, Van Mieghem NM, Kodali SK, Godino C, Landoni G, Colombo A, Latib A. Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: A systematic review and meta-analysis. International Journal of Cardiology 221 (2016) 97–106.

5. Naber CK, Ghanem A, Abizaid AA et al. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. EuroIntervention 8(1), 43–50(2012).

6. Van Mieghem NM, Schipper M, Ladich E et al. Histopathology of Embolic Debris Captured During Transcatheter Aortic Valve Replacement. Circulation. 2013; 127:2194-2201.

7. Van Mieghem NM, van Gils L. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. EuroIntervention. 2016 Jul 20;12(4):499-507.

8. Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. JAMA 2016; 316:592-601.

9. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation. Eur Heart J. 2015;36(31):2070-2078.

APPENDIX V:

Definitions (as stated in SENTINEL Investigational Plan)

20.1 Definitions:

Acute Cardiovascular Surgery
An immediate transfer from the catheterization lab to the operative room during the initial treatment phase due to the need for emergency coronary artery bypass graft surgery, cardiac valve surgery, or other vascular surgical intervention.

Acute delivery and retrieval success
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.

Access Related
Any adverse clinical consequence possibly associated with any of the access sites used during the procedure.

Access Site
Any location (arterial or venous) traversed by a guide wire, a catheter or a sheath, including the left ventricular (LV) apex and the aorta.

Acute Kidney Injury (AKI)

- Stage 1: Increase in serum creatinine to 150–199% (1.5– 1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 µmol/L) OR Urine output <0.5 ml/kg per hour for >6 but <12 hours
- Stage 2: Increase in serum creatinine to 200–299% (2.0– 2.99 × increase compared with baseline) OR Urine output <0.5 ml/kg per hour for >12 but <24 hours
- Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR Urine output <0.3 ml/kg per hour for ≥24 hours OR Anuria for ≥12 hours [Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria]

Adverse Event (AE)
An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational study.
NOTE: This definition includes events related to the investigational study or to the procedures involved but does not imply that there is a relationship between the adverse event and the study. Pre-existing conditions that worsen during a study are to be considered adverse events. For users or other persons this classification is restricted to events related to the study.

Bleeding
Life-threatening or disabling bleeding:

- Fatal bleeding (BARC type 5) **OR**
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) **OR**
- Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) **OR**
- Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)
- Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated; BARC: Bleeding Academic Research Consortium.

Major bleeding:

- Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, of causing hospitalization or permanent injury, or requiring surgery **AND**
- Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding:

- Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major

Clinical circumstances in which unstable angina occurs:

Class A:

- Secondary unstable angina. Subjects in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia. Such conditions reduce myocardial oxygen supply or increase myocardial oxygen demand and include anemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrhythmia, unusual emotional stress, thyrotoxicosis, and hypoxemia secondary to respiratory failure.

Class B:

- Primary unstable angina. Subjects who develop unstable angina pectoris in the absence of an extra cardiac condition that have intensified ischemia, as in class A.

Class C:

- Post infarction unstable angina. Subjects who develop unstable angina within the first 2 weeks after a documented acute myocardial infarction.

Cerebral Infarction

Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.

Cockcroft-Gault Formula
A proxy for Glomerular Filtration Rate in which creatinine clearance is estimated from age, weight, and serum creatinine by the formula:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Death
All-cause mortality. All deaths are considered cardiovascular mortality unless an unequivocal noncardiovascular cause can be established.

Cardiovascular Mortality:
Any one of the following criteria:

- Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by noncoronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease.

Encephalopathy
Altered mental state (e.g., seizures, delirium, confusion, hallucinations)

Intracranial Hemorrhage
Collection of blood between the brain and skull. Subcategorized as epidural, subdural, and subarachnoid bleeds.

Major Adverse Cardiac or Cerebrovascular Events (MACCE)
MACCE is defined as:

- All Death
- All Stroke (major, minor and TIA)
- Acute Kidney Injury – Adjudicated by the CEC – AKI-Class 3 at discharge or 72 hours post index procedure, whichever occurs first

Myocardial Infarction (MI)
Peri-procedural MI (≤72 h after the index procedure):

- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality),
- Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (> 99th

percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure):
Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischaemia with at least one of the following:

-Symptoms of ischemia
-ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch Block [LBBB]
-New pathological Q waves in at least two contiguous leads
-Imaging evidence of new loss of viable myocardium or new wall motion abnormality

- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Pathological findings of an acute myocardial infarction

New York Heart Association Functional Classification (NYHA)

Class I: Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
Class II: Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III: Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
Class IV: Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Procedural Success

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. A second device should be used in the event of an unsuccessful attempt in deploying both filters with the first device.

Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event (SAE)

A serious adverse event is an adverse event that:
1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury

b. Resulted in a permanent impairment of a body structure or a body function
c. Required in-patient hospitalization or prolongation of existing hospitalization
d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Stroke Diagnostic Criteria:

- Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, haemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Stroke - Duration of a focal or global neurological deficit ≥24 h; **OR** , <24 h, if available neuroimaging documents a new hemorrhage or infarct; **OR** the neurological deficit results in death
- TIA – Duration of a focal or global neurological deficit < 24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist*
- Confirmation of the diagnosis by at least one of the following:
  - Neurologist or neurosurgical specialist
  - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Ischemic Stroke:
An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhagic Stroke:
An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a intraparenchymal, intraventricular, or subarachnoid hemorrhage.

A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic

Stroke Definitions:

Disabling Stroke:
A mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline

Non-Disabling Stroke:
A mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from a n individual's pre-stroke baseline

Total Procedural Time
Time elapsed between first arterial access and removal of the last guide from the arterial access sheath

Transient Ischemic Attack (TIA)
A transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. No evidence of infarction if imaging performed.

Vascular access site and access-related complications
Major Vascular Complications:

- Any thoracic aortic dissection
- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurological impairment)
- Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage

Minor Vascular Complications:

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula or pseudoaneurysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥2 but not 4 U) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage
- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage
- Failure of percutaneous access site closure resulting in interventional (e.g., stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4 U), or irreversible end-organ damage

APPENDIX VI:

Draft Labeling

Sentinel® Cerebral Protection System

℞Only

CAUTION: Federal Law (USA) restricts this device to sale by or on the order of a physician.

WARNING Contents supplied STERILE using a radiation process. Do not use if sterile barrier is damaged. If damage is found, call your Claret Medical® representative.

For single patient use only. Do not reuse, reprocess, or re-sterilize as these may compromise the structural integrity of the device and/or lead to device failure, and may result in patient injury, illness, or death. Reuse, reprocessing, or re-sterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative, and/or local government policy.

PRODUCT DESCRIPTION

The Claret Medical **Sentinel® Cerebral Protection System** (Sentinel System) is a percutaneously delivered dual-filter embolic protection device, designed to capture and remove debris dislodged during endovascular procedures. The Sentinel System utilizes an embolic filter delivered to the brachiocephalic artery (Proximal Filter), and a second embolic filter delivered to the left common carotid artery (Distal Filter). At the completion of the procedure, the filters and debris are recaptured into the catheter and removed from the patient.

The Sentinel System consists of a 6 French catheter with deployable Proximal and Distal Filters, an Articulating Sheath, and an integral handle assembly. Table 1 and Table 2 provide information regarding the filter sizes and Sentinel System specifications.

Table 1: Filter-Vessel Sizing Guide

REF (Model) Number for Ordering	Proximal Filter Size (mm)	Target Proximal Vessel Size (mm)	Distal Filter Size (mm)	Target Distal Vessel Size (mm)
CMS15-10C	15	9.0 – 15.0	10	6.5 – 10.0

Table 2: Sentinel System Specifications

Delivery Profile	6F
Working Length	95 cm
Articulating Sheath Length	4 cm
Guidewire Compatibility	0.014" (0.36 mm) diameter floppy tip coronary guidewire, 175 cm minimum length

The Articulating Sheath tip, Proximal Sheath tip, Proximal Filter hoop, Proximal Articulating Sheath Marker, Distal Filter hoop and Distal Filter tip are radiopaque to enable visualization during use. See Figure 3 and Figure 4.

Package contains one (1) Sentinel System

INDICATIONS FOR USE

The Sentinel® Cerebral Protection System is indicated for use as a cerebral protection device to capture and remove embolic material while performing transcatheter aortic valve procedures in order to reduce ischemic injury to the brain peri-procedurally. The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 mm – 10 mm in the left common carotid.

CONTRAINDICATIONS FOR USE

- Do not use in patients for whom anticoagulant and antiplatelet therapy is contraindicated.
- Do not use in vessels with excessive tortuosity.
- Do not use in patients with uncorrected bleeding disorders.
- Do not use in patients with compromised blood flow to the right upper extremity.
- Do not use in patients who have arterial stenosis >70% in either the left common carotid artery or the brachiocephalic artery.
- Do not use in patients whose brachiocephalic or left carotid artery reveals significant stenosis, ectasia, dissection, or aneurysm at the aortic ostium or within 3 cm of the aortic ostium.

WARNINGS

- Carefully read all instructions and labeling prior to use. Observe all warnings, cautions, and precautions noted throughout these instructions. Failure to do so may result in complications.
- Refer to the instructions for use supplied with any interventional devices to be used in conjunction with the Sentinel System for their intended uses, sizing, warnings, and precautions.
- The appropriate antiplatelet/anticoagulation therapy should be administered pre- and post-procedure in accordance with standard medical practice.
- Prior to use, the packaging and product should be inspected for signs of damage. Never use a damaged product or product from a damaged package.

- Never advance or withdraw the Sentinel System without proper fluoroscopic guidance or against resistance until the cause is determined. Advancing with such resistance may lead to embolization of debris, and vessel and/or device damage.
- It is recommended that the patency of the right radial or brachial artery be assessed prior to the introduction of the Sentinel System.
- It is recommended that the patient be tested for occlusion of the radial artery prior to device introduction.
- Do not use the device in left radial or left brachial access.
- Do not use the Sentinel System to deliver any type of fluid to the patient e.g. contrast media, heparinized saline, etc. due to risk of air embolization and comprise to device performance.
- Minimize movement of the Sentinel System after initial placement. Excessive movement of filters may lead to embolization of debris, vessel and/or device damage.
- Do not deploy the filters within a previously repaired artery.
- Observe the Sentinel System under fluoroscopy and monitor the patient to verify the filters have not become occluded with debris resulting in slow or no flow. The filters should be recovered if they become occluded or if flow is compromised (See Procedural Use – Retrieval).
- Indwell time of the Sentinel System is not to exceed 90 minutes as occlusion could occur, resulting in slow or no flow.
- Failure to adequately close off the Flush Ports (Front Handle, Rear Handle) may result in air embolism.
- Do not undersize or oversize the filters in relation to the selected vessel diameter. This may result in inadequate vessel wall apposition or incomplete deployment of the filters. (Refer to Sizing Guide, Table 1).
- Do not apply excessive force to the Sentinel System. This may lead to distal embolization of debris, and vessel and/or device damage.

PRECAUTIONS

- Do not forcefully bend or reshape the Articulating Sheath of the Sentinel System. This may cause device damage.
- Do not use the product if the packaging sterile barrier has been damaged or compromised.
- Improper bending of the Sentinel System may damage the catheter.
- Do not re-sterilize or reuse on another vessel or patient.

ADVERSE EVENTS

Adverse events associated with transcatheter aortic valve replacement (TAVR) using the Sentinel System with commercially available TAVR devices and TAVR devices alone is presented in Table 3, all events adjudicated.

Table 3: Adverse Events, ≤ 30 Days

	Sentinel System Arms N=244		Control Arm N=119	
Event Type	Total Events	Subjects w/Event(s)	Total Events	Subjects w/Event(s)
Acute kidney injury	7	2.9% (7)	5	2.5% (3)
Vascular complication	21	8.6% (21)	9	7.6% (9)
TAVR Access Site	20	8.2% (20)	9	7.6% (9)
Radial Artery	0	0% (0)	N/A	N/A
Brachial Artery	1	0.4% (1)	N/A	N/A
Stroke	13	5.3% (13)	12	9.2% (11)
Disabling	2	0.8% (2)	1	0.8 (1)
Non-disabling	11	4.5% (11)	9	7.6% (9)
TIA	1	0.4% (1)	1	0.8% (1)
Death	11	4.5% (11)	4	3.4% (4)

Note: AKI includes Class I, II, and III

HOW SUPPLIED

- Do not use if package is opened or damaged.
- Do not use if labeling is incomplete or illeg ble

STORAGE

- Store in cool, dry and dark place.
- Use the device prior to the Expiration Date noted on the box and pouch.

PHYSICIAN TRAINING

The Sentinel System should only be used by physicians who have received appropriate training and are familiar with the principles, clinical applications, complications, side effects, and hazards commonly associated with endovascular procedures.

SENTINEL CLINICAL STUDIES SUMMARY

Cerebral Protection in Transcatheter Aortic Valve Replacement, The SENTINEL Study

Purpose: To assess the safety and efficacy of the Claret Medical Sentinel Cerebral Protection System used for embolic protection during Transcatheter Aortic Valve Replacement (TAVR) compared to TAVR standard of care (without embolic protection).

Design: A prospective, multi-center, randomized study using the Sentinel System in subjects with severe symptomatic calcified native aortic valve stenosis indicated for TAVR was conducted at 17 sites in the United States and 2 in Germany. The primary safety endpoint was the occurrence of all Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days compared to a historical performance goal, with MACCE defined as all death, all stroke, and all Class 3 Acute Kidney Injury (AKI). The primary efficacy endpoint was the reduction in median total new lesion volume in protected territories between the Imaging Arms (Test and Control) as assessed by DW-MRI at Day 2-7 post-procedure. The observational success criteria was to

demonstrate the true clinical treatment effect by showing the observed ratio of the median total new lesion volumes is ≥ 30% in favor of the Test Arm having a lower median new lesion volume in the protected territories as compared to the Control Arm.

The study population was comprised of patients with severe symptomatic calcified native aortic valve stenosis who meet the commercially approved indications for TAVR and complied with the study inclusion/exclusion criteria. Patients were randomized between the Safety Arm and the Imaging Cohort (Test Arm and Control Arm) on a 1:1:1 basis.

Demographics: The total population consisted of 428 patients. Of these, 65 were training phase non-randomized "Roll-In" subjects that utilized the Sentinel System during TAVR. Of the randomized (n=363) patients, the age ranged from 44 to 99 years with an average age of 82.3 ± 8.31 (mean ±SD) and 47.9% were male. The average STS score was 6.7 ± 3.79, 31.7% of patients had a history of atrial fibrillation, 83.1% of patients had NYHA classification of Class 3 and above, and 5.8% had a previous stroke with permanent deficit.

Methods: Patients randomized into the Safety Arm underwent TAVR with the Sentinel System. Patients enrolled in this arm of the study completed safety assessments post procedure, and again at 30 and 90 days post procedure. In the Imaging Cohort, Test Arm patients underwent TAVR with the Sentinel System and Control Arm patients underwent TAVR only. Patients participating in the Imaging Cohort underwent comparative Magnetic Resonance Imaging (MRI) exams and neurocognitive assessments prior to and following TAVR in addition to the same safety assessments as the Safety Arm. A Clinical Events Committee (CEC) adjudicated all MACCE event endpoints.

Results: The principle safety and efficacy results from patients treated in the SENTINEL Study are provided below. All data presented below is based on the Intent to Treat (ITT) population. For safety, the ITT population consists of all patients with clinical follow-up, for efficacy the ITT population consists of all patients with baseline and follow-up MRI imaging.

Table 4: Primary Safety Endpoint (Non-Inferiority) – 30-Day Adjudicated MACCE Rate

	Total Events	Subjects w/Event(s)	Performance Goal	Upper 95% Confidence Interval[1]	P-value[1]
ITT, with imputation[4]	NA[2]	18/244 (7.4%)	18.3%[3]	10.7%	<.0001

Note: MACCE, Major Adverse Cardiac and Cerebrovascular Events, are defined as All Death, All Stroke, and Acute Kidney Injury (Class 3) at 30 days compared to a historical performance goal.
[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
[3]Performance Goal of 18 3% was used for testing non-inferiority
[4]Imputation for missing data

Table 5: 30-Day Adjudicated MACCE and Component Rates (Evaluable Subjects)

	Sentinel System Arms	Control Arm	P-value*
Any MACCE	7.3% (17/234) [17] (4.3%,11.4%)	9.9% (11/111) [12] (5.1%,17.0%)	0.4047
Death	1.3% (3/234) [3] (0.3%,3.7%)	1.8% (2/111) [2] (0.2%,6.4%)	0.6584
All Stroke	5.6% (13/231) [13] (3.0%,9.4%)	9.1% (10/110) [10] (4.4%,16.1%)	0.2523
Disabling Stroke	0.9% (2/231) [2] (0.1%,3.1%)	0.9% (1/109) [1] (0.0%,5.0%)	1.0000
Non-disabling Stroke	4.8% (11/231) [11] (2.4%,8.4%)	8.2% (9/110) [9] (3.8%,15.0%)	0.2234
AKI (Class 3)	0.4% (1/231) [1] (0.0%,2.4%)	0% (0.0%,3.3%)	1.0000

Note: Data presented as: % of subjects with event (number of subjects with event/subjects per group evaluable at 30 days or experienced an event, i.e. evaluable) [number of events] (exact 95% CI)
*P-Value based on two-sided Fisher's exact test for Test compared to Control.

Table 6: Deployment and Retrieval

	Sentinel Safety Arm (N=123)	Sentinel Test Arm (N=121)	Control Arm (N=119)	Total (N=363)	p-value[1]
Acute Delivery and Retrieval Success[2]	96.6% (115/119)	92.0% (103/112)	N/A	94.4% (218/231)	0.1570
Distal filter successfully deployed	96.6% (115/119)	92.0% (103/112)	N/A	94.4% (218/231)	0.1570
Proximal filter successfully deployed	100.0% (119/119)	99.1% (111/112)	N/A	99.6% (230/231)	0.4848
Sentinel System retrieved successfully	100.0% (119/119)	100.0% (112/112)	N/A	100.0% (231/231)	N/A
TAVR procedure considered complete[3]	95.8% (114/119)	98.2% (110/112)	N/A	97.0% (224/231)	0.4474

Note: Categorical data presented using % (n/N).
[1] p-values are testing for statistical differences across randomized arms.
[2] 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.
[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 7: Treatment Effect Success Criteria - 2-7 Day DW-MRI Median Total New Lesion Volume (Protected Territories)

	Sentinel System Arms	Control Arm	Performance Goal	% Reduction: Sentinel System vs Control (Bootstrapped 95% CI)	95% Confidence Interval[1]
ITT[2], 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 (-10.6, 65.8)	-3.2, 67.6

[1]Calculated using the Price, et al. method
[2]Median Total New DW-MRI Lesion Volume based on Protected Territories

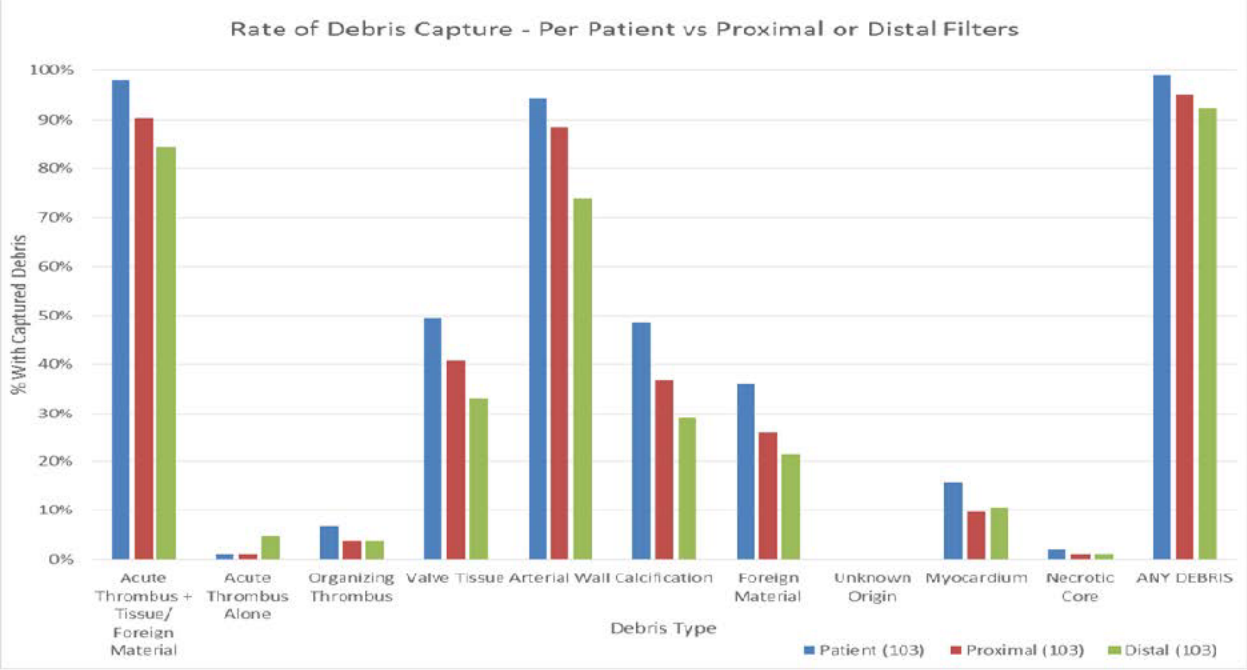

Figure 1: Histopathology Results

Table 8: Primary Efficacy Endpoint - 2-7 Day DW-MRI Median Total New Lesion Volume (Protected Territories)

	Sentinel System Arms	Control Arm	Observed Treatment Difference (test – control)	P-value[1]
ITT[2] with Imputation[3], 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	0.2354

[1]Based on two-sided Wilcoxon test
[2]Median Total New DW-MRI Lesion Volume based on Protected Territories
[3]Imputation for missing data

(b) (4)

(b) (4)

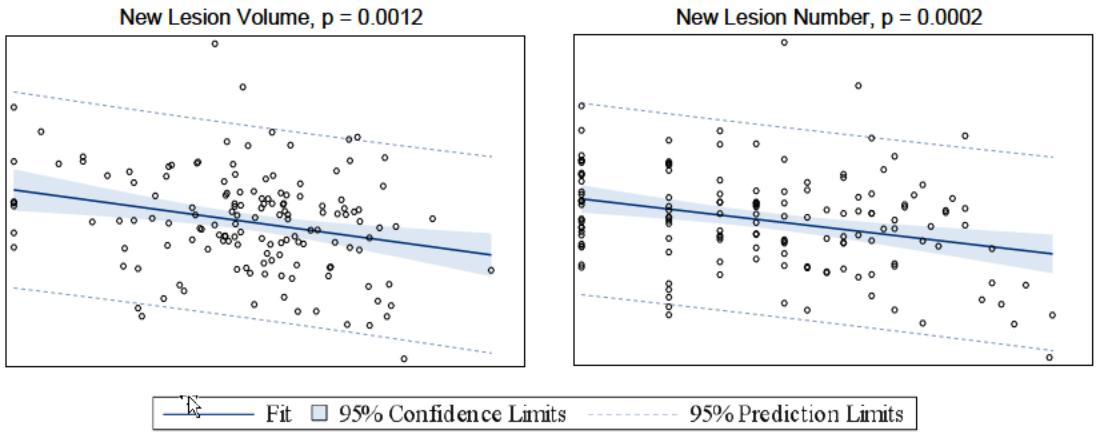

Figure 2: Change in Overall Z-Score Correlated to Volume & Number in All Territories (Follow-up – Baseline)

Conclusions: The SENTINEL trial demonstrated that the Sentinel System is safe and effective. The Sentinel System took less than 10 minutes to deploy in over 90% of patients and did not introduce any additional procedural risk. Sentinel System deployment was achieved in 94.4% of patients and 100% of devices were successfully retrieved. Histopathological analysis showed that a wide range of embolic material/debris was captured in 99% of patients. (b) (4) . The study also demonstrated a strong correlation between volumetric (p=0.0012) and numeric (p=0.0002) lesion burden in all territories of the brain and neurocognitive deterioration in patients.

INSTRUCTIONS FOR USE

Preparing the Sentinel System for Use

1. Administer anticoagulation medications and monitor activated clotting time per standard institutional guidelines. Anticoagulant therapy sufficient to maintain an Activated Clotting Time of at least 250 seconds for the duration of the procedure is recommended.
2. Perform angiogram of the aortic arch.
3. Identify the location within the vessels where the filters will be deployed to ensure appropriate vessel sizing.

WARNING: Do not use the filters in vessels outside the indicated target vessel diameter ranges. This may result in inadequate vessel wall apposition, incomplete deployment of the filters, and/or vessel damage.

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4. Ensure the introducer sheath size will accommodate the Sentinel System.
5. Using sterile techniques remove the Sentinel System from the packaging and place the system in a sterile work area.

CAUTION: Do not use the product if the packaging sterile barriers have been damaged or compromised.

WARNING: Inspect the device for any damage. Never use a damaged product or product from a damaged package.

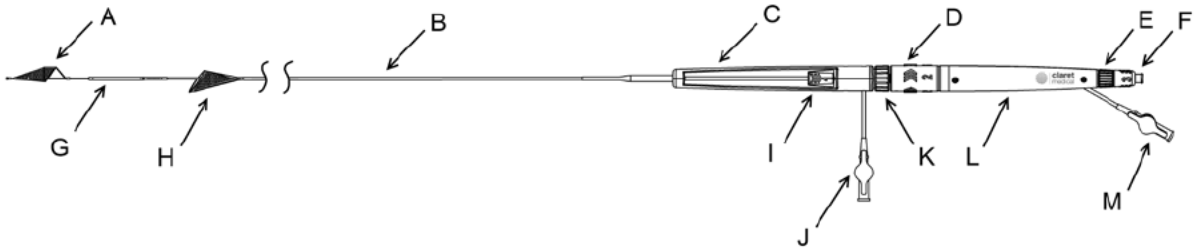

Figure 3: Sentinel Cerebral Protection System

A Distal Filter	**E** Rear Handle Lock	**I** Proximal Filter Slider **(#1)**	**M** Rear Handle Flush Port
B Proximal Sheath	**F** Distal Filter Slider **(#3)**	**J** Front Handle Flush Port	
C Front Handle	**G** Articulating Sheath	**K** Front Handle Lock	
D Articulation Knob **(#2)**	**H** Proximal Filter	**L** Rear Handle	

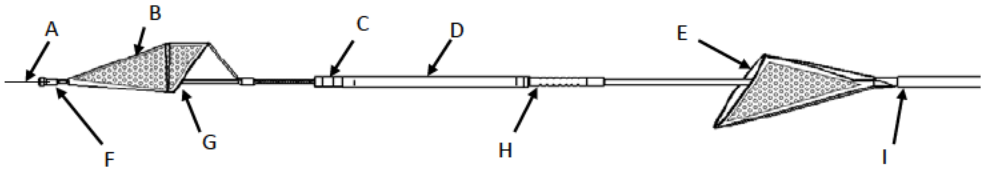

Figure 4: Sentinel Cerebral Protection System – Distal Section

A Guidewire	**D** Articulating Sheath	**G** Radiopaque Distal Filter Hoop
B Distal Filter	**E** Radiopaque Proximal Filter Hoop	**H** Proximal Articulating Sheath Radiopaque Marker
C Radiopaque Articulating Sheath Tip Marker	**F** Radiopaque Distal Filter Tip	**I** Proximal Sheath Radiopaque Marker

Flushing the Sentinel System

CAUTION: Do not prepare the Sentinel System or sheath the Proximal and Distal Filters until immediately prior to use.

Note: The device handle has two handle locks, the Rear Handle Lock, and the Front Handle Lock. Refer to Figure 3. Closing these locks facilitates flushing, prevents back-bleeding, and prevents motion of the device handle components and Distal Filter. The locks should be temporarily opened to facilitate movement of the handle components as required.
Note: The primary controls used to deploy the device, the Proximal Filter Slider **(#1)**, the Articulation Knob **(#2)**, and the Distal Filter Slider **(#3)**, are all marked with the number "1", "2' and "3" indicating the order in which they are used. In this document, these names will be shown with the control number appended to the name.

1. Remove the packaging stylet from the distal guidewire lumen and discard.
2. Ensure that both the Front Handle Lock and the Rear Handle Lock are tightened.
3. Flush through the Flush Port in the Distal Filter Slider **(#3)** with heparinized saline until all air is removed and fluid passes from Distal Filter Tip guidewire lumen. See Figure 3.
4. Flush through the Rear Handle Flush Port with heparinized saline until all air is removed and fluid passes from the tip of the Articulating Sheath. See Figure 3. Ensure that the flush port stopcock is closed following flushing.
5. Flush through the Front Handle Flush Port with heparinized saline until all air is removed and fluid passes from the tip of the Proximal Sheath. See Figure 3. Ensure that the flush port stopcock is closed following flushing.
6. Submerge the distal end of the device in heparinized saline, and loosen the Rear Handle Lock. With the distal tip submerged, slowly retract the Distal Filter by pulling back on the Distal Filter Slider **(#3)** until the filter is fully collapsed into the Articulating Sheath. The submerged filter may be agitated during sheathing in order to facilitate removal of bubbles. Tighten the Rear Handle Lock.
   Note: Flushing and sheathing of the Distal Filter may be repeated to ensure all air has been removed from the system.

CAUTION: Do not over-retract the Distal Filter as damage may occur.

7. Ensure the Articulating Sheath is fully advanced until the Articulation Knob **(#2)** is in contact with the Front Handle Lock to ensure it does not interfere with sheathing the Proximal Filter. Tighten the Front Handle Lock. While submerged, sheath the Proximal Filter by slowly advancing the Proximal Filter Slider **(#1)** relative to the Front Handle until the Proximal Filter is fully sheathed. The submerged filter may be agitated during sheathing in order to facilitate removal of bubbles. See Figure 3 and Figure 10.
   Note: Flushing and sheathing of the Proximal Filter may be repeated to ensure all air has been removed from the system.
8. While submerged, again flush through the Front Handle Flush Port with heparinized saline until all air is removed and fluid passes from the tip of the Proximal Sheath. See Figure 3. Ensure that the flush port stopcock is closed following flushing.

WARNING: Do not use a Sentinel System that has not been properly flushed. Failure to prepare and flush the device before use may introduce air and result in patient injury.

Note: Tighten both the Rear and Front Handle Locks prior to delivering device to prevent inadvertent movement.
Note: Use a minimum of 10cc of heparinized saline to flush through the Front Handle Flush Port to ensure all air has been removed from the system.
Note: Refer to the instructions for use supplied with any interventional devices to be used in conjunction with the Sentinel System for their intended uses, sizing, warnings, and precautions.

Procedural Use - Delivery and Deployment

WARNING: Do not use a Sentinel System that has not been properly flushed. Failure to prep and flush the device before use may introduce air and patient injury may result.

WARNING: To prevent damage to the System and/or harm to the patient, never advance, manipulate, or withdraw the Sentinel System without proper fluoroscopic guidance.

WARNING: The Sentinel System is not to be used to deliver any type of fluid to the patient e.g. contrast media, heparinized saline, etc.

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1. Using standard interventional technique, place a 6 French introducer sheath into the radial or brachial artery of the patient's right arm.
2. Backload a floppy tip 0.014" coronary guidewire into the Distal Filter Tip located at the distal end of the Sentinel System until the guidewire tip is located just inside the distal tip of the Sentinel catheter.
3. Introduce the Sentinel System into the introducer sheath.
4. In the patient's right arm, advance the guidewire relative to the Sentinel System until the distal tip of the guidewire is a minimum of 10 cm beyond the distal tip of the Sentinel System using fluoroscopic guidance.
5. Advance the Sheath Dilator distally until it contacts the introducer sheath hemostasis valve. Gently advance the Sheath Dilator until it is fully inserted into the introducer hemostasis valve, and advance the Sentinel System slightly to make sure that it can move easily through the Sheath Dilator.
6. Advance the Sentinel System and the guidewire together using standard interventional technique until the Proximal Filter is in the intended target location in the brachiocephalic artery with the Articulating Sheath section of the catheter extending down the ascending aorta. Should the catheter tip extend down the descending aorta, pull the system back and rotate to advance down the ascending aorta.

WARNING: Do not advance the Sentinel System without a guidewire extending distally past the tip of the catheter a minimum of 10 cm.

WARNING: Do not use excessive force on the Sentinel System while introducing or advancing through the introducer sheath or blood vessels. Excessive force may cause damage to the device and/or patient harm.

Note: The Articulating Sheath will protrude into the aorta during proximal filter deployment.
7. Deploy the Proximal Filter by holding the Front Handle in a fixed position and slowly retracting the Proximal Filter Slider **(#1)** fully.

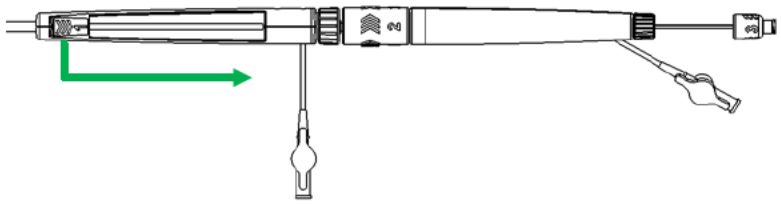

Figure 5: Proximal Filter Deployment

8. Confirm proper Proximal Filter position using fluoroscopy. The Proximal Filter should be positioned in the brachiocephalic artery to prevent any debris from reaching the right carotid artery. See Figure 5 and Figure 6.
9. If the filter position is not optimal, the filter may be retrieved and repositioned up to two times. This may be done by holding the Front Handle in a stationary position and advancing the Proximal Filter Slider **(#1)** until the Proximal Filter is re-sheathed. The Proximal Filter may then be repositioned by advancing or retracting the catheter until optimal positioning is achieved. Finally the Proximal Filter is redeployed by retracting the Proximal Filter Slider **(#1)** while holding the Front Handle in a fixed position.

CAUTION: Repositioning, if required, should only occur during initial placement.

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10. Confirm filter-to-vessel wall apposition using fluoroscopy, and ensure that the Proximal Filter and Proximal Sheath do not move after placement.
11. Withdraw the Sheath Dilator fully from the introducer sheath hemostasis valve to hold the Proximal Sheath stationary relative to the introducer sheath.
12. Withdraw the guidewire until the tip is located just within the distal tip of Sentinel catheter.
13. Loosen the Front Handle Lock to facilitate positioning of the Articulating Sheath.
14. Position the Articulating Sheath by manipulating the Rear Handle relative to the Front Handle in order to position the catheter tip. Rotate the Articulation Knob **(#2)** on the Rear Handle in the direction of the arrows in order to deflect the tip of the Articulating Sheath as necessary toward the left common carotid artery ostium.

CAUTION: Do not move the Front Handle, and thus the Proximal Filter, while manipulating the Rear Handle.

15. Advance the 0.014" guidewire beyond the distal tip of the Articulating Sheath in order to place the guidewire in the left common carotid artery.

CAUTION: Do not to advance the guidewire more than 5 cm into the left common carotid artery.

16. Position the Articulating Sheath so that the curvature matches the Brachiocephalic Artery – Aorta – Left Common Carotid Artery junction and is pulled up to the carina between the two vessels, see .
Note: Ensure that the Articulating Sheath is well apposed to the carina, and does not protrude into the aortic space. See Figure 7 for correct positioning and Figure 9 for incorrect positioning.

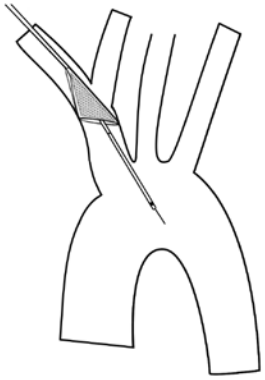

Figure 6

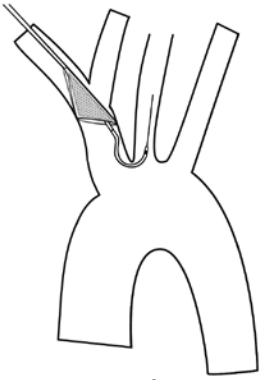

Figure 7

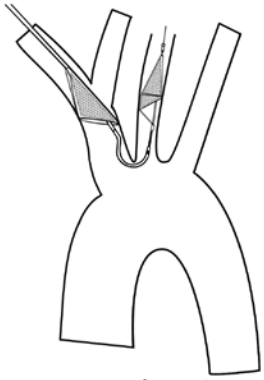

Figure 8

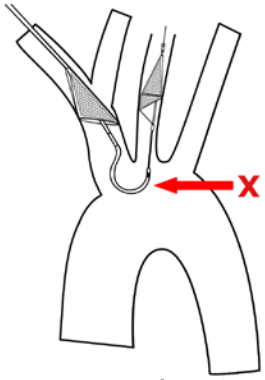

Figure 9

17. Secure the position of the Articulating Sheath by tightening the Front Handle Lock.
18. Loosen the Rear Handle Lock and advance the Distal Filter under fluoroscopy by pushing the Distal Filter Slider **(#3)** forward until the Distal Filter frame is fully expanded and apposed to the vessel wall. The Distal Filter should be positioned just beyond the Articulating Sheath tip and movement should be minimized once it is fully expanded in the vessel. See Figure 8.

WARNING: Minimize movement of the Sentinel System after filter deployment. Excessive movement may lead to embolization of debris, and vessel and/or device damage.

19. Confirm filter-to-vessel wall apposition of the distal filter using fluoroscopy. See Figure 8.
20. Tighten the Rear Handle Lock. See Figure 3.

CAUTION: Verify that the Front Handle Lock and the Rear Handle Lock are tight and secure before any subsequent procedures.

WARNING: The Sentinel System is not to be used to deliver any type of fluid to the patient e.g. contrast media, heparinized saline, etc.

CAUTION: Repositioning, if required, should only occur during initial placement.

21. Cover the exposed portion of the Sentinel System with a drape to prevent movement during subsequent endovascular procedures.

CAUTION: Care must be taken NOT to kink the exposed catheter.

WARNING: Minimize movement of the Sentinel System and its filters after filter deployment. Excessive movement may lead to embolization of debris, and vessel and/or device damage.

WARNING: If gross movement of either the Proximal or Distal Filter is noted, check to ensure filters remain apposed to the vessel walls by fluoroscopy.

WARNING: If the arterial flow is believed to be compromised (slow / no flow), the filters should be retrieved. See Retrieval below.

Procedural Use – Retrieval

WARNING: Do not pull excessively on the Sentinel System to avoid filter membrane tears, filter hoop detachment, system damage or patient harm during use.

WARNING: Never advance or withdraw the Sentinel System without proper fluoroscopic guidance.

WARNING: Never withdraw or move an intravascular device against any resistance until the resistance cause is determined. Advancing or retracting with resistance may lead to embolization of debris, and vessel and / or device damage.

There are two methods for Distal Filter recovery: Partial and Full Enclosure Recovery

1. Loosen the Rear Handle Lock. See Figure 3.
2. Recover the Distal Filter using one of the following two methods:
   a. **Full Enclosure Recovery:** Gently withdraw the Distal Filter Slider **(#3)** relative to the Rear Handle until the radiopaque Distal Filter Tip is flush with the Radiopaque Articulating Sheath Tip Marker as visualized on fluoroscopy. Tighten the Rear Handle Lock. If resistance is felt during Distal Filter recovery, or if it is believed that the Distal Filter is excessively full, follow the Partial Enclosure Recovery method detailed below.
   b. **Partial Enclosure Recovery:** Gently withdraw the Distal Filter Slider **(#3)** relative to the Rear Handle until the Distal Filter Radiopaque Hoop is collapsed inside the Articulating Sheath tip as visualized on fluoroscopy. Tighten the Rear Handle Lock.

WARNING: Exercise caution when using the partial enclosure recovery method. If resistance is felt during catheter withdrawal, advance the Distal Filter and Articulating Sheath together distally and withdraw the Distal Filter more fully into the Articulating Sheath before re-attempting withdrawal of the catheter.

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3. Loosen the Front Handle Lock and withdraw the Articulating Sheath tip from the left common carotid artery by manipulating, straightening, rotating, and advancing or withdrawing the Rear Handle and rotating the Articulation Knob **(#2)** until the Articulating Sheath tip is straight and is within the aorta.
4. Advance the Articulating Sheath completely by advancing the Rear Handle until the Articulation Knob **(#2)** contacts the Front Handle Lock to prevent interference with the Proximal Sheath or Proximal Filter during Proximal Filter retrieval. Tighten the Front Handle Lock. See Figure 3.
5. Advance the Sheath Dilator relative to the Proximal Sheath until it is fully inserted into the introducer sheath hemostasis valve.

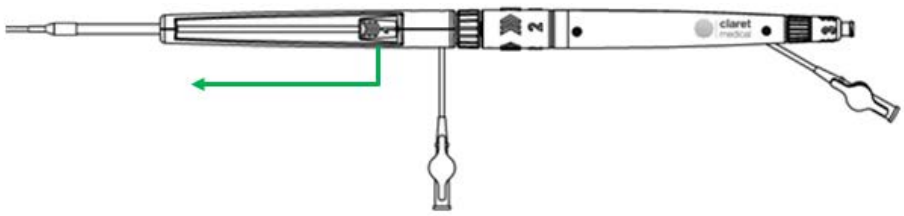

Figure 10: Sentinel Distal Filter Deployment

6. Re-sheath the Proximal Filter by holding the Front Handle in a stationary position and slowly advancing the Proximal Filter Slider **(#1)** until the Proximal Sheath Radiopaque Marker meets the Articulating Sheath as visualized on fluoroscopy. See Figure 10. Minimize retracting or advancing the Front Handle during this step. Vessel damage may occur or debris may be lost should the Proximal Filter be moved when in the deployed state.
7. Fully withdraw the Sheath Dilator from the introducer sheath hemostasis valve.
8. Advance the guidewire prior to withdrawal of the Sentinel System. Withdraw the catheter system while using fluoroscopy.
   Note: If there is any resistance to removing the Sentinel System from the introducer, remove the introducer and the Sentinel System together.

CAUTION: Do not re-sterilize or reuse this device.

Note: After use, dispose of product and packaging in accordance with hospital, administrative, and/or local government policy.

WARRANTY DISCLAIMER

Although the product has been manufactured under careful controlled conditions, Claret Medical, Inc. has no control over the conditions under which the product is used. Claret Medical, Inc. therefore disclaims all warranties, both expressed and implied, with respect to product including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Claret Medical, Inc. shall not be liable to any person or entity for any medical expenses or any direct, incidental or consequential damages caused by any use, defect, failure or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort or otherwise. No person has any authority to bind Claret Medical, Inc. to any representation or warranty with respect to the product. The exclusions and limitations set out above, are not intended to, and should not be construed so as to contravene mandatory provisions of applicable law. If any part of this Disclaimer of Warranty is held to be illegal, unenforceable or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and the rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular parts or term held to be invalid.

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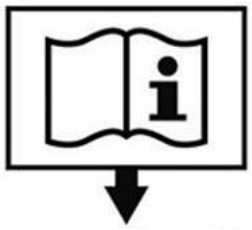

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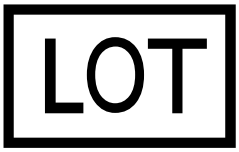
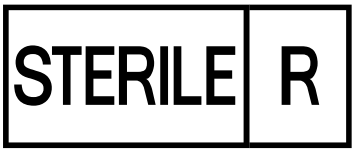


Lot number

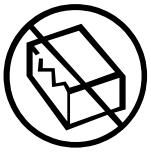
Use by Date

Single use



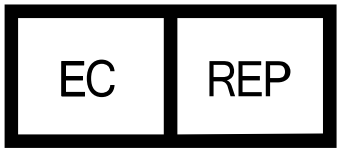
Sterile by Radiation Sterilization

Catalog number



Do not use if packaging is damaged

Do not re-sterilize



Keep dry

Recommended guidewire

Recommended introducer

Non-pyrogenic

U.S Patent Nos. 8,372,108; 8,876,796; 9,055,997; 9,326,843; 9,345,565, and 9,017,364. Other U.S. and Foreign patents pending.