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

DISCUSSION QUESTIONS

Circulatory System Devices Panel Meeting

February 23, 2017

Question 1: Safety Results

Primary safety analysis included comparison of the 30-day MACCE rate to a literature-based performance goal of 18.3%. The ITT with Imputation population is the pre-specified primary analysis population

	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

Question 1: Safety Results

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.

	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

Question 1

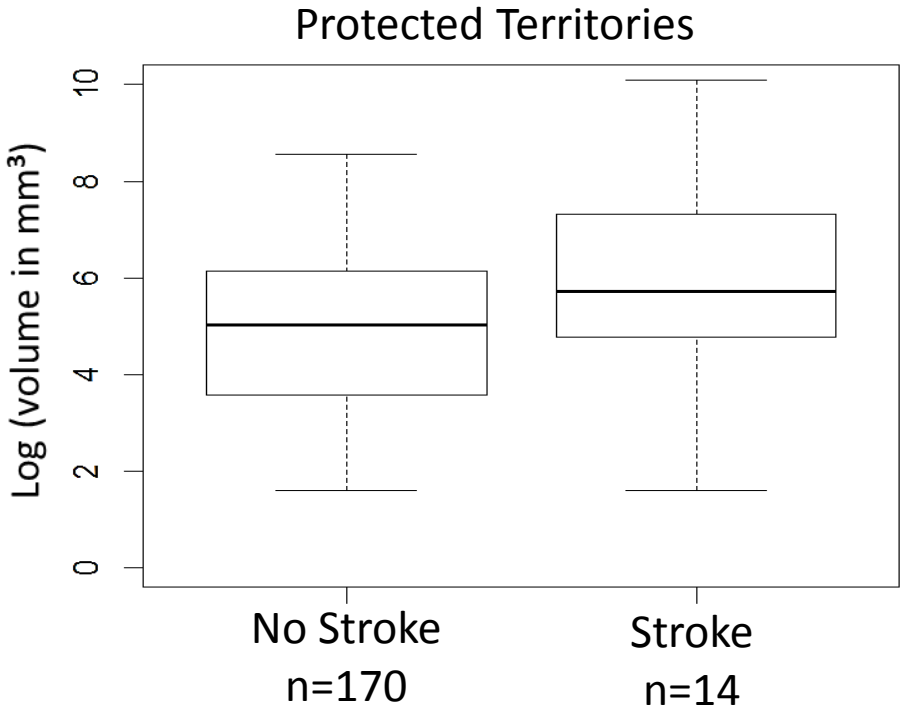
Please comment on the clinical significance of the safety results.

Question 2: Effectiveness Endpoints

The goal of the Sentinel 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 device as measured by cerebral infarct volume on DW-MRI.

Question 2: Effectiveness Endpoints

New Lesion Volume by 30Day Clinical Stroke Status
(Imaging Cohort - ITT)



Question 2a

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

Question 2b

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

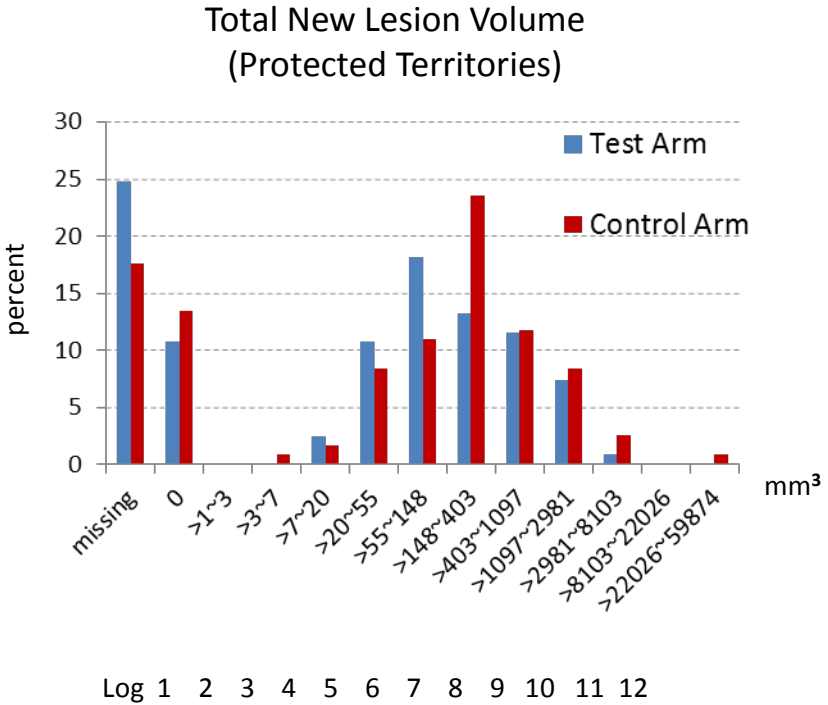
Question 3: Effectiveness Results

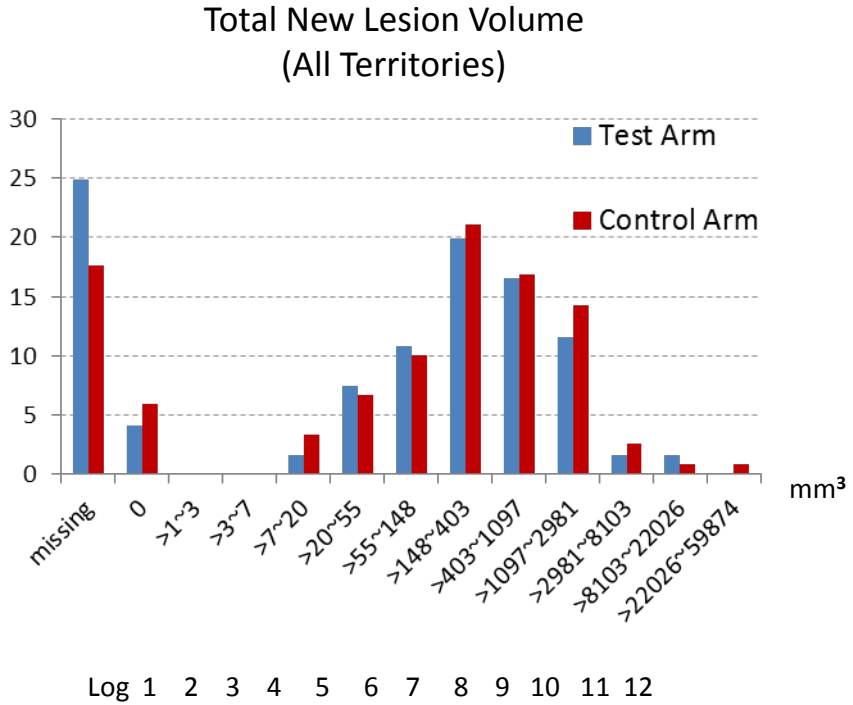
	Protected Territories (Effectiveness Criterion #1)				All Territories (secondary effectiveness endpoint 2)			
Population	**Test Arm (mm^3)**	**Control Arm (mm^3)**	**Observed Treatment Difference (Test - Control) (mm^3)**	**p-value**	**Test Arm (mm^3)**	**Control Arm (mm^3)**	**Observed Treatment Difference (Test - Control) (mm^3)**	**p-value**
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	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	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	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	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	321.7 (114, 928.8), n=83, 0 min, 14179 max	311.1 (110.7, 851.7), n=89, 0 min, 24300 max	10.6	0.7499

Question 3: Effectiveness Results

Population	Test Arm (mm^3)	Control Arm (mm^3)	Observed % Reduction
Protected Territories (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	321.7 (114, 928.8) n=83 0 min, 14179 max	311.1 (110.7, 851.7) n=89 0 min, 24300 max	-3.4

Question 3: Effectiveness Results





Question 3a

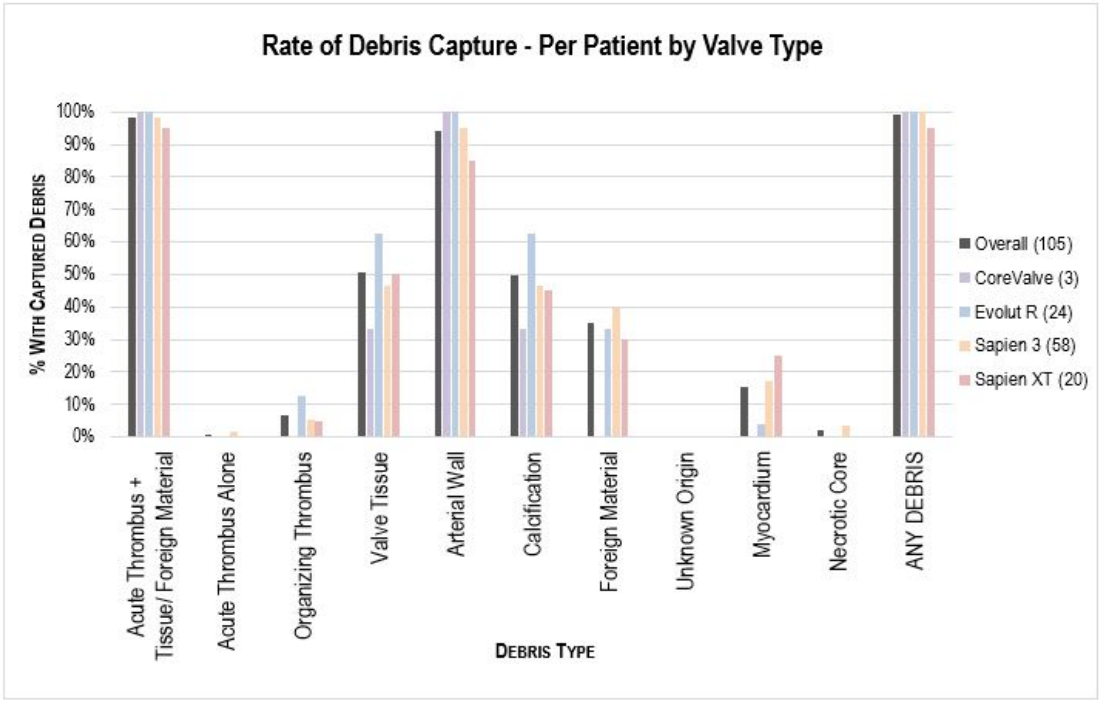
Please discuss whether the reduction in new lesion volume in protected territories observed in the Test Arm is clinically meaningful.

Question 3b

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.

Question 4: Debris Capture

The sponsor cites debris was captured in 99% of cases. Histopathology and histomorphometry results from the Test Arm patients showed a broad range of debris sizes and debris type. Acute thrombus with tissue and foreign material was the most commonly captured debris (98%) followed by arterial wall (94%), valve tissue (50%), calcifications (50%), foreign material (35%) and myocardium (15%).



Question 4

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.

Question 5: Neurocognitive Outcomes

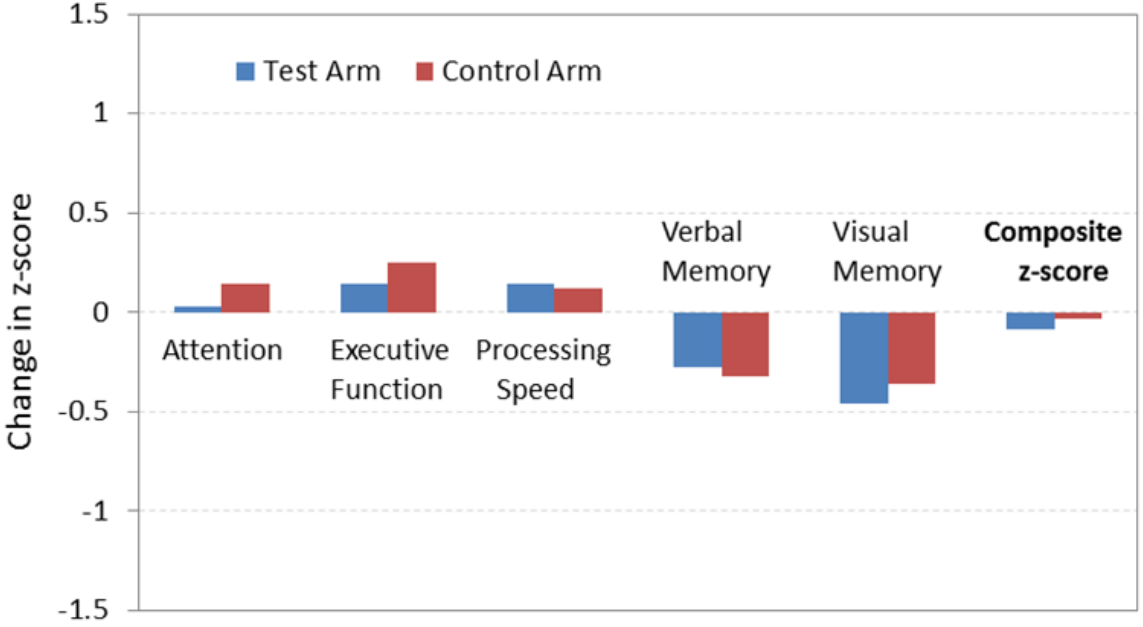
Although it is observed that the Neurocognitive Battery Composite z-score decreased at 30-day follow-up and then increased at 90-day follow-up, it is unclear whether the small change represents a clinically meaningful change in neurocognitive function or if it is merely due to random variation. Note 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-day and 90-day follow-up.

	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

Question 5: Neurocognitive Outcomes

This is also true for change in component z-scores for all five component domains at 30 days. Again, no meaningful clinical changes or trends regarding comparisons between groups were noted.

30-Day Change in Z-Score from Baseline (ITT)



Question 5

Please comment on the clinical significance of the neurocognitive outcomes.

Question 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."

Question 6

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.

Question 7: Labeling

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

Question 7a

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

Question 7b

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.

Question 8: Benefit-Risk

Sponsor-identified potential risks:

- Death
- Peripheral ischemia
- Stroke
- Systemic infection
- Vessel perforation

Probable clinical effectiveness benefit of the device is unclear

The SENTINEL Study demonstrated:

- Primary safety endpoint was met
- Device had low (0.4%) vascular injury complications and high delivery success (99.6%)
- Device successfully captured embolic debris in 99% of Test Arm patients

Question 8

Please discuss any additional benefit-risk considerations.

Question 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.

Question 9

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