DE NOVO CLASSIFICATION REQUEST FOR SENTINEL® CEREBRAL PROTECTION SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Temporary catheter for embolic protection during transcatheter intracardiac procedures.** This device is a single use percutaneous catheter system that has (a) blood filter(s) at the distal end. This device is indicated for use while performing transcatheter intracardiac procedures. The device is used to filter blood in a manner that may prevent embolic material (thrombus/debris) from the transcatheter intracardiac procedure from traveling towards the cerebral circulation.

NEW REGULATION NUMBER: 21 CFR 870.1251

CLASSIFICATION: II

PRODUCT CODE: PUM

BACKGROUND

DEVICE NAME: Sentinel® Cerebral Protection System

SUBMISSION NUMBER: DEN160043

DATE OF DE NOVO: September 19, 2016

CONTACT: Claret Medical, Inc.
1745 Copperhill Parkway, Suite 1
Santa Rosa, California 95403

INDICATIONS FOR USE

The Sentinel® Cerebral Protection System is indicated for use as an embolic protection device to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 – 10 mm in the left common carotid.

LIMITATIONS

The sale, distribution, and use of the Sentinel® Cerebral Protection System are restricted to prescription use in accordance with 21 CFR 801.109.

The Sentinel® Cerebral Protection 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.

The safety and effectiveness of the Sentinel® Cerebral Protection System have not been demonstrated with transcatheter aortic valves other than the Edwards SAPIEN XT, Edwards SAPIEN 3, Medtronic CoreValve®, and Medtronic CoreValve® Evolut R®.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Sentinel® Cerebral Protection System (Figure 1) is a 6 French, 95 cm working length, single use, temporary, percutaneously-delivered embolic protection catheter inserted into the right radial or brachial artery. The system is designed to capture and remove embolic material (thrombus/debris) during transcatheter aortic valve replacement (TAVR) procedures.

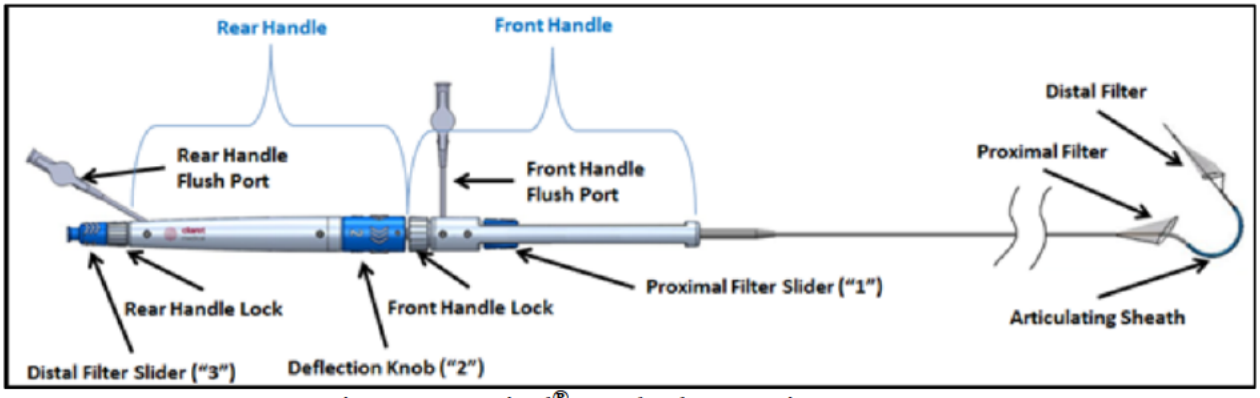

Figure 1: Sentinel® Cerebral Protection System

The Sentinel System employs two embolic filters, one delivered to the brachiocephalic artery (Proximal Filter), and one to the left common carotid artery (Distal Filter). The nominal filter diameters are 15 mm (Proximal Filter) and 10 mm (Distal Filter). Target vessels sizes are shown in Table 1 below.

Table 1: Filter and Target Vessel Sizes

Proximal Filter Size (mm)	Target Proximal Vessel Size (mm)	Distal Filter Size (mm)	Target Distal Vessel Size (mm)
15	9.0-15	10	6.5-10

Please refer to the Instructions for Use for additional details.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Sentinel System is an externally communicating device in contact with circulating blood with limited contact duration (< 24 hours). The biocompatibility testing summarized below was performed to demonstrate that the device is biocompatible for its intended use.

Table 2: Biocompatibility Testing Summary

Test	Description (Method)
Cytotoxicity	MEM Elution Assay with L-929 Mouse Fibroblast Cells (ISO 10993-5)
Sensitization	Guinea Pig Maximization (ISO 10993-10)
Irritation	Intracutaneous Reactivity (ISO 10993-10)
Acute System Toxicity	Acute System Injection (ISO 10993-11)
Hemocompatibility	ASTM Hemolysis Assay – Direct Contact & Extract Methods (ASTM Method F756-08)
	Complement Activation C3a and SC5b-9 Determination of SC5b-9 Terminal Chain Complex (TCC) and C3a-desArg Present in Normal Human Serum Through Enzyme Immunoassay (ISO 10993-4)
	In-vivo Thromboresistance (evaluated as part of the GLP animal study)
Pyrogenicity	Material-mediated Rabbit Pyrogen (USP Rabbit Pyrogen Test Procedure, Section 151)
	Endotoxin-mediated (LAL) (USP Rabbit Pyrogen Test Procedure, Section 85)

SHELF LIFE/STERILITY

The shelf-life of the Sentinel® Cerebral Protection System has been established at 1 year based on accelerated aging testing equivalent to 1 year (13 months) in accordance with *ASTM F1980 - 07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices*. Following aging, the devices were visually inspected per ASTM F1886, bubble leak tested per ASTM F2096, and package seals were tested per ASTM F88. Aged devices also underwent repeat engineering bench testing to confirm acceptable performance.

The Sentinel® Cerebral Protection System is labeled as sterile and has a validated sterility assurance level (SAL) of 10^{-6}. The Sentinel® Cerebral Protection System has been validated to be sterilized via (b) (4) radiation (b) (4). The validated dose range is 28kGy – 46kGy and was established using the $VD_{max}25$ protocol as defined by ISO 11137-2:2013.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Sentinel® Cerebral Protection System does not have any active or powered electrical components.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The Sentinel® Cerebral Protection System is intended as a temporary use device and has not been tested for MR compatibility.

SOFTWARE

The Sentinel® Cerebral Protection System does not contain software.

PERFORMANCE TESTING – BENCH

The Sentinel® Cerebral Protection System was subjected to a series of bench tests to assess its functional performance. These tests were performed on final, sterilized product. The engineering bench testing summarized in Table 3 below was performed to demonstrate acceptable mechanical performance of the device for its intended use.

Table 3: Performance Testing (Bench) Summary

Test		Description/Acceptance Criteria
Dimensional verification	Working length	• The outer sheath working length of the device must be 90 cm minimum. • The maximum catheter length must be 160 cm.
	Outer diameter profile (French size)	Characterization only (measure outer diameter of catheter with profile block)
	Filter pore size	The filter pore diameter must be 90 - 180 microns.
Simulated Use	Device preparation – Flushing	• The outer sheath lumen, articulating sheath lumen, and inner member lumen must be manually flushable with heparinized saline (via a syringe) • All luer connectors must meet ISO 594 requirements
	Hemostasis function	The device must maintain hemostasis for the outer sheath lumen and articulating distal sheath lumen.
	Procedural compatibility – Index device	The device must not interfere or entangle with commercially available TAVR devices
	Procedural compatibility – Accessory	The device must not limit movement of the 6Fr Pigtail Catheter in the aortic space for monitoring of the index procedure
	Introducer sheath compatibility	The device working length must have a 6Fr maximum profile
	Guidewire compatibility	The Guidewire lumen must have an inner diameter of 0.015" minimum
	Tip articulation	The catheter tip must be able to deflect a minimum of 150 degrees
	Torque response	The articulating sheath tip must be positioned rotationally within 30 of the specified target without uncontrolled distal rotation or "whipping"
	Dual filter operation (independence)	The articulating sheath must rotate and translate freely in order to deliver the distal filter without affecting the position of the deployed proximal filter
Kink resistance		The device must resist kinking following a 1.0" minimum radius bend without permanent deformation (e.g. compromised function)
Tip flexibility		The articulating sheath tip and distal filter tip must not cause excessive vessel trauma
Deployment and retrieval forces of both filters		Maximum deployment force and maximum sheathing force measured at the handle must be:

		• 6.0 lb max. for the proximal filter • 2.5 lb max. for the distal filter
Tensile strength		• Bonds/joints shall maintain mechanical integrity during use • Each bond/joint was tested against specifications based on the clinical use of the device
Torque strength		The articulating sheath must maintain integrity at a minimum of five full turns.
Filter performance (simulated conditions)	Embolic capture efficiency and retrievability	The filters shall be capable of capturing and retrieving 75% of embolic particles over the indicated vessel range
	Capacity and resistance to rupture	Both filters must be able to capture and retrieve a minimum of $3mm^3$ of total embolic volume
	Flow characteristics	The drop in mean arterial pressure (MAP) across each filter must not be greater than 15% when the filters are in place
Radial outward force		The radial outward force of the proximal and distal filters should not cause vessel injury

PERFORMANCE TESTING – ANIMAL &/OR CADAVER

Over the course of the Sentinel® Cerebral Protection System device development, six (6) pre-clinical animal studies were conducted on various versions of the device to support its safety and performance through simulated use in *in vivo* conditions. The two (2) studies conducted on the final device design are summarized in Table 4 below.

Table 4: Summary of Animal Studies

Purpose	Methods	Results
Evaluate the acute and chronic safety, hemolytic assessment, flow characteristics, embolic capture and retrieval, handling characteristics, fluoroscopic visibility, thrombus formation, and histopathological response of the final device design utilizing a worst-case embolic load according to Good Laboratory Practices	• GLP • Insert, track, deploy, and evaluate proximal and distal filters from a first device in the brachiocephalic and left subclavian arteries, dwell for 2 hours, remove and assess for presence of thrombus • Insert, track, deploy (in the same location as the first device), and evaluate proximal and distal filters from a second device in the brachiocephalic and left subclavian arteries under worst case embolic load conditions in four York swine models • N=2 (24-72 hrs), N=2 (30 days) • Full (N=2) & partial (N=2) filter re-sheathing • Mean Arterial Pressure (MAP) assessment across filters of both devices • Gross pathology of brain and heart • Histopathology of tissue at filter deployment sites • Neo-intimal analysis on 30 day survival animals only	• All pigs survived procedures as described in the protocol without incident • Device was deployed, placed, and retrieved as intended • No gross vascular injury was noted • No adverse events were noted in any animal • MAP assessment (6 of 8 filters) indicated minimal decrease in arterial pressure; no obvious deleterious effect on blood pressure • Device did not appear to be thrombogenic following 2 hour dwell • Filters were retrieved under worst case embolic load conditions both fully sheathed and partially sheathed • Vascular healing response, following deployment of two devices in the same location, was mild and typical for this type of device. No vascular damage or microscopic pathology noted
Evaluate the acute performance of a new handle in a porcine circulatory model. Given that the modifications relative to the device used in the previous GLP Study were to the handle only, no histopathology was performed.	• Non-GLP • Insert, track, deploy, and evaluate proximal and distal filters to both the innominate and iliac arteries in a single Duroc X swine model utilizing the Instructions for Use. • Assess performance and usability of new handle design	• The new handle worked well and allowed easy and controlled deflection of the Articulating Sheath. • Minor design changes were recommended to the handle design (changes implanted in final design)

SUMMARY OF CLINICAL INFORMATION

The primary pivotal study provided to support the De Novo request is "Cerebral Protection in Transcatheter Aortic Valve Replacement – The SENTINEL Study". Details of the study design and selected clinical results are provided below.

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

Design: The SENTINEL Study was a prospective, single blind, multi-center, randomized study using the Sentinel® Cerebral Protection System in patients with severe symptomatic calcified native aortic valve stenosis indicated for TAVR. A total of three hundred and sixty-three (363) patients at nineteen (19) centers in the United States and Germany were randomized across three arms (Safety, Test, and Control) in a 1:1:1 fashion. Subjects who met the commercially approved indications for TAVR and complied with the study inclusion/exclusion criteria were enrolled.

Subjects randomized to the Safety, Test and Control Arms underwent the following regimen:

1) Safety Arm: TAVR + the Sentinel System. Subjects enrolled in this arm of the study underwent safety follow up post procedure, 30 and 90 days post procedure. Safety Arm subjects did not undergo Magnetic Resonance Imaging (MRI) or neurocognitive assessments.
2) Test Arm: TAVR + the Sentinel System. Subjects enrolled in this arm of the study underwent safety follow up post-procedure, 30 and 90 days; effectiveness with MRI follow up at 2-7 days, and 30 days; and neurocognitive evaluation at 2-7, 30 and 90 days post-procedure.
3) Control Arm: TAVR only. Subjects enrolled into this arm of the study underwent safety follow up at post-procedure, 30 and 90 days; effectiveness with MRI follow up at 2-7 days and 30 days; and neurocognitive evaluation at 2-7, 30 and 90 days post-procedure.

A Clinical Events Committee (CEC) remained blinded throughout the trial and adjudicated all Major Adverse Cardiac and Cerebrovascular Events (MACCE) endpoints. Independent blinded MRI and neurocognitive core labs analyzed all the MRI and neurocognitive endpoint data.

Primary Endpoints:

1) Safety: The primary safety endpoint was the occurrence of all 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 safety endpoint analysis was based on the combination of the Safety and Test Arms.
2) Effectiveness: The primary effectiveness endpoint was total new lesion volume in protected territories (i.e. regions of the brain perfused by the Brachiocephalic and Left Common Carotid arteries) at 2-7 days post procedure as assessed by diffusion weighted MRI (DW-MRI). Two assessments were 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 a 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.

Secondary Endpoints: Secondary endpoints consisted of the following:

1) Safety: In-hospital MACCE (Safety + Test); MACCE rate at 30 days (Test vs Control); Major vascular complications during the index procedure and within 30 days of the index procedure (Safety + Test); Incidence of serious adverse events within 30 days (Safety + Test vs Control)
2) Effectiveness (Test vs. Control): 2-7 day median number of new lesions in protected territories; 2-7 day median total new lesion volume in all territories; 2-7 days median number of new lesions in all territories; change in neurocognitive battery z-score from baseline to 30 days; 30 day median new lesion volume in protected territories; 30 day median number of new lesions in protected and all territories; 2-7 day maximum new lesion volume in protected and all territories; 2-7 day maximum new lesion number in protected and all territories 30 day maximum new lesion volume in protected and all territories; 30 day maximum new lesion number in protected and all territories; Captured debris histopathology (Test Arm only); Correlation of 2-7 day MRI lesion volume with changes in neurocognitive battery composite z-score at 90 days, 30 days, and 2-7 days; Correlation of 30 day MRI lesion volume with changes in neurocognitive battery composite z-score at 90 days and 30 days; 30 day new lesion volume in all territories; Change in neurocognitive battery composite z-score from baseline to 2-7 days and to 90 days; Acute delivery and retrieval success; Change in neurocognitive domain scores from baseline to 2-7 days, 30 days, and 90 days

Eligibility Criteria Summary: The study population consisted of male and female patients, at least 18 years of age.

Key inclusion criteria included the following:

- Symptomatic severe aortic stenosis eligible for treatment with a US commercially approved TAVR system
- Acceptable aortic arch anatomy and vessel diameters without significant stenosis

Key exclusion criteria included the following:

- Anatomic:
  - Right extremity vasculature not suitable
  - Brachiocephalic, left carotid or aortic arch not suitable
- Clinical:
  - Cerebrovascular accident or transient ischemic attack within six months
  - Neurological disease with persistent deficits
  - Carotid disease requiring treatment within six weeks
  - Contraindications to MRI
  - Renal insufficiency
  - Severe LV dysfunction
  - Balloon valvuloplasty within 30 days

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

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

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

Table 5: Study Exit Summary (30 Days)

	Safety Arm	Test Arm	Control Arm	Total Randomized
Voluntary Withdrawal	2.4%	2.5%	5.9%	3.6%
Lost to Follow-Up	1.7%	0.8%	1.7%	1.4%
Physician's Decision	0.00%	0.8%	0.8%	0.5%
Death	1.6%	0.8%	1.7%	1.4%
Other	0.8%	0.8%	0.8%	0.8%
Overall "exited" Patients **Overall LTFU patients not evaluable for 30d MACCE**	6.5%	5.7%	10.9%	7.7% 1.1% (4/363)

One patient had a stroke and exited at day 29 and was evaluable for 30d MACCE
One patient died at day 19 and was evaluable for 30d MACCE

Table 6: Study Exit Summary (90 days)

	Safety Arm	Test Arm	Control Arm	Total Randomized
Completion of Study as Planned	84.6%	79.3%	71.4%	78.5%
Voluntary Withdrawal	3.3%	3.3%	9.2%	5.2%
Lost to Follow-Up	5.7%	7.4%	9.2%	7.4%
Physician's Decision	0.0%	1.7%	2.5%	1.4%
Death	4.1%	5.0%	4.2%	4.4%
Other	2.4%	3.3%	3.4%	3.0%
Overall	100%	100%	100%	100%

Among 244 subjects assigned to receiving the Sentinel System, 13 subjects were not treated with Sentinel System (3 no TAVR, 6 inadequate vascular access, 3 late screen failure, 1 treated as Control). Acute delivery and retrieval success (i.e. both filters successfully deployed) was achieved in 94.4% (218/231) of patients treated with the Sentinel System and Procedural Success (at least one filter deployed) was achieved in 99.6% (230/231) of the treated patients.

The SENTINEL study also allowed for up to 5 training phase non-randomized roll-in patients at each investigational site. In total, 65 roll-in subjects were treated in SENTINEL with follow-up results similar to those observed in the randomized cohort.

Demographics: The total population consisted of 428 patients. Information on the randomized (n=363) patients is provided in Table 7 below.

Table 7: Patient Demographics

Attribute	Safety Arm (N=123)	Test Arm (N=121)	Control Arm (N=119)
Age (mean, yrs)	82	82	83
Female (%)	55	52	49
STS PROM Score (mean, %)	6.2	6.4	7.5
Previous stroke (%)	8	4	5
Previous TIA (%)	8	7	7
Diabetes (%)	27	41	38
h/o atrial fibrillation (%)	30	35	30
Heavily calcified aorta (%)	3	2	3
h/o CAD (%)	54	50	56
h/o PVD (%)	16	14	15
NYHA III/IV (%)	83	85	82
Valve area (cm^2)	0.7 ± 0.18	0.7 ± 0.17	0.7 ± 0.20
Mean aortic valve gradient (mmHg)	42 ± 15	44 ± 15	41 ± 14

Adverse Events: The adverse events presented in Table 8 and Table 9 were observed in SENTINEL through 30 days and 90 days, respectively. All events were adjudicated by an independent Clinical Events Committee (CEC).

Table 8: Adverse Events Through 30 Days

	(Safety + Test 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)	10	8.4% (10)
Disabling	2	0.8% (2)	1	0.8% (1)

Event Type	(Safety + Test Arms) N=244		Control Arm N=119	
	Total Events	Subjects w/Event(s)	Total Events	Subjects w/Event(s)
Non-disabling	11	4.5% (11)	9	7.6% (9)
Transient Ischemic Attack (TIA)	1	0.4% (1)	0	0.0% (0)
Death	3	1.2% (3)	2	1.7% (2)

Note: AKI includes Class 1, 2, and 3

Table 9: Adverse Events Through 90 Days

Event Type	(Safety + Test Arms) N=244		Control Arm N=119	
	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)	3	2.5% (3)
Non-disabling	11	4.5% (11)	9	7.6% (9)
Transient Ischemic Attack (TIA)	1	0.4% (1)	1	0.8% (1)
Death	11	4.5% (11)	4	3.4% (4)

Note: AKI includes Class 1, 2, and 3

Results: The principal safety and effectiveness results from patients in the SENTINEL study are provided below. The primary safety analysis was based on all patients as randomized to the Safety and Test Arms, referred to as Intention to Treat (ITT) population. The primary safety endpoint included imputation for missing clinical outcomes data using the logistic regression method. The imputation model included baseline characteristics including age, sex, BMI, history of diabetes, atrial fibrillation, stroke with permanent deficit, and geography.

Primary Safety Endpoint: The primary safety endpoint of the SENTINEL trial was met with a p-value of <0.0001 in both ITT populations (with and without imputation), see Table 10. The primary safety endpoint analysis was based on a one-sided binomial test, compared to an a priori performance goal (PG) threshold of 18.3% for determination of non-inferiority. The point estimate for the historical performance goal was derived from published FDA documents as well as the published literature.

Table 10: 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
ITT	17	17/234 (7.3%)	18.3%	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

Primary Effectiveness Endpoint: The primary effectiveness endpoint analysis (Criterion 1 and 2) was based on the ITT population comparing the Test Arm and Control Arm. The primary effectiveness endpoint included imputation for missing clinical outcomes data using the predictive mean matching method based on blinded, aggregate, SENTINEL data.
The primary effectiveness endpoint based on ITT was not found to be statically significant with a p-value 0.33 (Table 11). Criterion 2 was met and the observed treatment effect of 42% in protected territories was > 30% target (Table 12).

Table 11: Primary Effectiveness Criterion 1 - Median 2-7 Day DW-MRI Total New Lesion Volume (Protected Territories)

	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	Observed Treatment Difference (Test - Control)	p-value[1]
ITT with Imputation, mm³	109.1 (36.9, 379.7), n=121, 0 min, 5175.9 max	174 (39.6, 469.3), n=119, 0 min, 24300 max	-64.9	0.24
ITT, mm³	102.8 (36.9, 423.2), n=91, 0 min, 5175.9 max	178 (34.3, 482.5), n=98, 0 min, 24300 max	-75.1	0.33

[1]Based on two-sided Wilcoxon test

Table 12: Primary Effectiveness Criterion 2 - 30% Reduction in 2-7 Day DW-MRI Median Total Lesion Volume (Protected Territories)

	Test Arm median (IQR), n, min, max	Control Arm median (IQR), n, min, max	Target	Observed % Reduction (Test-Control)/Control
ITT, mm³	102.8 (36.9, 423.2), n=91, 0 min, 5175.9 max	178 (34.3, 482.5), n=98, 0 min, 24300 max	30%	42.2

Key Secondary Safety Endpoints: A breakdown of the MACCE components compared to the concurrent Control Arm is provided in Table 13.

Table 13: 30-Day MACCE and Component Rates (ITT)

	(Safety + Test Arms) % patients with event (n patients with event/N patients) [exact 95% CI]	Control Arm % patients with event (n patients with event/N patients) [exact 95% CI]
Any MACCE	7.3% (17/234) [4.3%,11.4%]	9.9% (11/111) [5.1%,17.0%]
Death	1.3% (3/234) [0.3%,3.7%]	1.8% (2/111) [0.2%,6.4%]
Stroke	5.6% (13/231) [3.0%,9.4%]	9.1% (10/110) [4.4%,16.1%]
Disabling	0.9% (2/231) [0.1%,3.1%]	0.9% (1/109) [0.0%,5.0%]
Non-disabling	4.8% (11/231) [2.4%,8.4%]	8.2% (9/110) [3.8%,15.0%]
AKI (Class 3)	0.4% (1/231) [0.0%,2.4%]	0% [0.0%,3.3%]

Secondary Safety Analyses are provided below (ITT population).

- In-Hospital MACCE: Numerically lower between the Safety + Test Arms [5.7% (14/244)] versus the Control Arm [8.4% (10/119)]. The observed stroke rate in the Safety + Test Arms (4.9%) versus the Control Arm (8.4%) resulted in a 41.7% relative reduction.
- 30-Day MACCE (Test Arm vs Control Arm): 6.0% (7/117) and stroke rate of 4.3% (5/116) in the Test Arm were numerically lower than the Control Arm, [9.9% (11/111) and 9.1% (10/110) respectively].
- Major vascular complications (Index procedure and within 30 days): Incidence of adjudicated major vascular events were low during the index procedure with no radial or brachial events during the procedure, and only one brachial event (0.4%) within 30 days of the index procedure.
- Serious Adverse Events (30 days): Site reported serious adverse events were similar between the Safety + Test Arms and the Control Arm. The events did not exceed rates reported from contemporary TAVR studies, with 42.6% (104/244) being reported for the Safety + Test Arms and 42.9% (51/119) for the Control Arm.

Safety was evaluated out to 90 days for all patients. Similar to the 30-Day MACCE rate, 90-Day MACCE was numerically lower between the Safety Cohort [11.3% (24/213)] and Control Arm [12.9% (12/93). Specifically, strokes were numerically lower between the Safety + Test Arms [6.4% (13/202)] and the Control Arm [12.0% (11/92)].

Key Secondary Effectiveness Endpoints:

The table below compares results observed in the regions of the brain protected by the Sentinel System and the entire brain (all territories).

Table 14: Protected and All Territories 2-7 Day Median Total New Lesion Volume

	Protected Territories			All Territories		
	Test Arm median (IQR), n, min, max	**Control Arm** median (IQR), n, min, max	**Observed Treatment Difference (Test – Control) (mm^3)**	**Test Arm** median (IQR), n, min, max	**Control Arm** median (IQR), n, min, max	**Observed Treatment Difference (Test – Control) (mm^3)**
ITT with Imputation, mm^3	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	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
ITT, mm^3	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	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

A neurocognitive test battery of composite z-scores from baseline to follow-up between the Test and Control Arms was performed at 30 days, no difference in the mean change in z-score between the Test Arm and the Control Arm were observed, possibly due to 82% of the population having been below the age adjusted norm (i.e. floor effect). The composite z-score is an overall cognition score that is the average of the z-scores from each of the five cognitive domains assessed: attention, executive function, processing speed, verbal memory and visual memory. A relative negative z-score indicates worsening neurocognition while a relative positive z-score indicates an improvement in neurocognition. In SENTINEL, the range of changes in z-score from baseline to 30 days was -1.45 to 1.39 and was not statistically significant between the test and control arms (reference Table 15 for the mean change in z-score).

Table 15: Change in Composite Z-Score (Baseline - 30 Days)

	Test Arm Mean ± SD, n	**Control Arm** Mean ± SD, n
ITT	-0.09 ± 0.44, 93	-0.03 ± 0.37, 92

Remaining Secondary Endpoint Results: Results for prospectively defined secondary endpoints not discussed above as performed on the ITT population are included below:

- 2-7 Day Median Number of New Lesions (Protected Territories): The number of new lesions was numerically lower in the Test Arm (2) versus the Control Arm (3).
- 2-7 Day Median Number of New Lesions (All Territories): The number of new lesions was numerically lower in the Test Arm (3) versus the Control Arm (5) but was not statistically significant.
- Difference in Neurocognitive Battery Composite Z-Score from Baseline to 30 Days: The difference in composite z-score was not statistically different between the Test Arm and Control Arm.

- 30-Day Median Total New Lesion Volume (Protected Territories): The total new lesion volume at 30 days was zero for both the Test Arm and Control Arm and was not significant.
- 30-Day Median Number of New Lesions (Protected & All Territories): The number of new lesions at 30 days was zero for both the Test Arm and Control Arm in both protected and all territories and was not significant.
- 2-7 Day Maximum and Median New Lesion Volume (Protected & All Territories): None of the results from this evaluation were found to be statistically significant.
- 30-Day Maximum and Median New Lesion Volume (Protected & All Territories): None of the results from this evaluation were found to be statistically significant.
- Correlation of 2-7 Day Lesion Volume to 2-7 Day and 90 Day Z-Score: The correlations were not found to be statistically significant at these time points.
- Correlation of 30-Day Lesion Volume to 30 Day and 90 Day Z-Score: The correlations were not found to be statistically significant at these time points.
- 30-Day Median Total New Lesion Volume (All Territories): The total new lesion volume at 30 days was zero for both the Test Arm and Control Arm and was not significant.
- Difference in Neurocognitive Battery Composite Z-Score from Baseline to 2-7 Days & 90-Days: The difference in composite z-score was not statistically different between the Test Arm and Control Arm at either time point.
- Acute Delivery and Retrieval Success: Acute delivery and retrieval success was achieved in 94.4% (218/231) of patients (both filters deployed). At least on filter was deployed in 99.6% of patients.
- Change in Individual Neurocognitive Domain Scores: No statistically significant changes were observed in any of the domain analyses.

Conclusions: The SENTINEL trial demonstrated that the Sentinel System is safe and effectively captures debris. Sentinel System deployment was achieved in 94.4% of patients and 100% of devices were successfully retrieved with only one vascular injury (0.4%). The primary safety endpoint was met and 30-day MACCE events in patients treated with the Sentinel System were less than the prespecified performance goal of 18.3% with a p-value <0.0001. The effectiveness success Criterion #1 was not met and a statistically significant reduction in DW-MRI lesions post-TAVR was not seen; however, effectiveness success Criterion #2 was met by showing a 42% observed treatment effect in DW-MRI median lesion volume reduction in protected territories in favor of the Test Arm. The SENTINEL study demonstrated that debris was captured in 99% of patients.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

Panel Meeting

FDA convened the Circulatory System Devices Panel of the Medical Devices Advisory Committee on February 23, 2017 to discuss and make recommendations on the clinical information related to the De Novo request for Claret Medical Inc.'s Sentinel® Cerebral Protection System. While the SENTINEL study met the primary safety endpoint, the study failed to meet the effectiveness endpoint to demonstrate statistical superiority of reduced total new lesion volume in protected territories as assessed by DW-MRI at Day 2-7 post-procedure. The Panel members were requested to provide input on the interpretation of the clinical outcomes from the study, specifically with respect to reasonable assurance of device effectiveness and probable benefit.

The panel agreed that the device demonstrated reasonable assurance of safety, but only possible benefit for reducing ischemic injury to the brain peri-procedurally given the uncertainty regarding interpretation of the effectiveness outcomes. The panel also agreed that new lesion volume as evaluated with DW-MRI had limitations as a surrogate endpoint for clinical stroke. However, the panel agreed that the Sentinel® device captures debris, which is a meaningful outcome to clinicians and patients, and therefore, the panel recommended that if the De Novo for the device were granted, the indications should reflect its ability to capture and remove debris rather than reference to reduction in ischemic injury, which was not clearly demonstrated. FDA agreed with the Panel recommendations.

The Panel meeting materials, summary, and transcript can be found at:

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm542254.htm

LABELING

The Sentinel® Cerebral Protection System labeling consists of Instructions for Use and packaging labels. The Instructions for use include the indications for use; a description of the device, contraindications, warnings, precautions; a list of transcatheter intracardiac procedure devices that are compatible with the device; a detailed summary of the clinical data collected in support of the device; a shelf life; and instructions for the safe use of the device. The labeling satisfies the requirements of 21 CFR 801.109.

Please see the Limitations section above for important warnings and precautions presented in the device labeling.

RISKS TO HEALTH

Table 16 identifies the risks to health that may be associated with use of a temporary catheter for embolic protection during transcatheter intracardiac procedures and the measures necessary to mitigate these risks.

Table 16: Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
Device failure leading to debris embolization and stroke or death	Non-clinical Performance Testing Animal Testing Clinical Performance Testing
Impeded or disrupted blood flow leading to peripheral ischemia	Non-clinical Performance Testing Animal Testing Clinical Performance Testing Labeling
Device incompatibility with transcatheter intracardiac procedure device leading to prolonged treatment time or device failure	Non-clinical Performance Testing Animal Testing Clinical Performance Testing Labeling
Adverse tissue reaction	Biocompatibility Evaluation
Infection	Sterilization Validation Shelf Life Testing Labeling
Vascular Injury due to device delivery, deployment, placement, or retrieval	Non-clinical Performance Testing Animal Testing Clinical Performance Testing Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Sentinel® Cerebral Protection System is subject to the following special controls:

1. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   a. Simulated-use testing in a clinically relevant bench anatomic model to assess the following:
      i. Delivery, deployment, and retrieval, including quantifying deployment and retrieval forces, and procedural time
      ii. Device compatibility and lack of interference with the transcatheter intracardiac procedure and device
   b. Tensile strengths of joints and components, tip flexibility, torque strength, torque response and kink resistance
   c. Flow characteristics
      i. The ability of the filter to not impede blood flow
      ii. The amount of time the filter can be deployed in position and retrieved from its location without disrupting blood flow
   d. Characterization and verification of all dimensions

2. Animal testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be assessed:
   a. Delivery, deployment, and retrieval, including quantifying procedural time

b. Device compatibility and lack of interference with the transcatheter intracardiac procedure and device
c. Flow characteristics
    i. The ability of the filter to not impede blood flow
    ii. The amount of time the filter can be deployed in position and retrieved from its location without disrupting blood flow
d. Gross pathology and histopathology assessing vascular injury and downstream embolization

3. All patient contacting components of the device must be demonstrated to be biocompatible.

4. Performance data must demonstrate the sterility of the device components intended to be provided sterile.

5. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

6. Labeling for the device must include:
    a. Instructions for use;
    b. Compatible transcatheter intracardiac procedure devices;
    c. A detailed summary of the clinical testing conducted; and
    d. A shelf life and storage conditions.

7. Clinical performance testing must demonstrate:
    a. The ability to safely deliver, deploy, and remove the device;
    b. The ability of the device to filter embolic material while not impeding blood flow;
    c. Secure positioning and stability of the position throughout the transcatheter intracardiac procedure; and
    d. Evaluation of all adverse events including death, stroke, and vascular injury.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study described above. Types of harmful events include access site complications, hypotension, hematoma, pseudoaneurysm, bleeding, bruising, and pain at the access site. The probability of a harmful event is very low and reversible – only one vascular complication was noted in the randomized cohort of the SENTINEL study (0.4%).

The probable benefits of the device are also based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study as described above. The SENTINEL study demonstrated that 99% of patients may benefit from the capture and removal of embolic material.

Additional factors to be considered in determining probable risks and benefits for the Sentinel® Cerebral Protection System include: Physician and patient feedback confirms the value of

capturing and removing embolic material. Patients are willing to accept the low risk associated with use of the device versus the probable benefit of debris capture.

Patient Perspectives

Patient perspectives were considered as part of the Open Public Hearing at the February 23, 2017 Advisory Panel meeting. Patients place value on a device that captures debris.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for embolic protection during TAVR procedures, the probable benefits outweigh the probable risks for the Sentinel® Cerebral Protection System. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The De Novo request for the Sentinel® Cerebral Protection System is granted and the device is classified under the following:

Product Code: PUM
Device Type: Temporary catheter for embolic protection during transcatheter intracardiac procedures
Class: II
Regulation: 21 CFR 870.1251