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

FDA Review of DEN160043

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February 23, 2017

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FDA Presentations

- **CDR Sadaf Toor**
  Introduction and Summary of SENTINEL Study Design

- **Dr. Donna Buckley**
  SENTINEL Clinical Results and Considerations

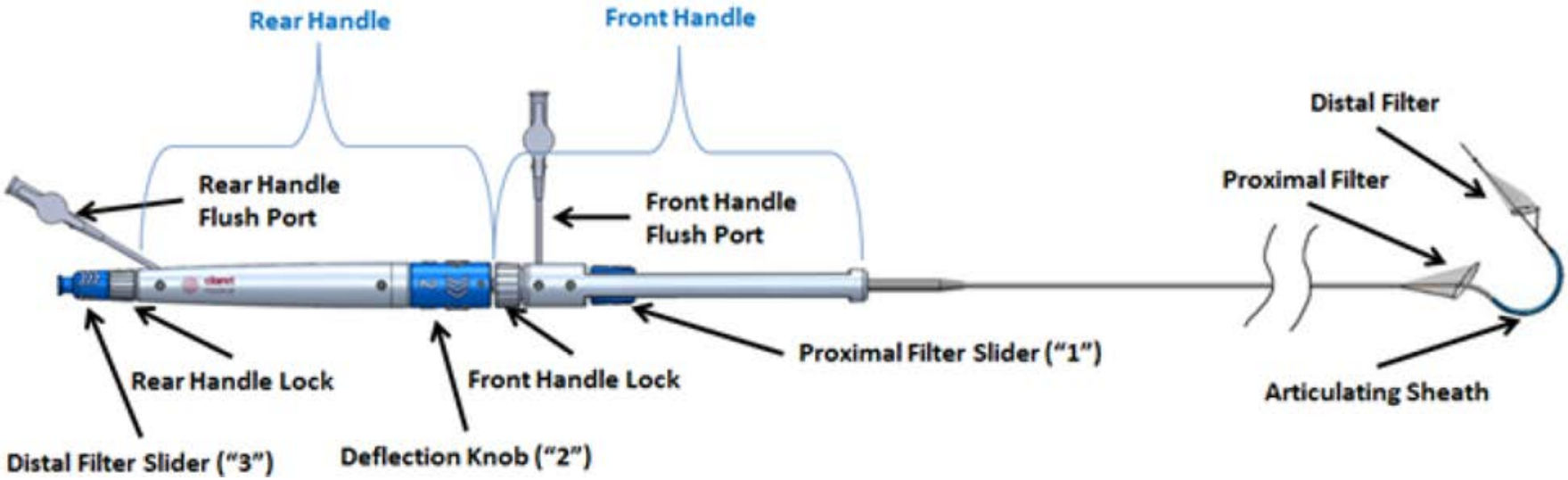
- **Dr. Li Ming Dong**
  SENTINEL Statistical Results and Considerations

- **CDR Sadaf Toor**
  Conclusions

Introduction Outline

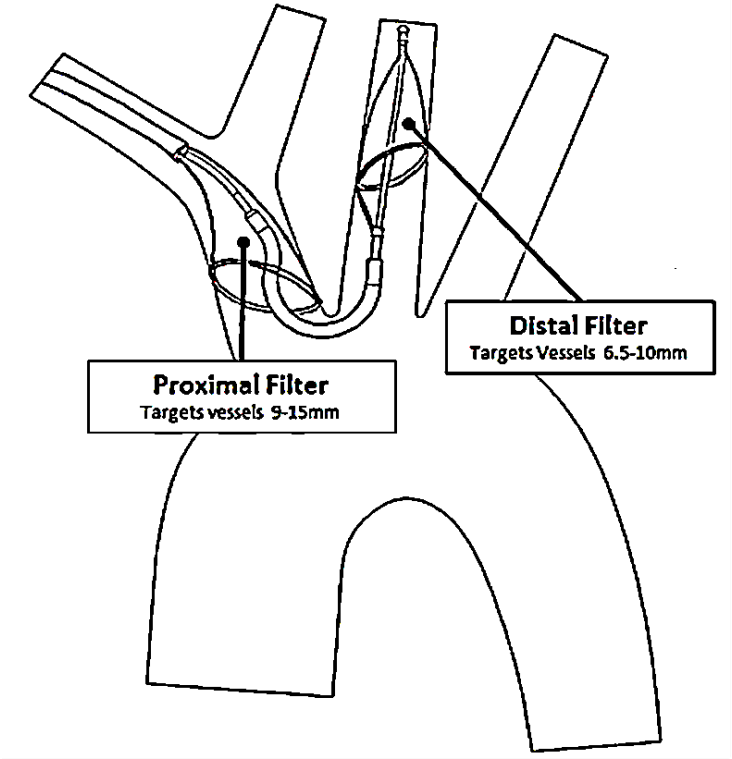
- **Device Description**
- **Proposed Indications for Use**
- **Regulatory History**
- **SENTINEL Study Design**
- **Discussion Points**

Device Description



Ref: Figure 1: FDA Executive Summary

Device Description



Ref: Figure 2: FDA Executive Summary

Indications for Use (as proposed by the Sponsor)

"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."

Regulatory History

February 14, 2014 – FDA conditionally approved an Investigational Device Exemption (IDE) for the SENTINEL study (G130276)

- Edwards SapienXT valve only commercially available transcatheter aortic valve replacement (TAVR) device in the U.S.

October 2, 2014 – First SENTINEL patient enrolled

May 11, 2015 – Protocol modified to allow Medtronic CoreValve TAVR System

- Approximately 10% of randomized patients had been enrolled

Regulatory History (cont.)

July 27, 2015 – Protocol modified to allow the use of any FDA approved TAVR device

- Approximately 15% of the randomized patients had been enrolled

March 10, 2016 – Final SENTINEL patient enrolled

May 6, 2016 – FDA approved a Continued Access cohort of the SENTINEL study.

- Ultimately, not initiated by the sponsor

September 20, 2016 – FDA received De Novo request DEN160043

- Included the clinical study report of subjects enrolled in the SENTINEL study.

Scope of Meeting

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 request.

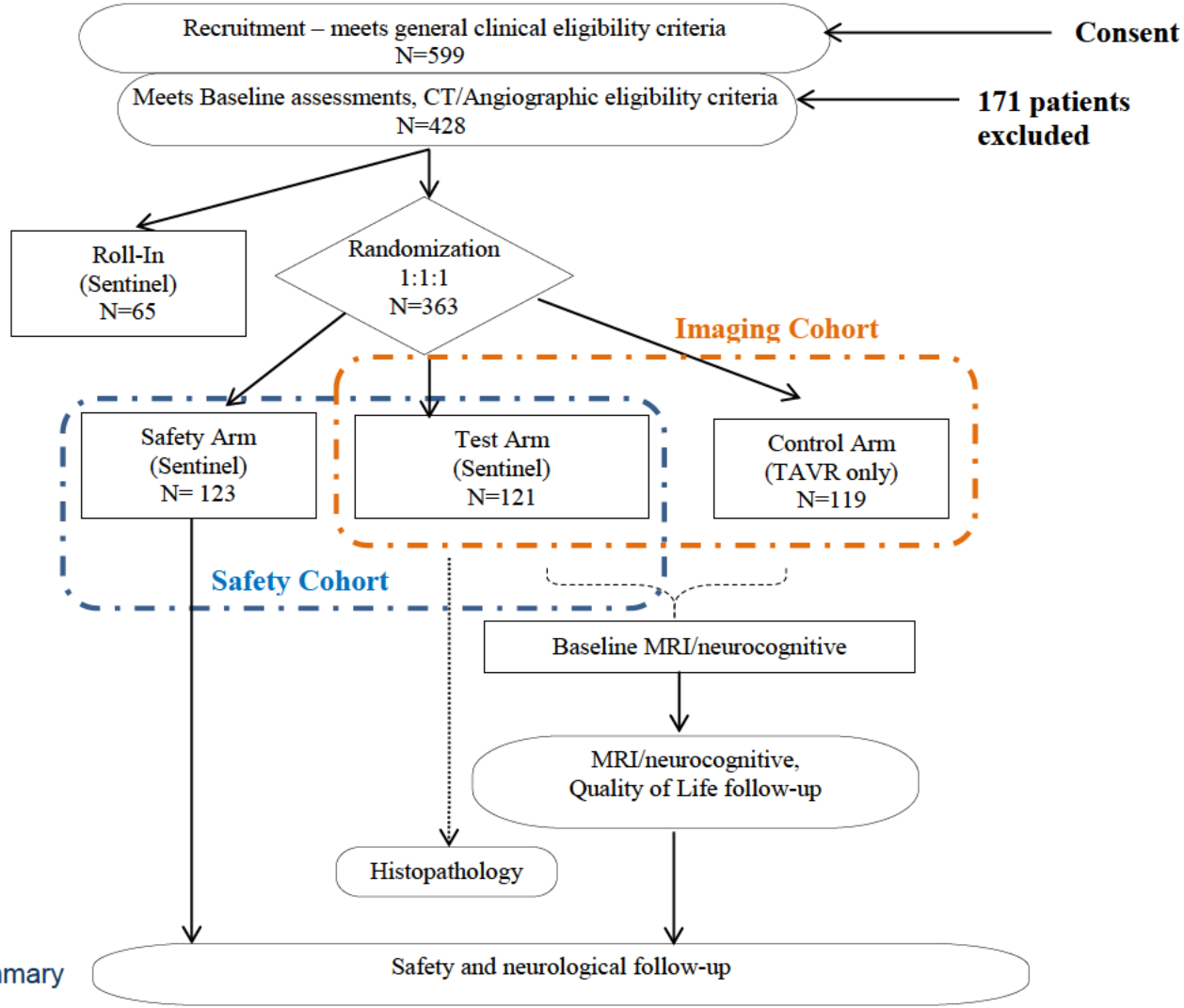
SENTINEL Study Design

Objective:

- Assess the safety and effectiveness of the Sentinel System used for cerebral protection during TAVR compared to TAVR without cerebral protection.

Key study attributes:

- Prospective
- Single blind
- Multi-center
- Randomized
- Patients with severe symptomatic calcified native aortic valve stenosis indicated for TAVR



Ref: Figure 4:
FDA Executive Summary

Primary Endpoints

Safety

- Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 Days.

MACCE = 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.

Effectiveness

- Total new lesion volume in protected territories as assessed by DW-MRI at 2-7 days post-procedure.

Ref: Appendix V: FDA Executive Summary

Study Success Criteria

1. Primary safety endpoint: 30-Day MACCE rate for the Safety Cohort (Safety Arm and Test Arm) < Performance Goal of 18.3%.

2. Superiority with respect to the primary effectiveness endpoint (Primary Effectiveness Criterion #1): The Test Arm is superior to the Control Arm with respect to the median total new lesion volume in protected territories at Day 2-7 post-procedure.

3. Observed Clinical Treatment Effect (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 median total new lesion volume in the protected territories in the Control Arm is ≥ 30%.

Primary Discussion Points

1. DW-MRI as a surrogate effectiveness endpoint
2. Primary and secondary effectiveness results
3. Debris capture
4. Neurocognitive outcomes
5. Indications for Use
6. Labeling considerations
7. Benefit-risk considerations
8. Post-market data

FDA Presentations

- **CDR Sadaf Toor**
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  Conclusions

SENTINEL Clinical Results and Considerations

Donna Buckley, MD, MS

Division of Cardiovascular Devices
Office of Device Evaluation

SENTINEL Clinical Results and Considerations Outline

- **Patient Accountability & Baseline/Procedural Characteristics**
- **Safety Results**
- **Effectiveness Results**

SENTINEL Clinical Results and Considerations Outline

- **Patient Accountability & Baseline/Procedural Characteristics**
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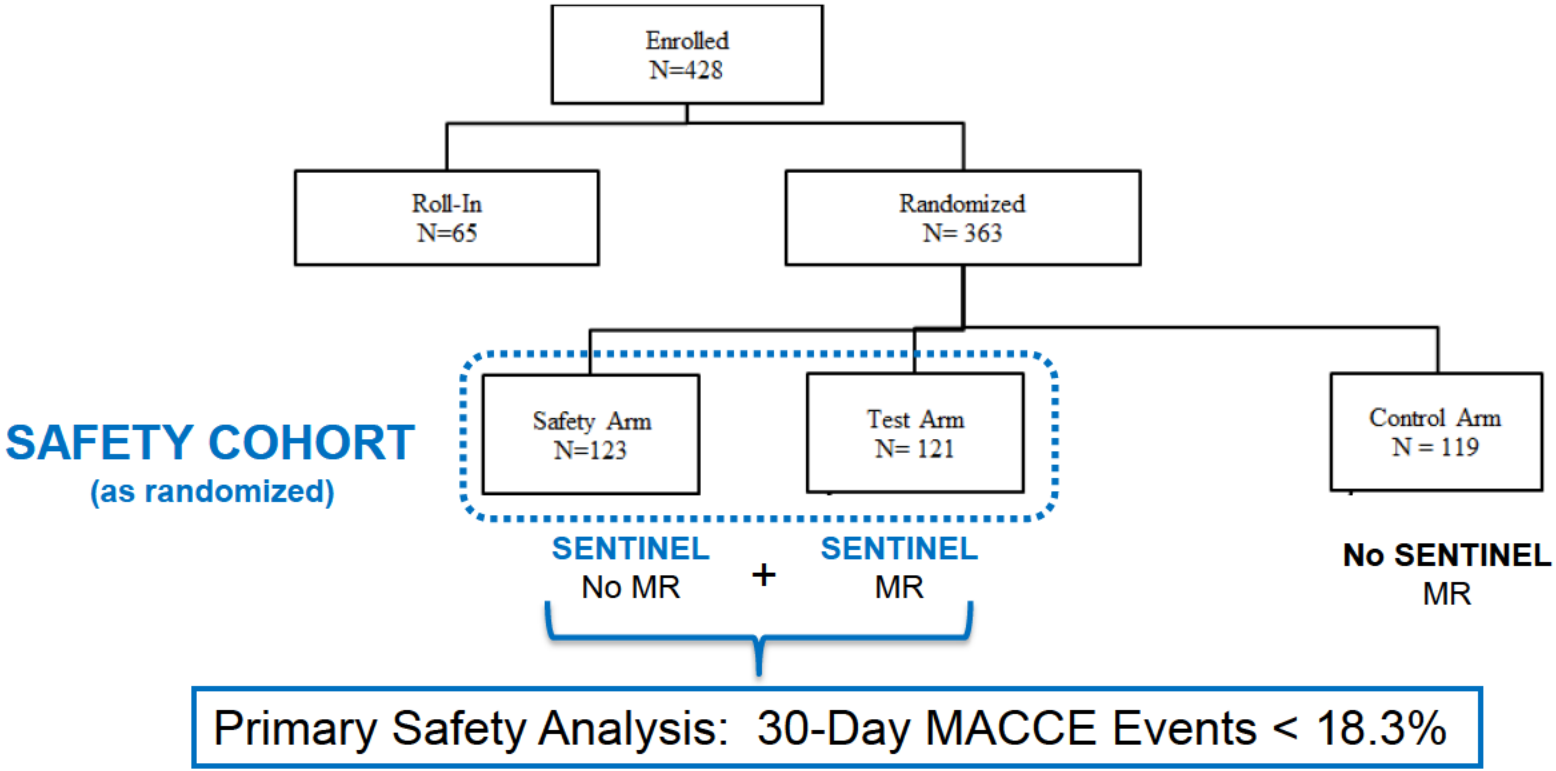
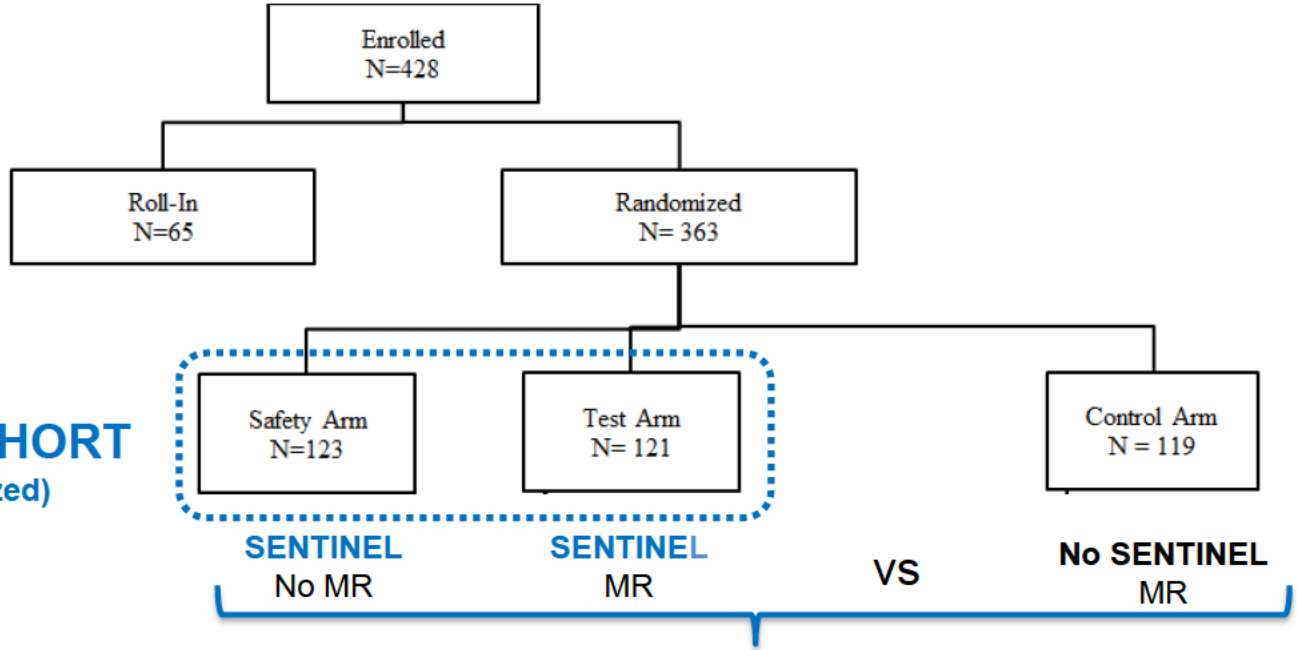
- **Effectiveness Results**

Patient Enrollment and Accountability



Ref: Figure 6: FDA Executive Summary

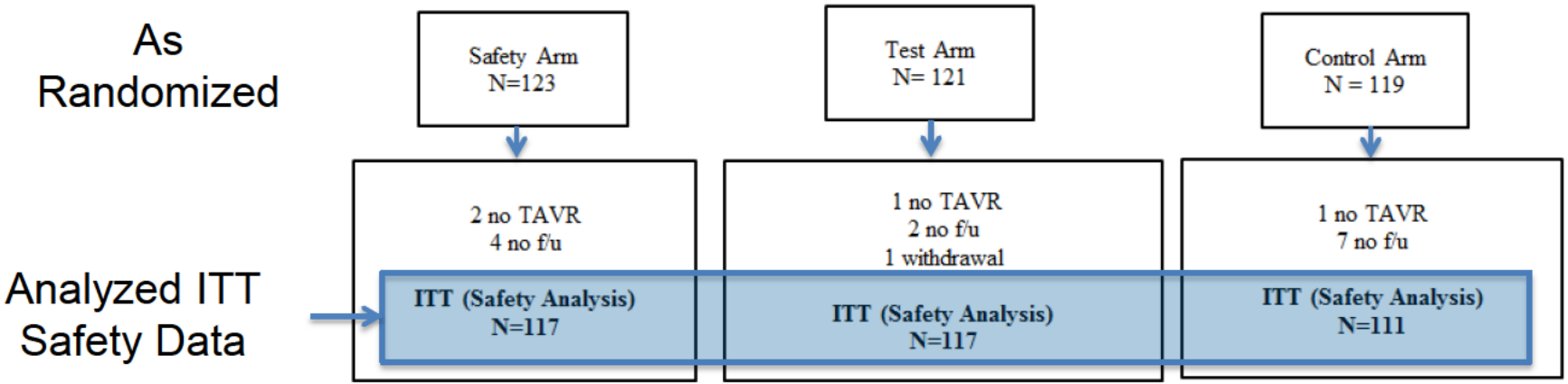
Patient Enrollment and Accountability



Secondary Safety Analyses: 30 day MACCE comparing Test vs Control and (Test + Safety) vs Control

Ref: Figure 6: FDA Executive Summary

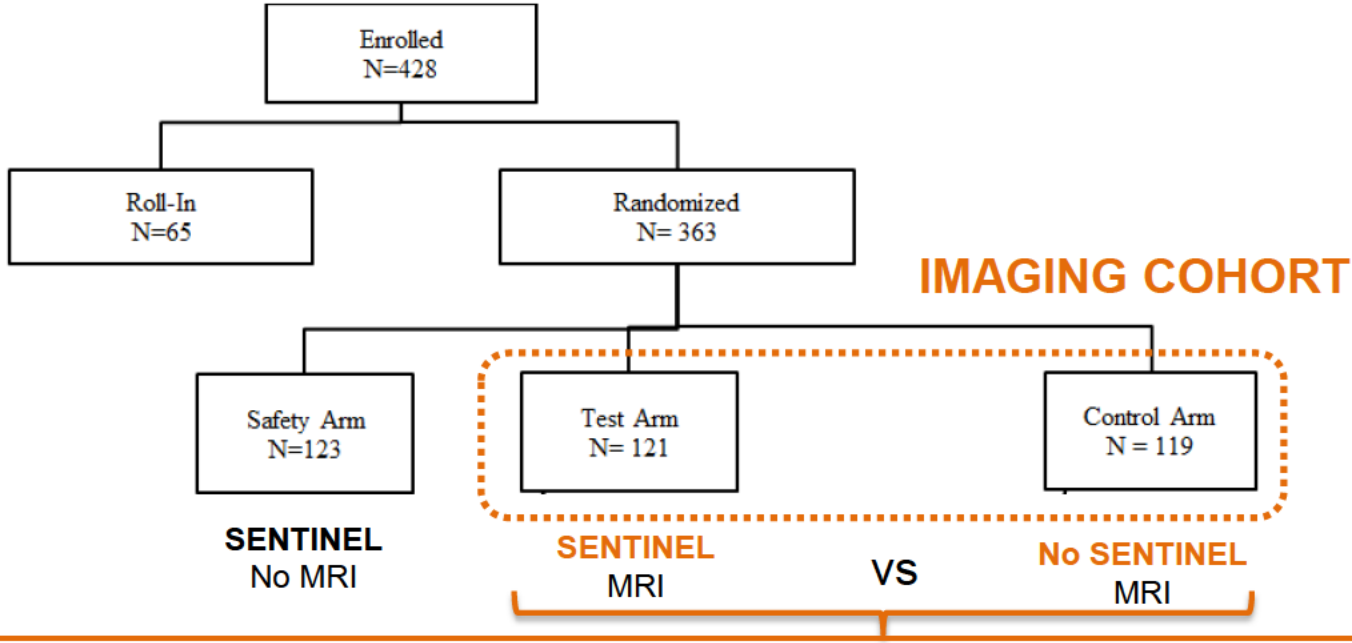
Patient Enrollment and Accountability



> 95% of randomized patients were included in the ITT Safety Analysis

Ref: Figure 6: FDA Executive Summary

Patient Enrollment and Accountability

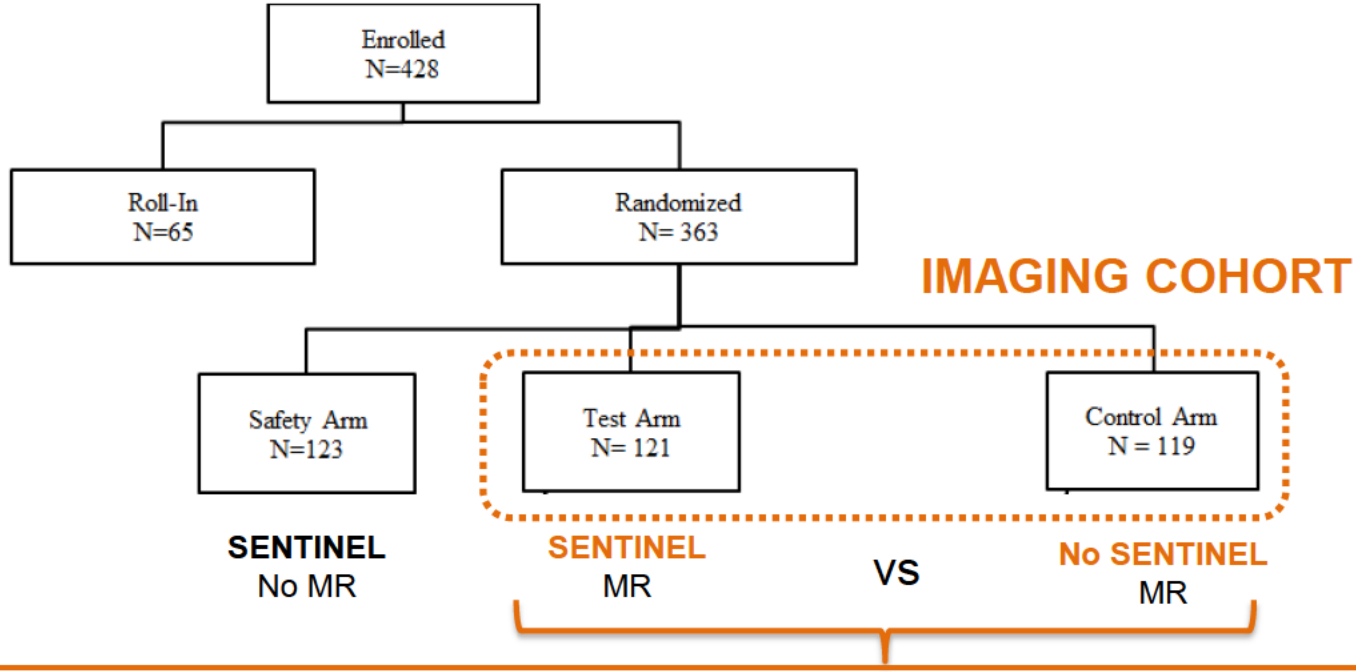


Primary Effectiveness Analysis: median new DW-MRI lesion volume at 2-7 days

- Effectiveness Criterion #1: (superiority) statistically lower for Test Arm vs Control Arm in protected territories
- Effectiveness Criterion #2: (observed treatment effect) 30% lower for Test vs Control in protected territories

Ref: Figure 6: FDA Executive Summary

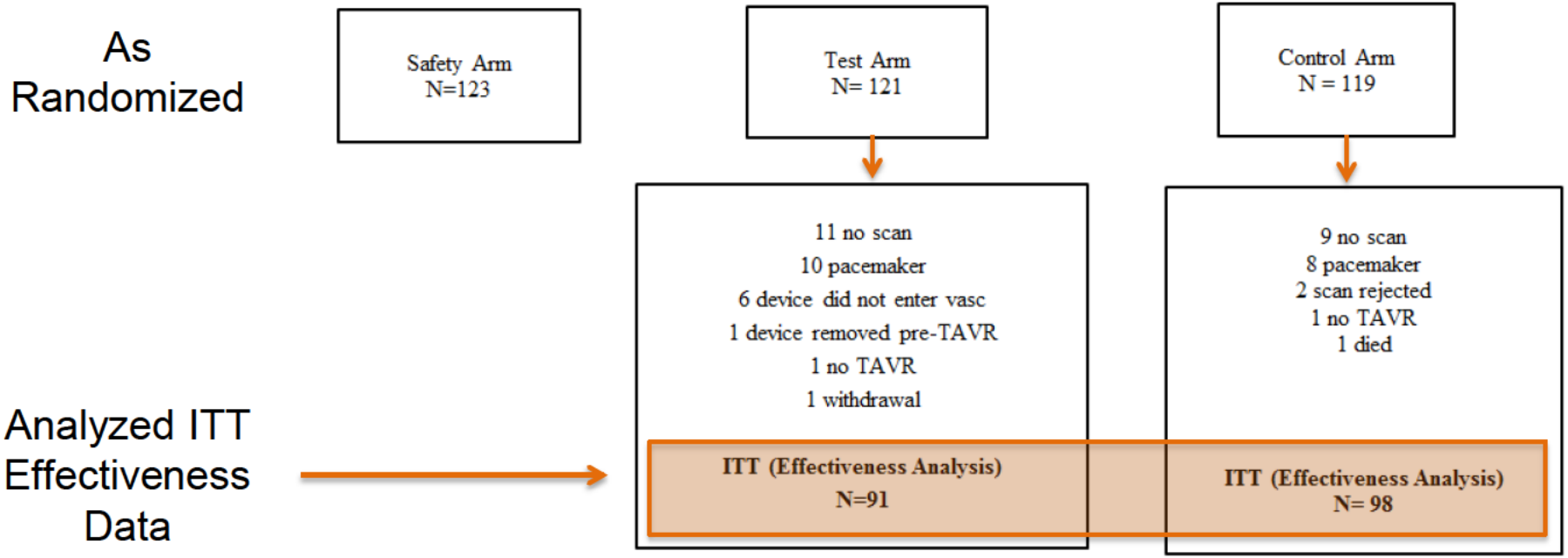
Patient Enrollment and Accountability



Secondary Effectiveness Analyses: primary analysis endpoints assessed for all territories

Ref: Figure 6: FDA Executive Summary

Patient Enrollment and Accountability



> 20% of randomized patients were excluded from the ITT Effectiveness Analysis

Ref: Figure 6: FDA Executive Summary

Baseline & Procedural Characteristics

There were observed statistical differences in:

- Diastolic blood pressure
- STS score
- Stroke severity
- Procedure time
- Fluoroscopy time

No concerning trends in Baseline or Procedural Characteristics

SENTINEL Clinical Results and Considerations Outline

- Patient Accountability & Baseline/Procedural Characteristics
- Safety Results
- Effectiveness Results

Safety – Primary

30-day MACCE Events (Safety + Test) < 18.3% PG

	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**
ITT with imputation	N/A	18/244 (7.4%)		10.7%	<.0001
ITT	17	17/234 (7.3%)	18.3%	10.7%	<.0001
AT	17	17/225 (7.6%)		11.1%	<.0001

The ITT Primary Safety Analysis demonstrated that the 30-day MACCE rate for the Safety Cohort was 7.3%. The 95% CI upper limit of this value is 10.7% which is below the PG of 18.3%.

Primary Safety Endpoint was Met.

Ref: Table 7: FDA Executive Summary

Safety – Primary

Composite Endpoint Components (ITT)

Population	Total Events	Patients w/ Events	Performance	Upper Limit of 95%	p-value[1]
ITT with imputation	N/A[2]				
ITT	17				
AT	17				

	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	5.6% (13/231) [13] (3.0%, 9.4%)	9.1% (10/110) [10] (4.4%, 16.1%)	[-10.3%, 3.3%]
Disabling	0.9% (2/231) [2] (0.1%, 3.1%)	0.9% (1/109) [1] (0.0%, 5.0%)	[-3%, 3%]
Non-disabling	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%]

Ref: Tables 7 and 8: FDA Executive Summary

Safety: 30-day MACCE

Safety Cohort (Safety + Test Arms) vs. Control Arm(no Sentinel) (ITT)

	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	5.6% (13/231) [13] (3.0%, 9.4%)	9.1% (10/110) [10] (4.4%, 16.1%)	[-10.3%, 3.3%]
Disabling	0.9% (2/231) [2] (0.1%, 3.1%)	0.9% (1/109) [1] (0.0%, 5.0%)	[-3%, 3%]
Non-disabling	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%]

Ref: Table 8: FDA Executive Summary

Safety: 30-day MACCE

Imaging Cohort (ITT): Test (Sentinel) vs. Control (no Sentinel)

	Test Arm	Control Arm	p-value*
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

Ref: Table 11: FDA Executive Summary

Safety: Major Vascular Complications

	Safety Cohort (Safety + Test Arms)	Control Arm
ITT		
During the index procedure	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	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

One Sentinel Related Major Vascular Complication

Ref: Table 12: FDA Executive Summary

Safety: 30-Day SAE Rate

	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%)

Similar overall 30-Day SAE rates in patients who received the Sentinel and those who did not receive the Sentinel

Ref: Table 13: FDA Executive Summary

Safety

The prespecified safety success criterion was met. No major concerns were noted regarding safety of the Sentinel device.

SENTINEL Clinical Results and Considerations Outline

- Patient Accountability & Baseline/Procedural Characteristics
- Safety Results
- Effectiveness Results

Effectiveness – Primary

median new DWMR lesion volume at 2-7 days

Success Criterion #1

Population	Test Arm (mm^3)	Control Arm (mm^3)	Observed Treatment Difference (Test - Control)	p-value
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

median, (25th percentile, 75th percentile), n, min, max

For the Imaging Cohort, there was a reduction of 75 mm^3 in median new lesion volume in *protected territories* for patients who received the Sentinel device. The difference was not statistically significant (p=0.33).

Primary Effectiveness Criterion #1 was <u>not</u> met.

Ref: Table 9: FDA Executive Summary

Effectiveness – Primary

median new DWMR lesion volume at 2-7 days

Success Criterion #2

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	30%	34.8 (-8.1, 60.6)

median, (25^{th} percentile, 75^{th} percentile), n, min, max

For the Imaging Cohort, there was a reduction of 42.2% in median new lesion volume *in protected territories* for patients who received the Sentinel device. This is above the prespecified threshold of 30%.

Primary Effectiveness Criterion #2 was met.

Ref: Table 10: FDA Executive Summary

Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

Population	Protected Territories: Test Arm (mm^3)	Protected Territories: Control Arm (mm^3)	Protected Territories: Observed Treatment Difference (Test - Control) (mm^3)	Protected Territories: p-value	All Territories: Test Arm (mm^3)	All Territories: Control Arm (mm^3)	All Territories: Observed Treatment Difference (Test - Control) (mm^3)	All Territories: 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	[redacted]	(b) (4)			

median, (25th percentile, 75th percentile), n, min, max

There was 75.1 mm^3 median lower lesion volume for protected territories for the Sentinel device which was reduced to a 15.8 mm^3 difference when all territories were considered.

Ref: Table 9 and 14: FDA Executive Summary

Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

	Protected Territories				All Territories			
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	(b) (4)			

Assessment of different analysis populations for All Territories yields inconsistent trends in results.

Ref: Table 9 and 14: FDA Executive Summary

Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

	Protected Territories				All Territories			
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	(b) (4)			

median, (25th percentile, 75th percentile), n, min, max

Assessment of different analysis populations for All Territories yields inconsistent trends in results.

Ref: Table 9 and 14: FDA Executive Summary

Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

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)		

Protected Territories (ITT)

All Territories (ITT)

median, (25th percentile, 75h percentile), n, min, max

There was 42.2% reduction in median lesion volume for protected territories for the Sentinel device which was reduced to a 5.1% reduction when all territories were considered. Percent reduction was not tested for statistical significance.

Ref: Table 15: FDA Executive Summary

Effectiveness – Protected vs All Territories

median new DWMR lesion volume at 2-7 days

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]		

median, (25th percentile, 75th percentile), n, min, max

Assessment of different analysis populations for All Territories yields inconsistent trends in results.

Ref: Table 15: FDA Executive Summary

Effectiveness – Neurocognitive

Change in Battery Composite Z-Score From Baseline (ITT)

	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

No meaningful clinical trends between Test and Control Arms were noted with respect to changes in overall z-scores at both 30 days and 90 days follow-up.

Ref: Table 21: FDA Executive Summary

Effectiveness – Neurocognitive

Change in Battery Composite Z-Score From Baseline (ITT)

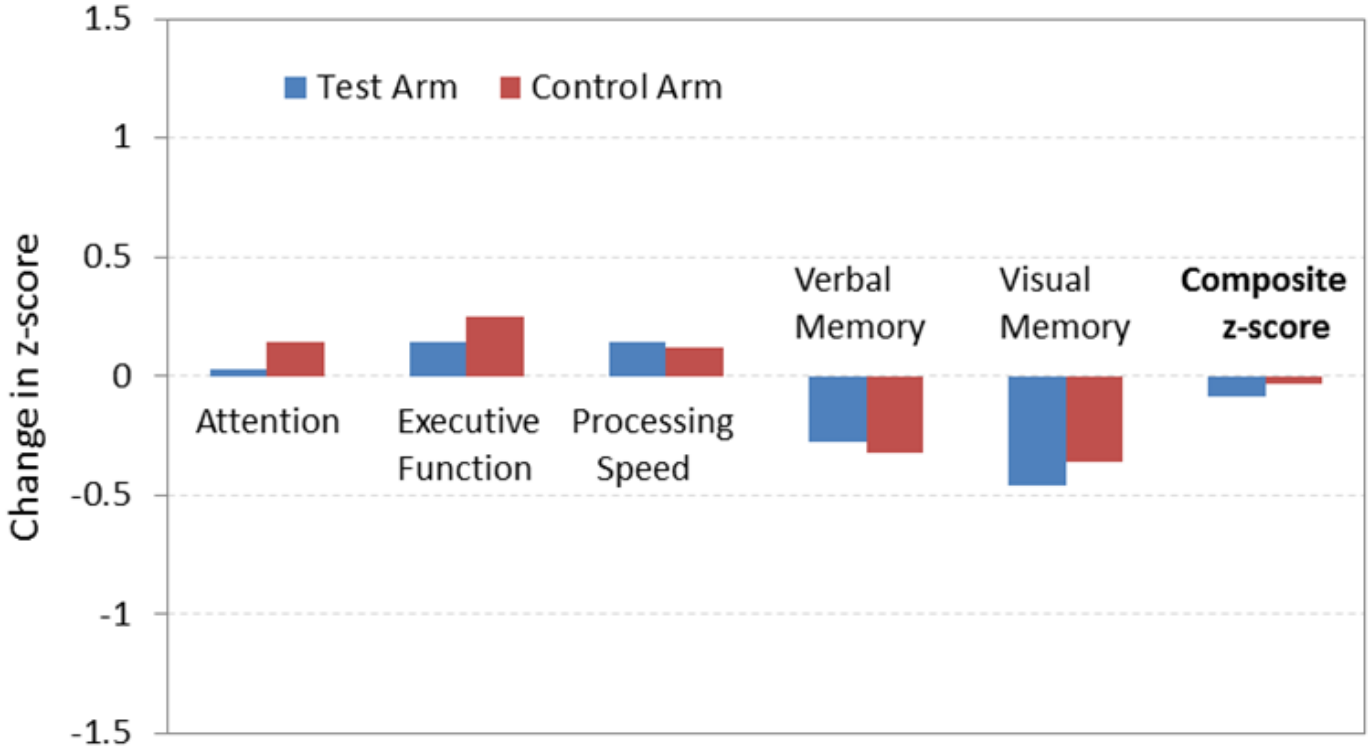
	Test Arm Mean ± SD, n	Control Arm Mean ± SD, n
30 Days	-0.09 ± 0.44, 93	-0.03 ± 0.37, 92
90 Days	0.18 ± 0.38, 77	0.18 ± 0.35, 76

No meaningful clinical trends between Test and Control Arms were noted with respect to changes in overall z-scores at both 30 days and 90 days follow-up.

Ref: Table 21: FDA Executive Summary

Effectiveness – Neurocognitive

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



Ref: Figure 7: FDA Executive Summary

Effectiveness – Additional Analyses

- Quality of Life
  - No statistical/clinical differences between groups
- Valve Type Subanalysis
  - Study not designed to assess differences between groups and data are inadequate to support inferences regarding performance of one valve type over another

Ref: Table 21: FDA Executive Summary

Effectiveness – Additional Analyses

- Debris Capture
  - 99% of cases debris was captured – acute thrombus with tissue and foreign material was the most commonly removed debris.
  - The distinction of embolic capture versus possible filter generated debris (e.g., arterial wall, acute thrombus) is unclear.

Ref: Table 21: FDA Executive Summary

Effectiveness

The SENTINEL study met one of the prespecified effectiveness study success criteria and did not meet the other. Primary analysis did not demonstrate statistical significance. A clinically meaningful reduction in cerebral ischemia is also difficult to interpret.

FDA Presentations

- **CDR Sadaf Toor**
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- **Dr. Donna Buckley**
  SENTINEL Clinical Results and Considerations

- **Dr. Li Ming Dong**
  SENTINEL Statistical Results and Considerations

- **CDR Sadaf Toor**
  Conclusions

SENTINEL Statistical Results and Considerations

Li Ming Dong, PhD

Division of Biostatistics
Office of Surveillance and Biometrics

SENTINEL Statistical Results and Considerations

- **Analysis Populations**
- **Analyses of Primary Safety Endpoint**
- **Analyses of Primary Effectiveness**
- **MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia**

Analysis Populations

Primary Safety Endpoint

- ITT with imputation
  - Multiple Imputation for missing 30-Day MACCE evaluations
- ITT
  - Completers of Safety Cohort (Safety Arm and Test Arm)
- AT (As-Treated)
  - Patients received Sentinel

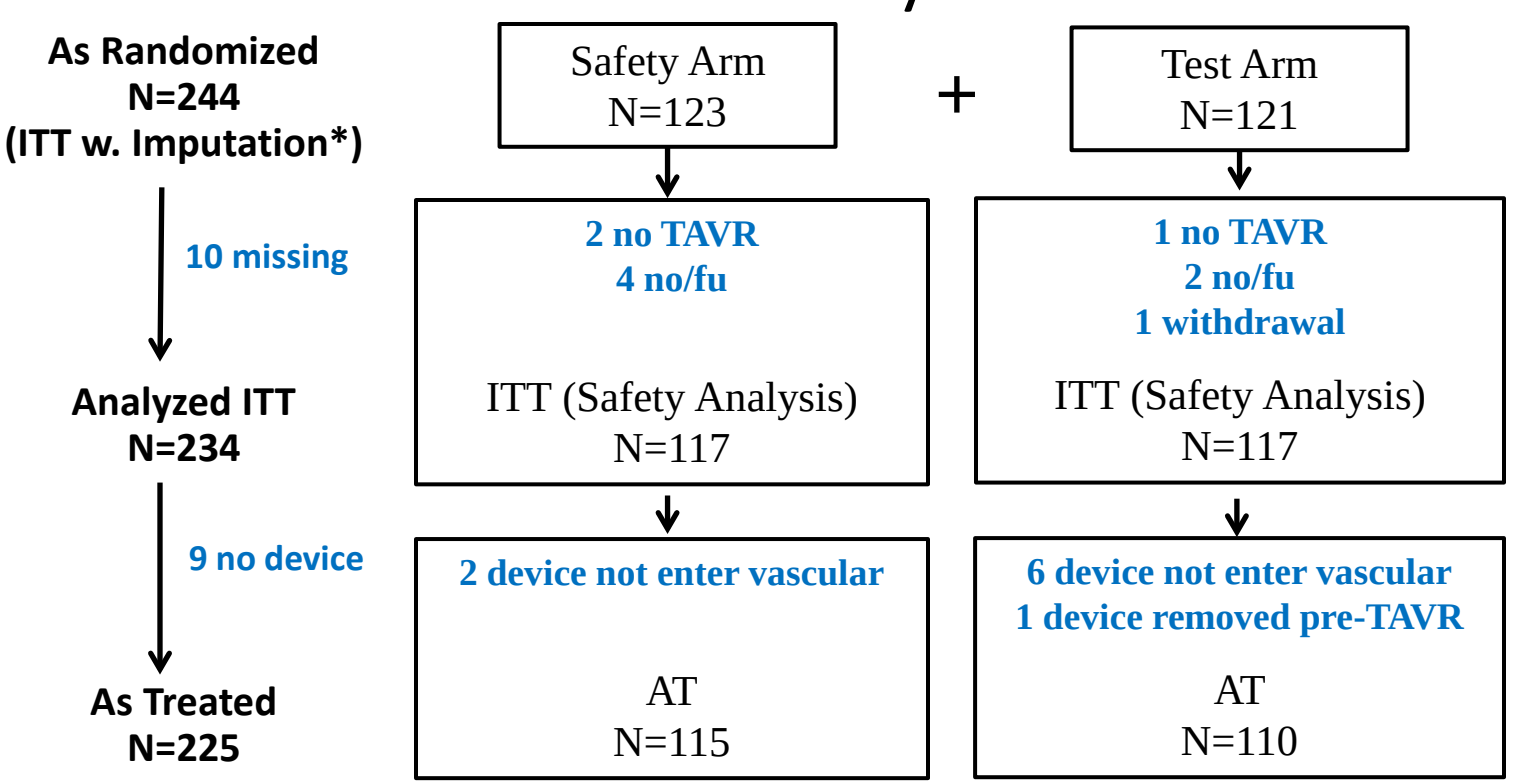
Primary Effectiveness Endpoint

- ITT with imputation
  - Multiple imputation for missing MRI scans
- ITT
  - Completers of Imaging Cohort (Test Arm and Control Arm)
- PP (Per-Protocol)
  - ITT further excludes out-of-window MRI scans

SENTINEL Statistical Results and Considerations

- **Analysis Populations**
- **Analyses of Primary Safety Endpoint**
- **Analyses of Primary Effectiveness**
- **MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia**

Analysis of Primary Safety Endpoint



* Through multiple imputation

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

Ref: Table 7: FDA Executive Summary

Primary Safety: Sensitivity Analysis

Worse-case scenario: Assuming that all 10 subjects with missing 30-day MACCE data had a MACCE event, then

the MACCE rate would be 11.1% (27/244)

with upper 95% confidence bound 14.9% < PG of 18.3%.

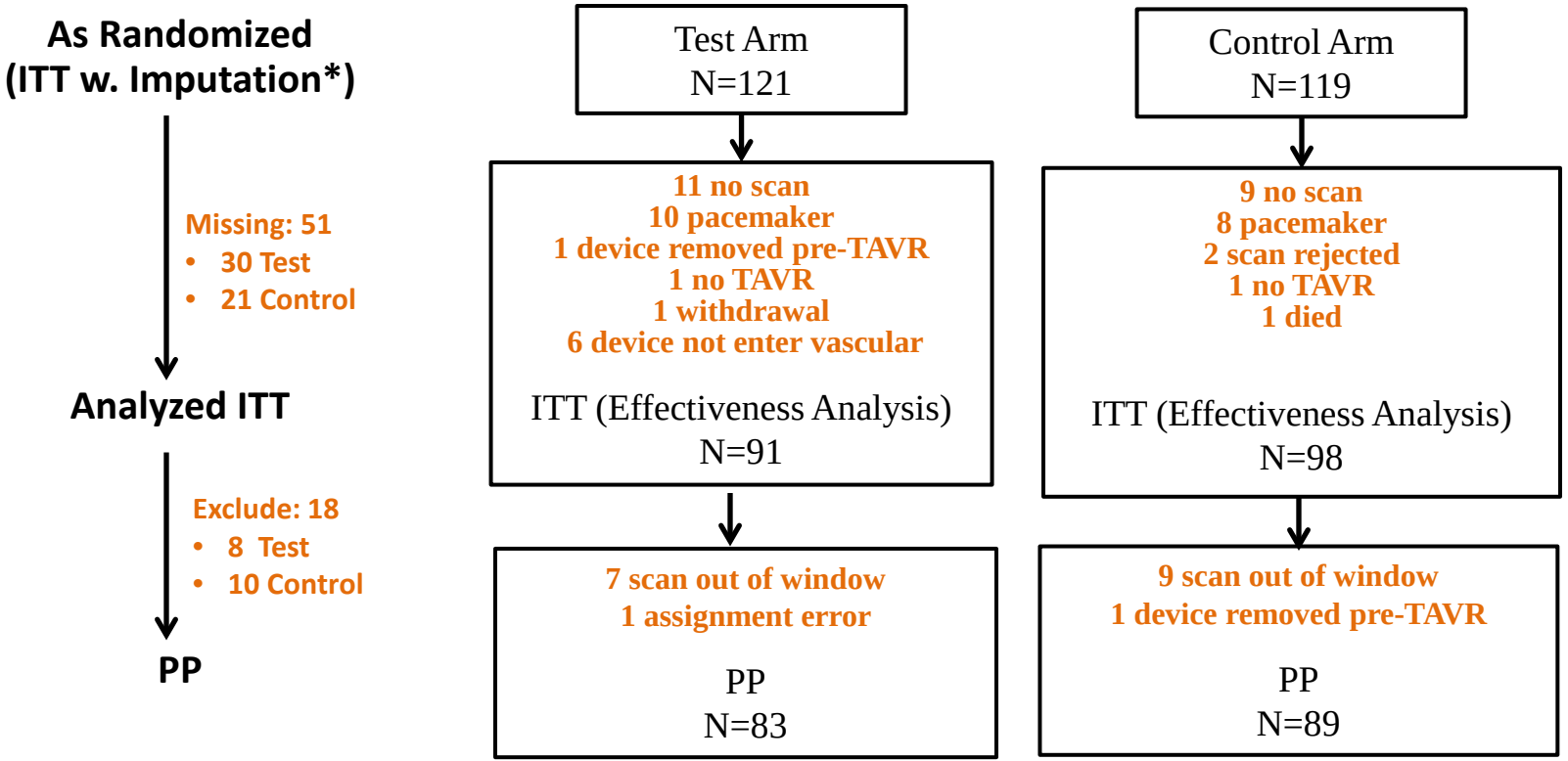
Safety

The primary safety endpoint is met and missing data is unlikely to alter the conclusion.

SENTINEL Statistical Results and Considerations

- **Analysis Populations**
- **Analyses of Primary Safety Endpoint**
- **Analyses of Primary Effectiveness**
- **MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia**

Analysis of Primary Effectiveness Endpoint
Imaging Cohort



* Through multiple imputation

Analysis of Primary Effectiveness Endpoint: Statistical Considerations

- Medians of the Test Arm and Control Arm were compared using Wilcoxon Rank Sum Test
  - Due to expected non-normal skewed distribution of lesion volumes

- Missing data
  - High rate of missing endpoint data for Imaging Cohort: 21% (51/240)
  - Missing rates per Arm: Test 25% (30/121)
    Control 18% (21/119)

Analysis of Primary Effectiveness Endpoint

	Protected Territories				All Territories			
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	(b) (4)			

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

Analysis of Primary Effectiveness Endpoint

	Protected Territories				All Territories			
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**
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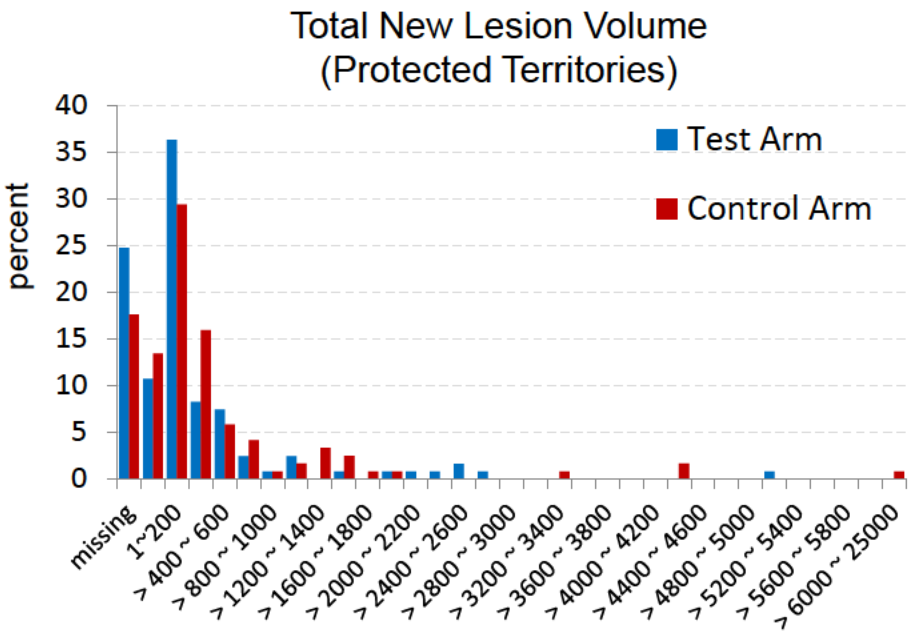
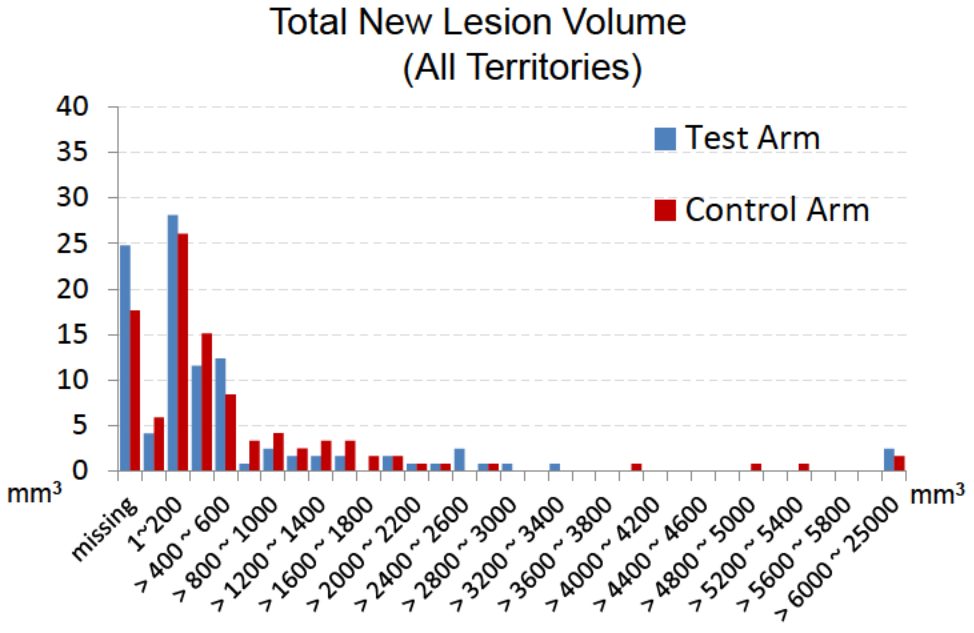
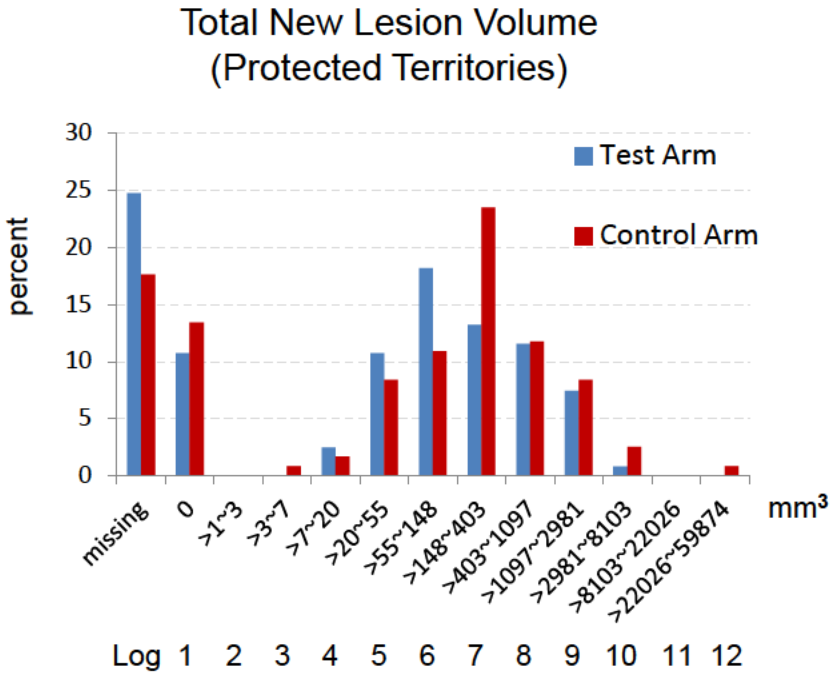
Note: Data presented as: median, (25th percentile, 75th percentile), n, min, max.

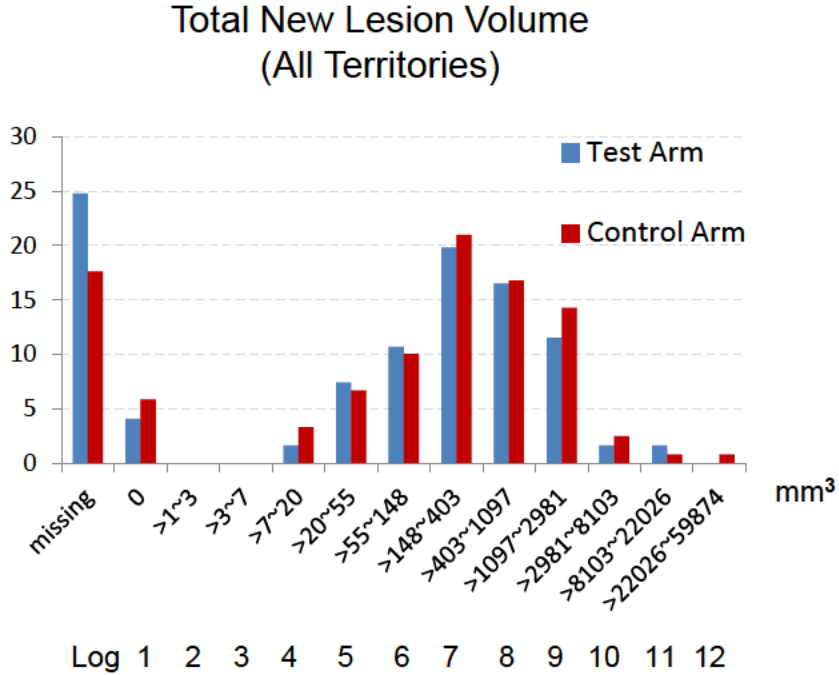
Analysis of Primary Effectiveness Endpoint





Analysis of Primary Effectiveness Endpoint





Effectiveness

Lesion volume distributions showed a small, non-statistically significant shift towards lower lesion volumes in the protected territories for patients in the Test Arm compared with patients in the Control Arm.

When all territories are analyzed, there is no clear trend of lesion volume reduction.

SENTINEL Statistical Results and Considerations

- **Analysis Populations**
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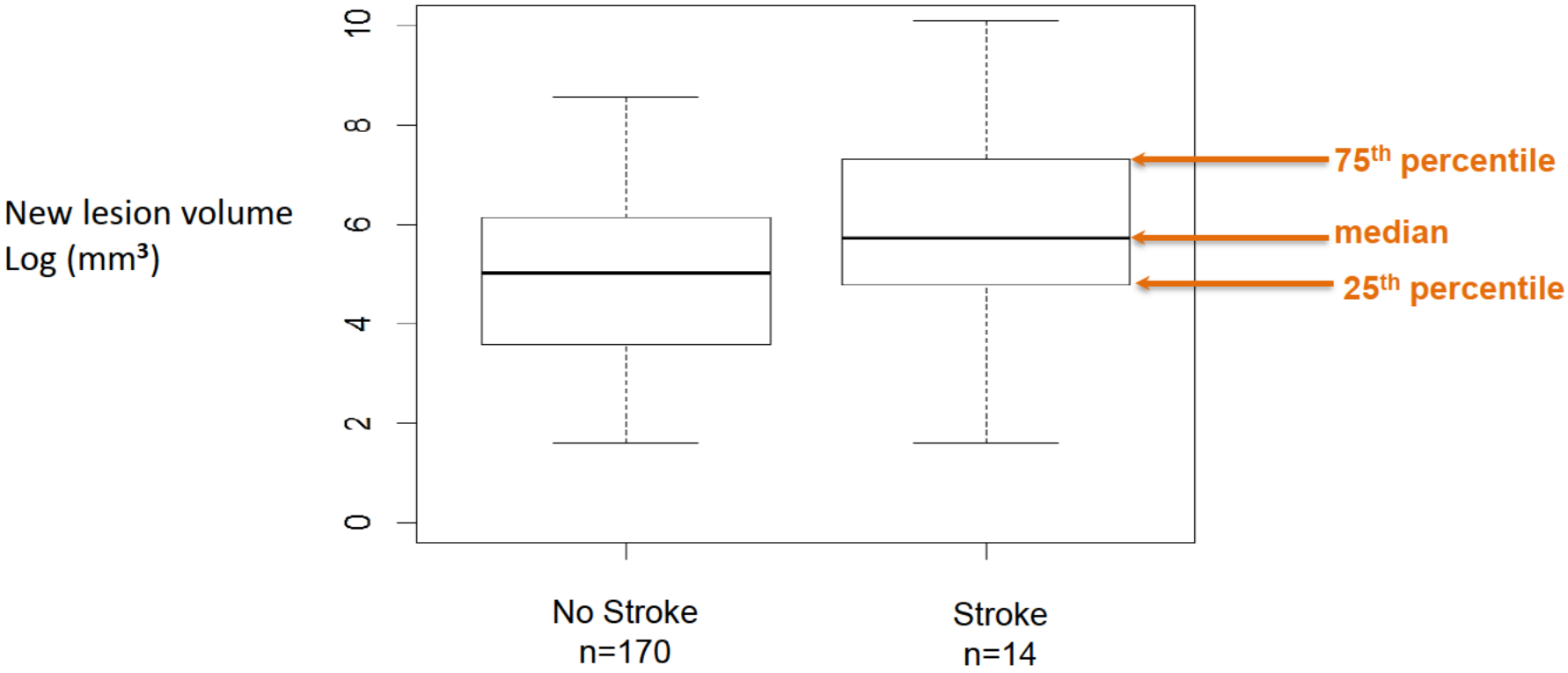
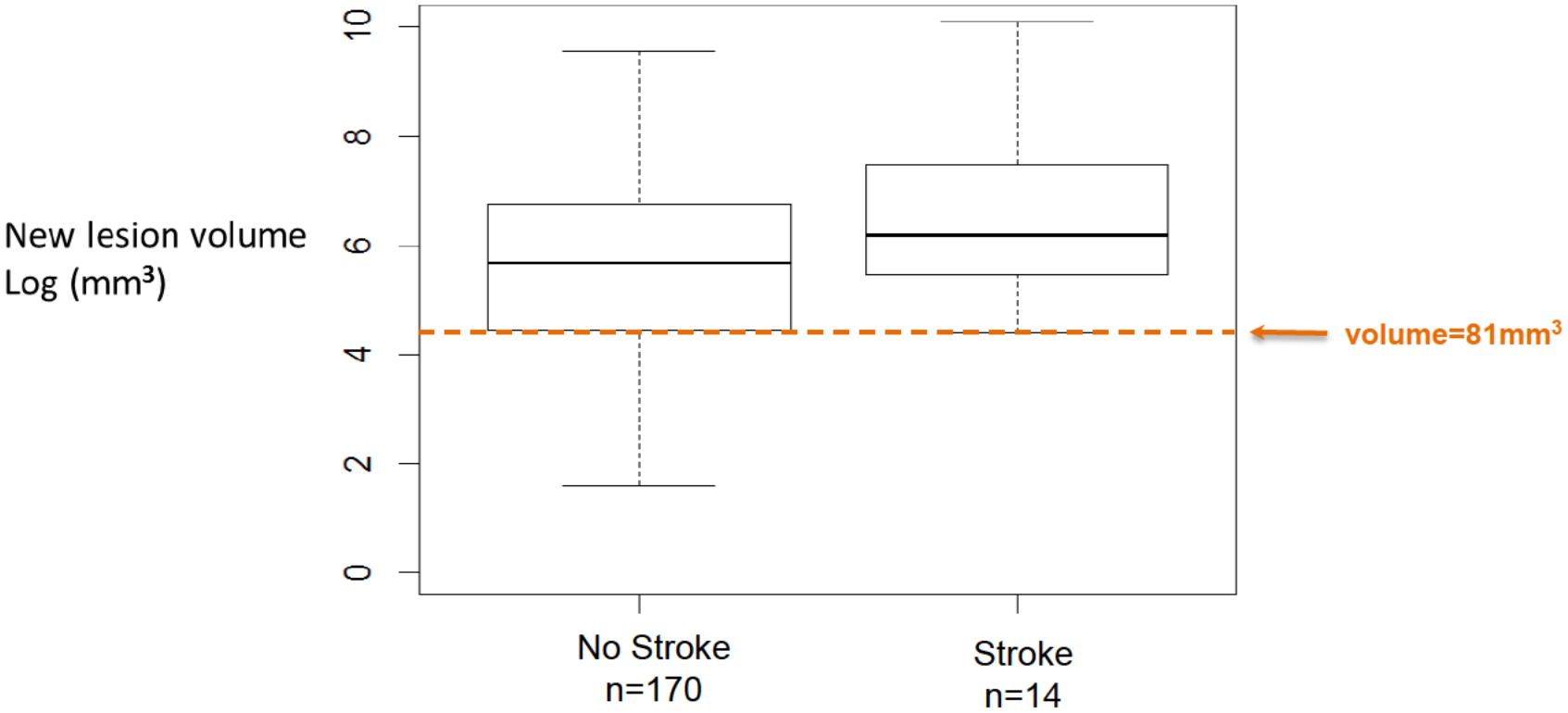
- **MRI based Lesion Volume Measurement as a Measure of Cerebral Ischemia**

2-7day new lesion volume in *protected territories* by 30day clinical stroke status (Imaging Cohort - ITT)



2-7day new lesion volume in *all territories* by 30day clinical stroke status (Imaging Cohort - ITT)



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

	Test Arm	Control Arm
2 to 7 Days Post-TAVR	-0.53 (49)	-0.25 (53)
30 Day Follow-Up (23-45 days)	-0.21 (74)	-0.20 (72)
90 Day Follow-Up (46-100 days)	-0.24 (54)	-0.10 (55)

Note: Data presented as: r (n)

Ref: Table 19: FDA Executive Summary

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

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

Note: Data presented as: r (n)

Ref: Table 20: FDA Executive Summary

Summary: Lesion Volume Measurement as a Surrogate Effectiveness Endpoint

- DW-MRI based new lesion volume at Day 2-7 in protected territories: patients with clinical stroke tend to have somewhat higher lesion volume.
- DW-MRI based new lesion volume at Day 2-7 in all territories: similar trend.
- Weak correlation (-0.2) between Day 2-7 lesion volume and 30-day change in neurocognitive composite z-score.

FDA Presentations

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  SENTINEL Study Statistical Conclusions and Considerations

- **CDR Sadaf Toor**
  Conclusions

Conclusions

- Safety:
  - Prespecified safety success criterion was met
  - No safety concerns with use of the device

- Effectiveness:
  - Study design: Imaging + clinical evidence of reduced ischemic events
  - Met criterion for prespecified observed treatment effect (>30% reduction)
  - Did not demonstrate superiority with respect to the primary effectiveness endpoint

Conclusions (cont.)

- Although device traps debris, correlation with DW-MRI findings (protected vs. all territories) remains unclear

- Neurocognitive outcomes showed no clear clinical trend

Thank you


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