FDA U.S. FOOD & DRUG ADMINISTRATION

Questions for the Circulatory System Devices Advisory Panel

February 23, 2017

DEN160043

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

1. Safety Results

The SENTINEL study primary safety analysis included comparison of the 30-day MACCE (i.e., All Death, All Stroke, Acute Kidney Injury) rate to a literature-based performance goal of 18.3% (i.e., 13.3% literature rate plus 5% margin). Results are presented in Table 1 below. The ITT with Imputation population is the pre-specified primary analysis population.

Table 1: Primary Safety Results: 30-Day MACCE

	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

As noted above, 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 was conducted as Secondary Safety Endpoint 2.

Table 2: 30-Day MACCE Component Rates (Test Arm vs. Control Arm) – 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.

Q1. Please comment on the clinical significance of the safety results.

2. Effectiveness Endpoints

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 this 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 the effectiveness/benefit of the Sentinel® Cerebral Protection System as measured by cerebral infarct volume on DW-MRI. Note that some have reported that 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.

FDA created box plots (see page 3) displaying the observed Day 2-7 DW-MRI total new lesion volume in protected territories only (Figure 1) and in all cerebral territories (Figure 2). The data presented in Figures 1 and 2 consist of Imaging Cohort patients separated by 30 day stroke status. The bold line represents the median and the box length represents the interquartile range (IQR=Q3-Q1). The whiskers represent the spread of the data. More specifically, the whiskers represent the lowest and highest datum still within 1.5 times the IQR. Data available for 14 of the 15 clinical strokes in the Imaging Cohort (5 in the Test Arm; 10 in the Control Arm) show a trend (slightly more pronounced for the protected territory analysis) that patients with stroke had larger lesion volumes than those without stroke, as expected. There is slightly more separation of the two boxes in protected territories (Figure 1), suggesting that new lesion volume in protected territories may be slightly more sensitive to stroke status compared to new lesion volume in all territories. However, new lesion volume measurement does not seem to differentiate patients with clinical stroke, as the ranges for the two groups overlap greatly.

Q2a. Please comment on the appropriateness of DW-MRI as a primary effectiveness endpoint for the SENTINEL study.

Q2b. Please discuss any recommendations for future trial design/clinically significant effectiveness endpoints.

Figure 1: New Lesion Volume by Clinical Stroke Status (Protected Territories)

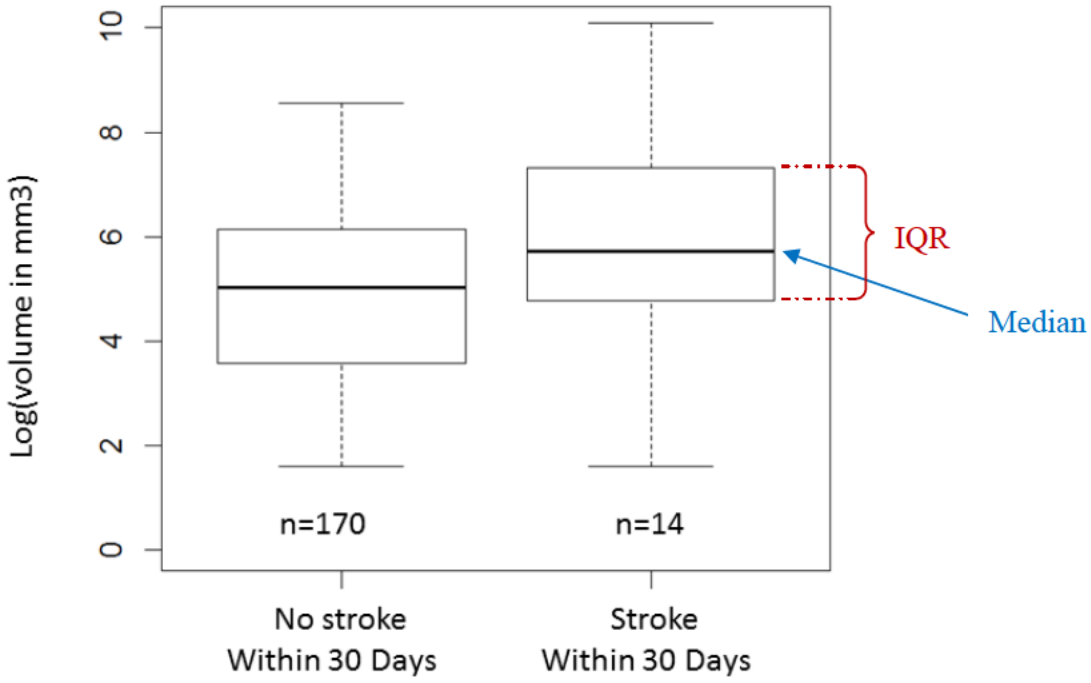
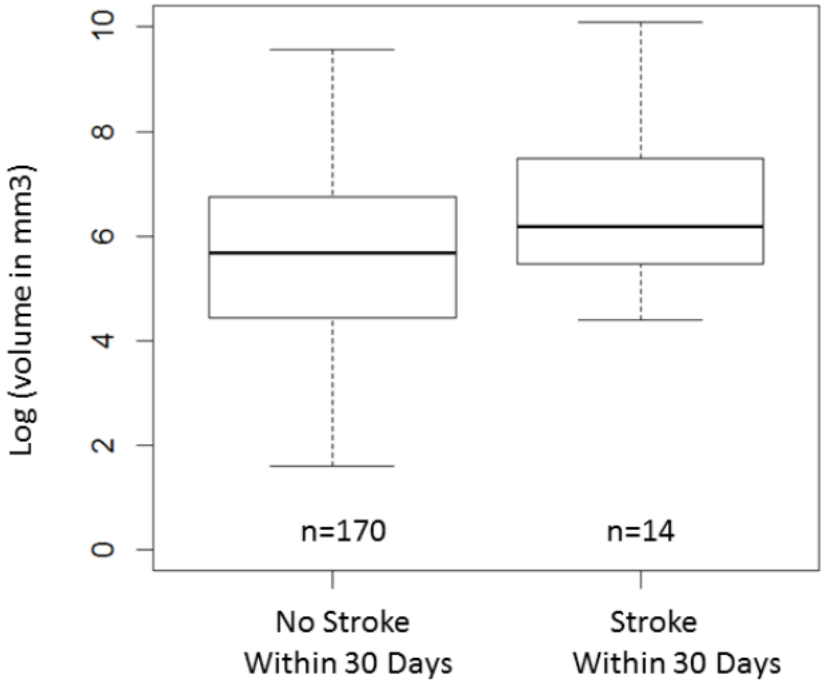


Figure 2: New Lesion Volume by Clinical Stroke Status (All Territories)



3: Effectiveness Results

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 SENTINEL pivotal study was performed with a goal of demonstrating that the device had superior effectiveness with regard to reduction in cerebral ischemic events as measured by new lesion volumes detected by DW-MRI after TAVR. Note that the study was not designed to show reduction in clinical stroke. The effectiveness assessment included a statistically driven component (Criterion #1) and an observed treatment effect component (Criterion #2). Study success required both assessments be met. Observed treatment effect (Criterion #2) was achieved; however, statistical superiority with regard to DW-MRI lesion volume reduction (Criterion #1) was not met. Therefore, the study did not meet the pre-specified study success criterion for effectiveness.

The following results were provided in the Executive Summary and repeated here for reference. Note that the ITT population is without imputation and represents "all completers" (i.e., those with available paired baseline and 2-7 day DW-MRI data). Per protocol (PP) excludes those whose follow-up evaluations were done out-of-window.

Table 3: Effectiveness Results - Reduction in Median Total New Lesion Volume 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) (mm^3)	p-value[1]
Protected Territories Only – Pre-specified Study Success Criterion 2 (Effectiveness Criterion #1)				
ITT with Imputation	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
All Territories – Secondary Effectiveness Endpoint 2				
ITT with Imputation	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, (25th percentile, 75th percentile), n, min, max.
[1]Based on two-sided Wilcoxon test

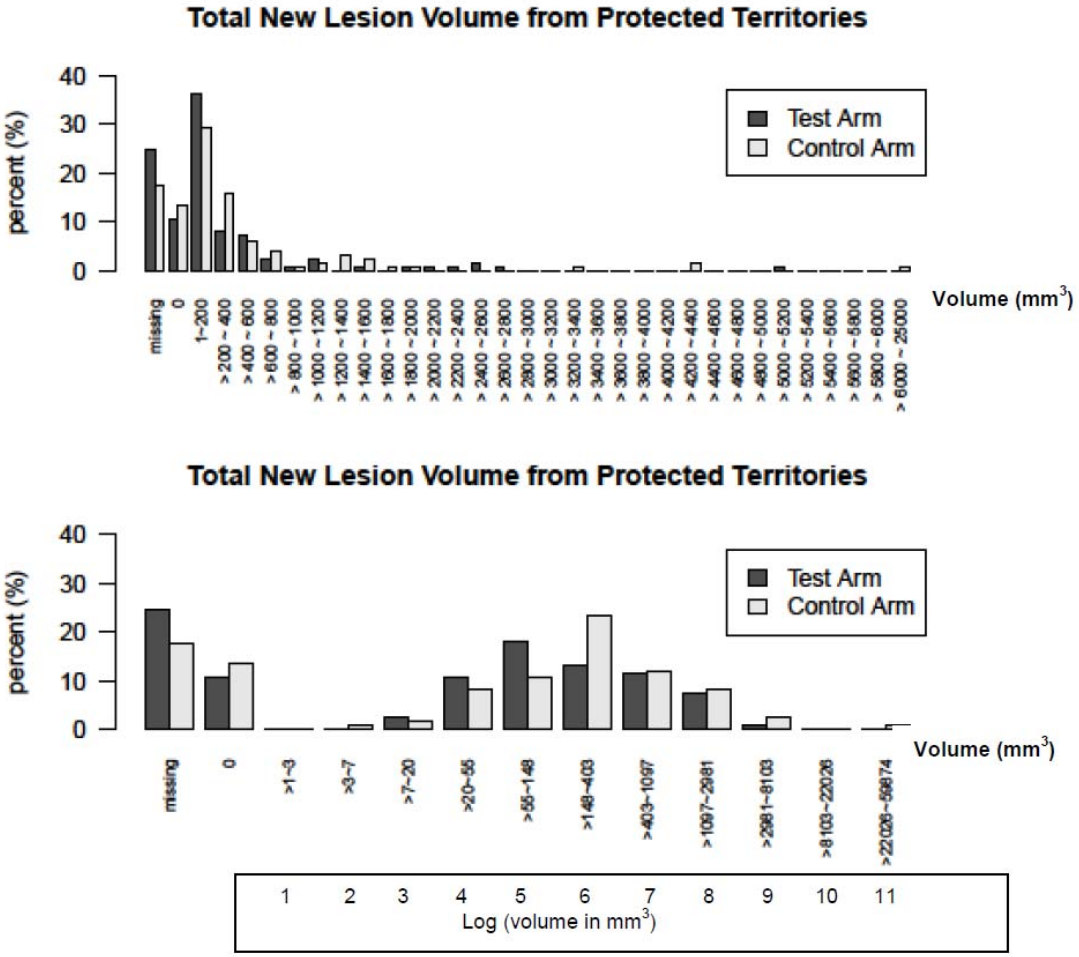
Table 4: Effectiveness Results - 30% Reduction in Median Total New Lesion Volume as assessed by DW-MRI at Day 2-7 post-procedure

Population	Test Arm (mm^3)	Control Arm (mm^3)	Observed % Reduction
Protected Territories Only – Pre-specified Study Success Criterion 3 (Effectiveness Criterion #2)			
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 presented as: median, (25 percentile, 75 percentile), n, min, max.

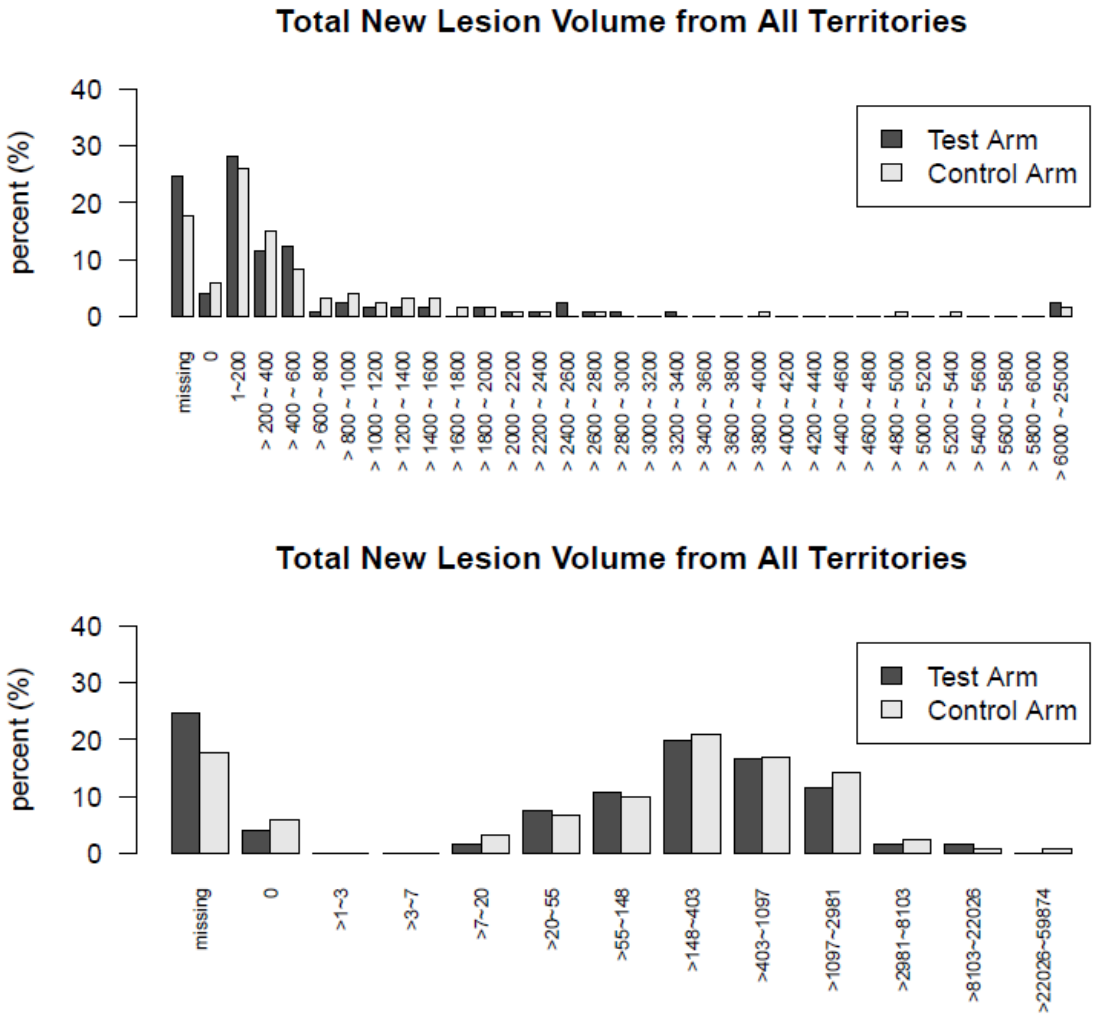
FDA also plotted the frequency distribution of the observed total new lesion volume in protected territories for the Test and the Control Arms (see Figure 3 below). The two plots differ only in how the data are grouped: the top plot uses equal width intervals (in an increment of 200 mm^3), while the 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 3



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 4 below).

Figure 4



Q3a. Please discuss whether the reduction in new lesion volume in protected territories observed in the Test Arm is clinically meaningful.

Q3b. Please discuss the clinical appropriateness of reporting the effectiveness outcomes for protected territories versus all territories in the labeling, if the De Novo request were to be granted.

(b) (4)

[redacted]

Q4. Please comment on the meaning and clinical significance of debris capture. Specifically, please comment on the discernment of the debris captured from TAVR versus that related to placement of the Sentinel device.

5: Neurocognitive Outcomes

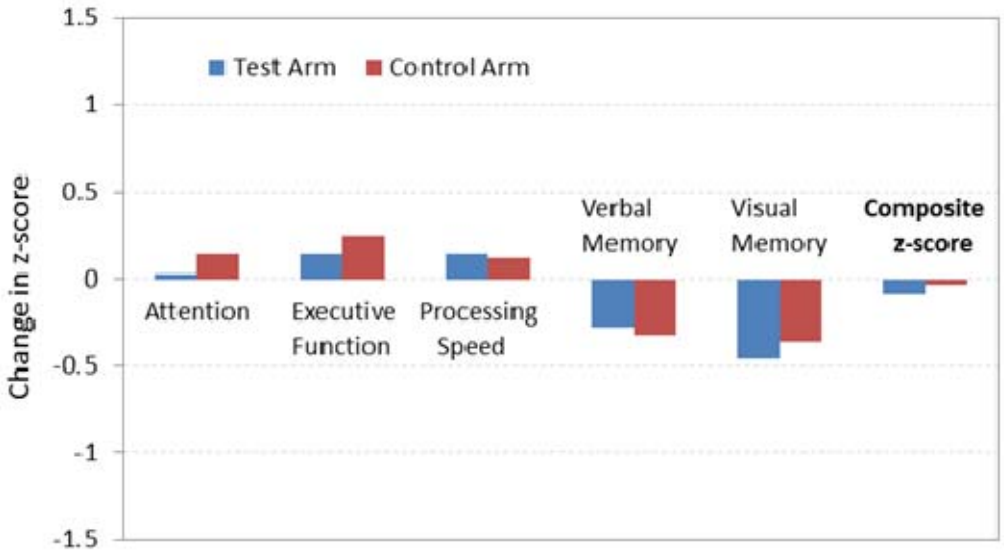
Secondary effectiveness endpoints 4 and 14 included assessment of neurocognitive decline at 2-7 days, 30 days and 90 days.

Table 5: Change in Neurocognitive Battery Composite Z-Score

	Population	Test Arm Mean ± SD, n	Control Arm Mean ± SD, n
Baseline to 2-7 Days (Secondary Effectiveness Endpoint 14)	**ITT**	-0.33 ± 0.65, 66	-0.16 ± 0.58, 66
	PP (2-7 days)	-0.29 ± 0.64, 58	-0.15 ± 0.59, 62
Baseline to 30 Days (Secondary Effectiveness Endpoint 4)	**ITT**	-0.09 ± 0.44, 93	-0.03 ± 0.37, 92
	PP (23-45d)	-0.09 ± 0.45, 89	-0.03 ± 0.37, 87
Baseline to 90 Days (Secondary Effectiveness Endpoint 14)	**ITT**	0.18 ± 0.38, 77	0.18 ± 0.35, 76
	PP (46-100d)	0.16 ± 0.38, 68	0.19 ± 0.36, 70

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 3 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. Note that a positive z-score indicates improvement. 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 (see Figure 6 below). FDA generated the following bar graph in Figure 6 from the data presented in the sponsor's Clinical Study Report. This data is also presented in Table 44 of the sponsor's Executive Summary

Figure 6: Change in Neurocognitive Test Battery Z-Scores from Baseline to 30 Days



These assessments did not show any discernable difference between patients with protection with the Sentinel System and those patients without protection. However, in a post-hoc analysis, the sponsor showed a secondary correlation of decrease in neurocognitive testing z-score with increase in lesion volume and number.

Q5. Please comment on the clinical significance of the neurocognitive outcomes.

6: Indications for Use

The sponsor has proposed the following 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.

Q6. Please comment on the appropriateness of the proposed Indications for Use and discuss any revisions to the indications that you would recommend based on the information in the Panel Pack and/or discussed today.

7: Labeling

Draft labeling has been provided by the sponsor in the Panel Pack.

Q7a. Please comment on their appropriateness of the contraindications, warnings, and precautions.

Q7b. Please comment on the appropriateness of the SENTINEL data included in the labeling, and discuss whether there are any analyses or data not provided in the labeling that would be important to provide to the user in the labeling.

8: Benefit-Risk

A reasonable assurance of safety and effectiveness can be achieved, in part, if it can be determined that the probable benefits of using the device outweigh the probable risks. The sponsor has identified death, peripheral ischemia, stroke, systemic infection, and vessel perforation as potential risks. The Sentinel System easily met its primary safety endpoint. The study also showed the device had low (0.4%) vascular injury complications and high delivery success (99.6%). The sponsor has also shown that the device successfully captured embolic debris in 99% of Test Arm patients. However, the probable clinical effectiveness benefit of the device is unclear.

Q8. Please discuss any additional benefit-risk considerations.

9: Post-Market Data

FDA may consider the collection of post-market data 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-market data collection for De Novo devices.

Q9. Please discuss any recommendations for post-market data collection if the subject De Novo request for the Sentinel device is granted.