A Randomized Evaluation oF the TriGUARD3™ Cerebral Embolic Protection Device to Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation

The REFLECT II Trial

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on behalf of the REFLECT Trial Investigators

Disclosure Statement of Financial Interest

I, (Jeffrey Moses) DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

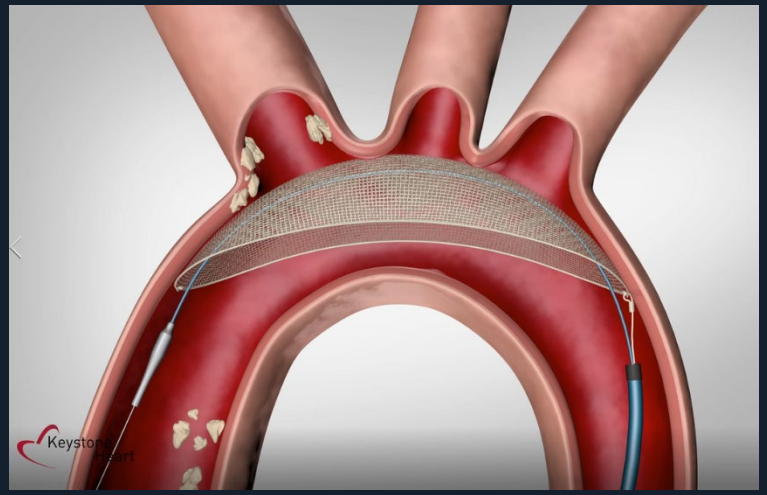
- Neurologic events are a persistent problem in TAVR procedures occurring in 2–6% of cases[1-8]
- Thus far there have been no adequately powered randomized trials demonstrating efficacy of CEP devices
- Preliminary randomized data with the first generation TriGUARD HDH in TAVR indicated a reduction in measures of cerebral ischemic lesions[9]

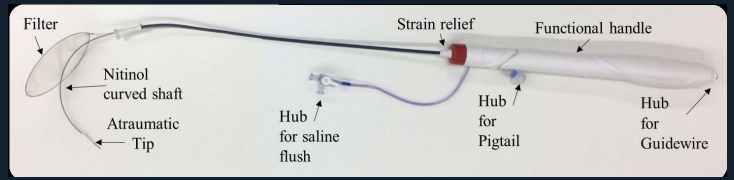
1. Smith C et al. *N Engl J Med*. 2011;364(23):2187-2198.
2. Leon M et al. *N Engl J Med.* 2010;363(17):1597-1607.
3. Adams D et al. *N Engl J Med*. 2014;370(19):1790-1798.
4. Leon MB, et al. *N Engl J Med*. 2016;374(17):1609-1620.
5. Reardon M et al. *N Engl J Med*. 2017;376(14):1321-1331.
6. Mack M et al. *N Engl J Med*. 2019.
7. Popma J et al. *N Engl J Med*. 2019.
8. Carroll J et al. *J Am Coll Cardiol*. 2017;70(1):29-41.
9. Lansky A et al. *European Heart Journal*. 2015;36(31):2070-2078.

Purpose

- To evaluate the safety and efficacy of the new generation TriGUARD *3* cerebral embolic protection device in reducing clinical events and cerebral lesions during transcatheter aortic valve replacement

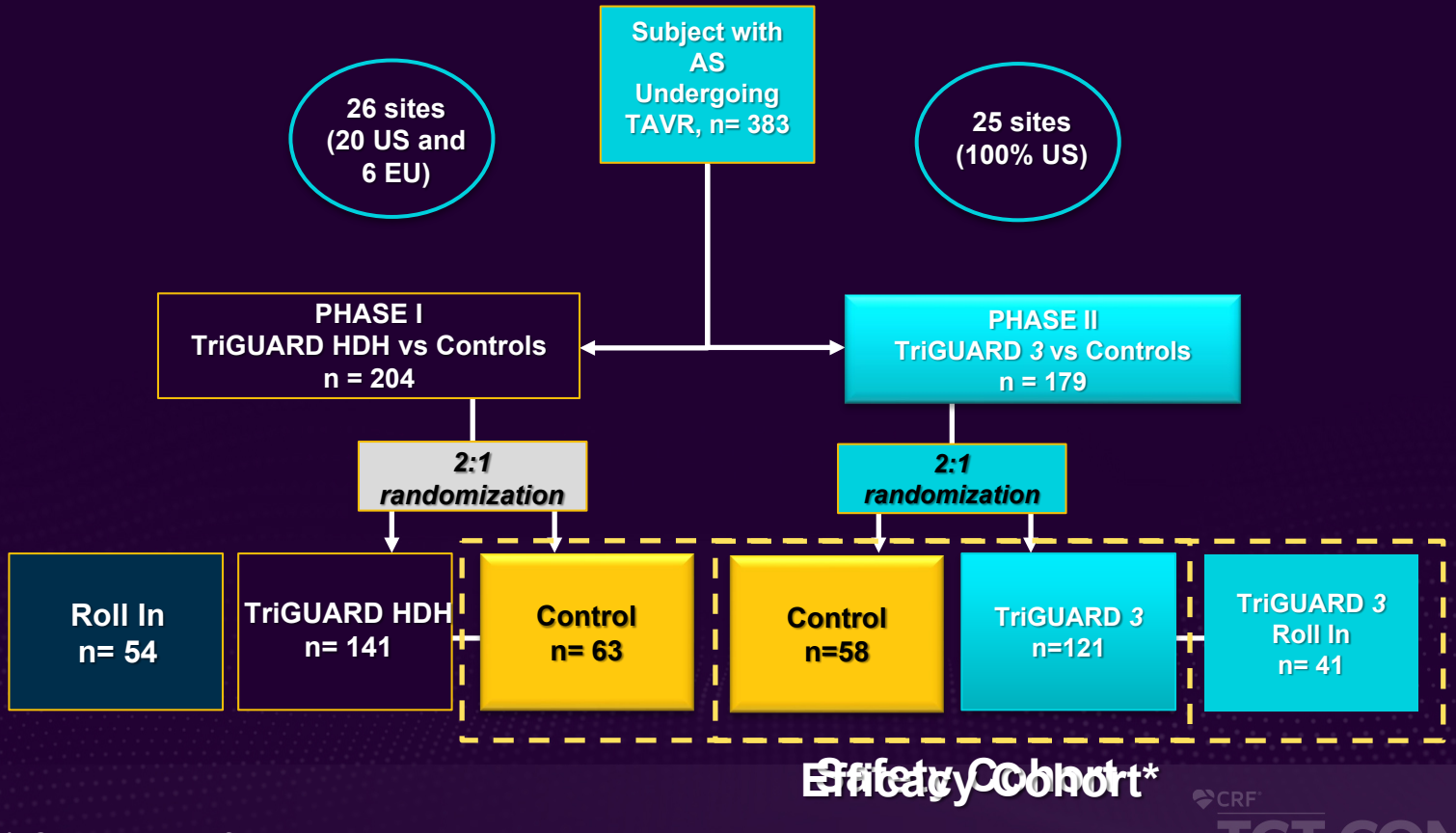
Keystone Heart TriGUARD *3*





- Self-positioning, nitinol frame without stabilizers
- PEEK mesh (pore size 115 x 145 µm)
- Filter area = 68.3 cm^2
- 8 Fr OTW delivery
- Accommodates a diagnostic pigtail

REFLECT Study



* Outcomes of Phase I controls remained blinded

Trial Administration

- Study Leadership: Jeffrey Moses (chair), PI: Tamim Nazif,
  - CoPI: A. Lansky; Raj R Makkar
- CEC: Yale Cardiovascular Research
- DSMB: Yale Cardiovascular Research
- Angiographic core lab: Yale Cardiovascular Research
- MRI core lab: Buffalo Neuroimaging Analysis Center
- Statistical analysis: Leslee Willis Consulting
- CT core lab: Cedars Sinai
- Sponsor: Keystone Heart

Top Enrollers

Institution	No. Enrolled	Principal Investigator
University of Texas	44	Abhijeet Dhoble, MD
Baylor Research Center	19	David Brown, MD
Morton Plant	19	Joshua Rovin, MD
Columbia University Medical Center	18	Tamim M. Nazif, MD
University of Iowa	17	Phillip Horwitz, MD
Baylor Heart and Vascular Hospital	16	Robert Stoler, MD
Cedars-Sinai Medical Center	16	Rajendra Makkar, MD
MedStar Washington Hospital Center	13	Ron Waksman, MD
University of Virginia	11	Scott Lim, MD
Yale University School of Medicine	10	John Forrest, MD
Pinnacle Health	7	Mubashir Mumtaz, MD
Other	30	
TOTAL	**220**	

- **Key Inclusion**
  - Severe native aortic valve stenosis with planned transfemoral treatment with an FDA approved TAVR system
- **Key Exclusions**
  - Prior AVR
  - Stroke/TIA < 6 months
  - Contraindication to antiplatelet or anticoagulation treatment
  - eGFR <30 ml/min
  - CT angiograms of the chest, abdomen, and pelvis were analyzed by the independent CT core lab and reviewed by a screening committee
  - Severe peripheral vascular disease (iliofemoral MLD <3.5mm)
  - Severely calcified or atheromatous aorta
  - Contraindication to MRI

Primary Endpoints: 30-day Safety

- Composite of all-cause mortality, stroke, life-threatening or disabling bleeding, stage 2/3 acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring intervention (VARC 2 defined)[1]
- Null hypothesis tested at alpha=0.05 with one sample Z test of proportions
- Performance Goal: 34.4%
  - Estimated historical control of 25% + absolute margin 9.4%
- Prespecified primary safety population: pooled TG3 randomized + Roll-in

[1]Kappetein AP,. *JTCS* 2013;145(1):6-23

Primary Endpoints: Efficacy

- **Hierarchical composite efficacy endpoint score (Finkelstein Schoenfeld methodology[1,2]) including:**
  - **All-cause mortality or any stroke at 30 days**
  - **NIHSS worsening from baseline to 2 to 5 days**
  - **Freedom from any cerebral ischemic lesions on DW-MRI at 2 to 5 days**
  - **Total volume of cerebral ischemic lesions on DW-MRI at 2 to 5 days**
- **Test of superiority: 80% power, one-sided alpha=0.05**
- **Efficacy ITT (eITT): Primary efficacy population *excludes conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to DW-MRI***
- **Per Treatment (PT): Prespecified analysis in patients with *Core lab confirmed 3-vessel cerebral coverage throughout TAVR***

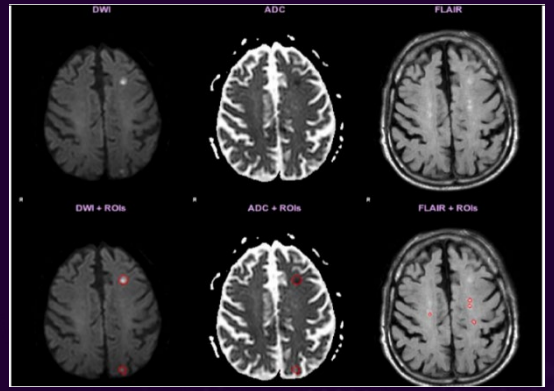
1. Finkelstein DM, Statistics in medicine. 1999;18(11):1341-1354
2. Pocock SJ,. *Eur Heart J.* 2012;33(2):176-182

Secondary Endpoints

- **Primary trial success required meeting both primary endpoints**
- **Secondary hypothesis-driven Endpoint: tested if trial success met in the following sequence:**
  - **All stroke at 7 days,**
  - **Worsening NIHSS from baseline to 2-5 days,**
  - **Composite of all-cause mortality and all stroke at 7 days,**
  - **Central Nervous System (CNS) infarction (Neurologic Academic Research Consortium (NeuroARC) defined) at 30 days,**
  - **Total volume of cerebral ischemic lesions detected by DW-MRI at 2-5 days**
- **Secondary Performance Endpoints**
  - **Device performance: Core Lab defined TG3 cerebral coverage (Full coverage, partial coverage, no coverage throughout TAVI)**
  - **Device Interference: Site reported interference with TAVI system**
  - **Technical Success: Full coverage in the absence of device interference**
  - **Procedure success: Technical success without TG3-related in-hospital MACCE**

MRI Methods and Endpoints

- **Diffusion Weighted MRI Acquisition**
  - 1.5 T MR was used consistently at all sites
  - DWI acquired with 2D echo planar sequence: Acute lesions
  - Fluid Attenuated Inversion Recovery (FLAIR): Chronic lesions
- **MRI Analysis**
  - Buffalo Neuroimaging Analysis Center, Buffalo, NY
  - Reader and evaluation blinded to treatment arms
- **Secondary DWI Imaging Endpoints**
  - Presence of cerebral ischemic lesions
  - Number of cerebral ischemic lesions
  - Per-patient average single cerebral ischemic lesion volume
  - Single cerebral ischemic lesion volume (lesion-level analysis)
  - Total volume of cerebral ischemic lesions



Semi automated Contour detection

Study Closure

- After enrollment of 179 of the 225 planned randomized patients, Sponsor suspended trial enrollment with the concurrence of the FDA and DMC
- After limited unblinding and review of the data, KSH decided formally close the study and proceed with marketing application (510(k))

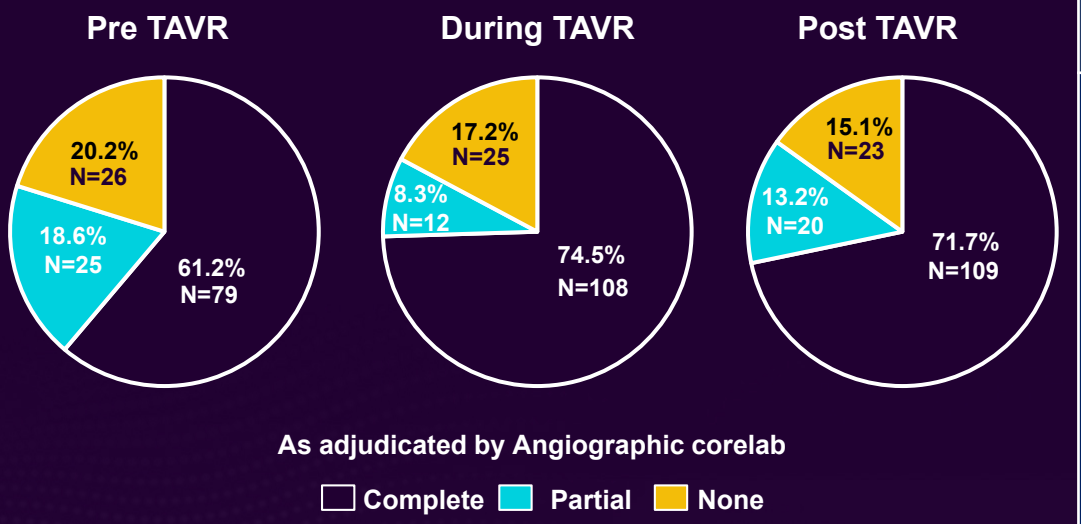
Baseline Characteristics

	As Treated Population (Primary Safety)			eITT Population (Primary Efficacy)		
	Combined TG3 (Roll In N=41 and Randomized TG3 N=116)	Randomized Controls	*P* Value	Randomized TG3	Combined Controls	*P* Value**
	157	57		112	119	
Age (yrs) Mean ± SD	80.31 ±7.73	78.05 ± 8.19	0.065	79.71 ± 7.96	79.88 ± 7.84	0.865
Male sex, (%)	54.8	61.4	0.437	55.4	64.7	0.179
STS Score, Mean ± SD	4.64 ± 2.77	4.54 ± 2.50	0.790	4.49 ± 2.79	4.69 ± 2.81	0.495
Diabetes Mellitus (DM) (%)	39.1	40.4	0.875	34.8	35.3	1.000
Prior atrial fibrillation/atrial flutter, (%)	28.0	29.8	0.864	28.6	28.0	1.000
Prior CABG, (%)	18.5	19.3	1.000	18.8	17.6	0.866
Prior PCI, (%)	31.2	26.3	0.613	32.1	28.2	0.566
Prior stroke or TIA, (%)	17.2	5.3	0.026	17.9	8.5	0.049
History of PVD, (%)	12.9	19.3	0.274	13.5	16.5	0.580
Carotid artery disease, (%)	19.9	23.2	0.700	17.6	16.7	0.861
Chronic Obstructive Lung disease, (%)	17.8	21.4	0.555	15.2	19.1	0.484
NYHA class III/IV at baseline, (%)	52.5	56.2	0.852	53.6	67.3	0.045

Procedure Characteristics

	TriGUARD *3* (Rand and roll-ins)	Combined Controls
Procedure Details	157	119
Successful Valve Deployment (%)	100	100
Self Expanding THV, (%)	36.9	35.3
Balloon Expandable THV, (%)	62.4	60.5
Other, (%)	0.6	4.2
Aortic Balloon Valvuloplasty (BAV) performed, (%)	25.5	39.5
Femoral Access, (%)	100	100
Number of TAVR devices implanted		
1, (%)	96.8	97.5
2, (%)	3.2	2.5

TriGUARD *3* Performance and Cerebral Coverage

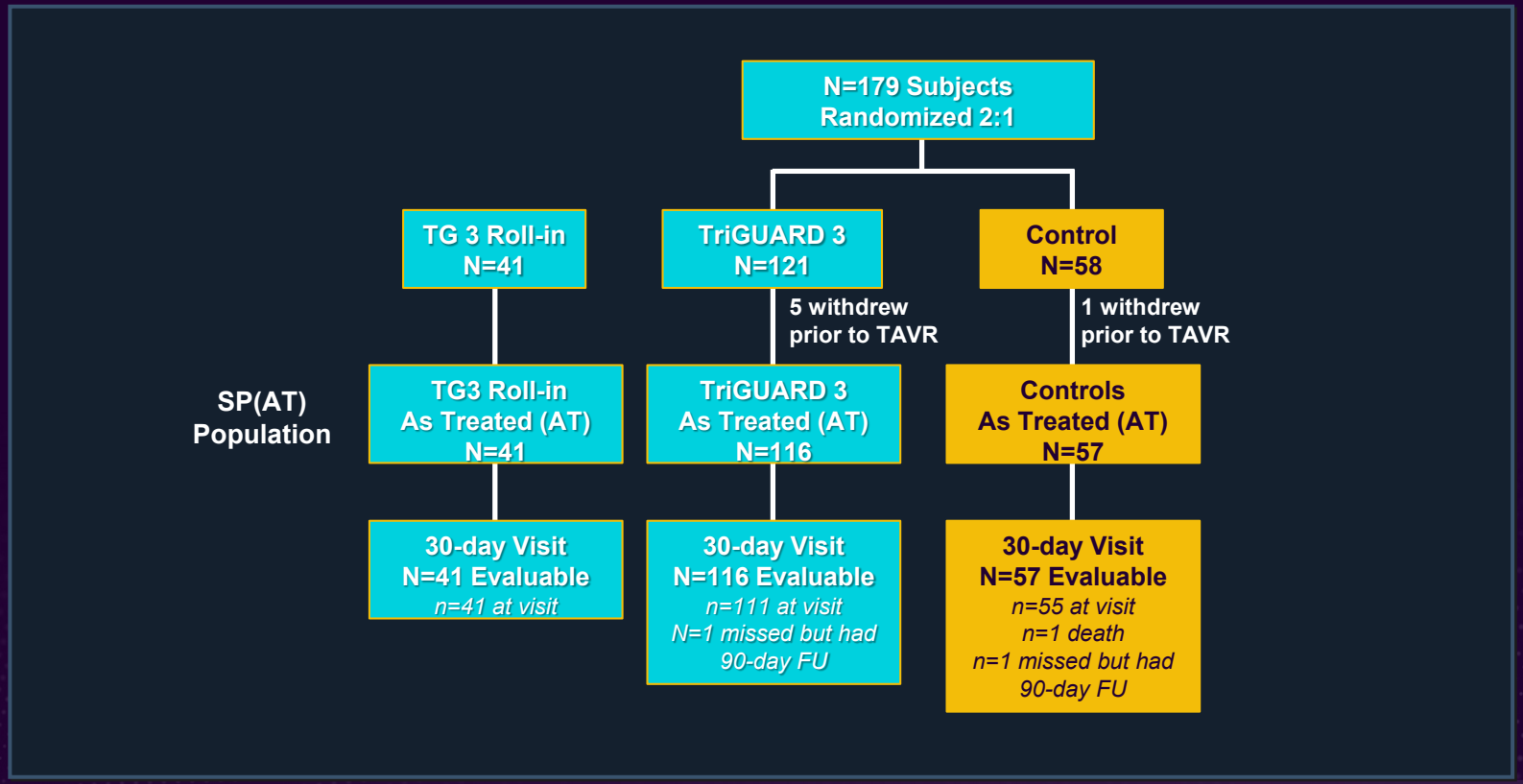


Performance Measures	Combined TriGUARD *3* (N=157)
Successful deployment	100%
Successful on 1st attempt	98.1%
Technical Success	71%
Procedure Success	69.7%
Device Interaction	9.6%
Deployment Time Mean ± SD	2.81 ± 5.69

Full Coverage Throughout: 59.3%
All devices successfully deployed and retrieved

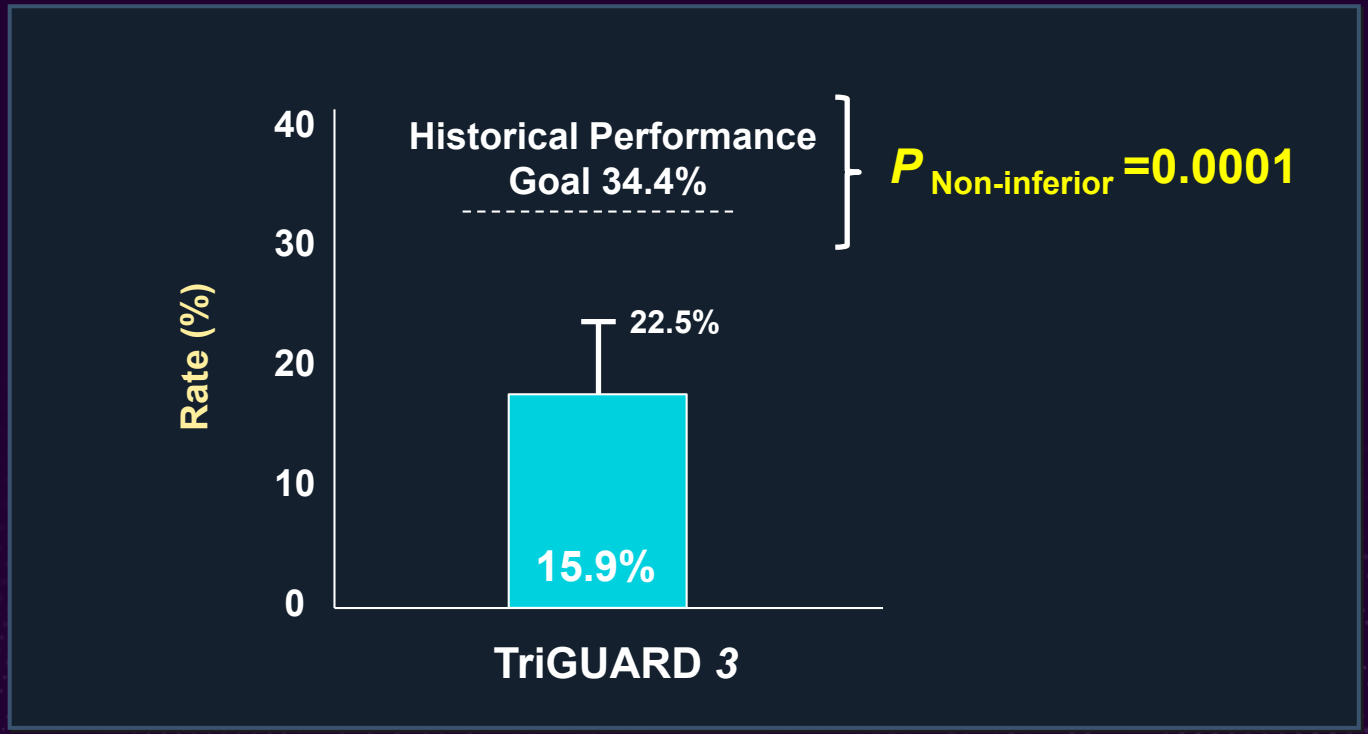
Technical Success: Full coverage in the absence of device interaction
Procedure success: Technical success without TG3-related in-hospital MACCE

Safety Cohort Patient Flow



A follow-up telephone contact assessed the occurrence of death or stroke at 90 days.

Primary Safety Endpoint: 30 Day MACE

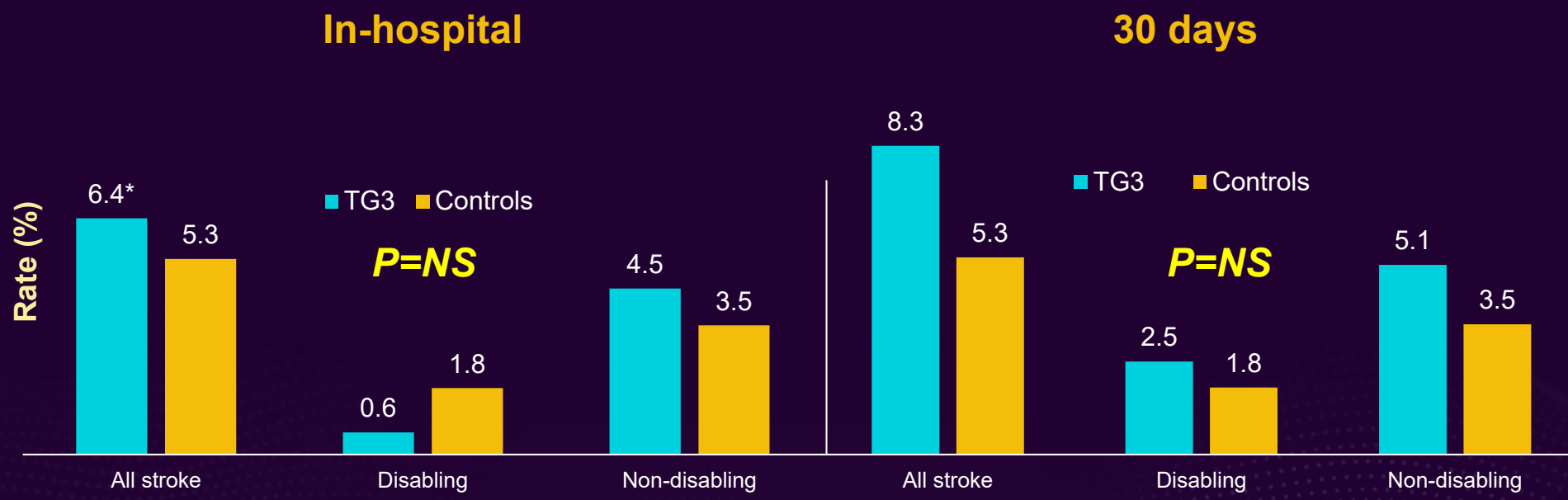


Safety Comparisons
Clinical Outcomes (VARC 2 defined)

	TriGUARD *3**	Controls	*P* value
Primary Outcomes	157	57	
Composite Primary Safety, (%)	15.9	7.0	0.11
Death, (%)	2.5	1.8	1.00
Stroke, (%)	8.3	5.3	0.57
Life-threatening or disabling bleeding, (%)	5.7	0.0	0.12
Acute kidney injury (stage 2/3) , (%)	2.5	0.0	0.58
Coronary artery obstruction requiring intervention, (%)	0.6	0.0	1.00
Major vascular complication, (%)	7.0	0.0	0.04
TG*3* related, (%)	1.9	0.0	0.57
TAVR related, (%)	4.5	0.0	0.19
Aortic vascular injury, (%)	1.3	0.0	1.00
Valve related Dysfunction requiring intervention , (%)	0.0	0.0	–

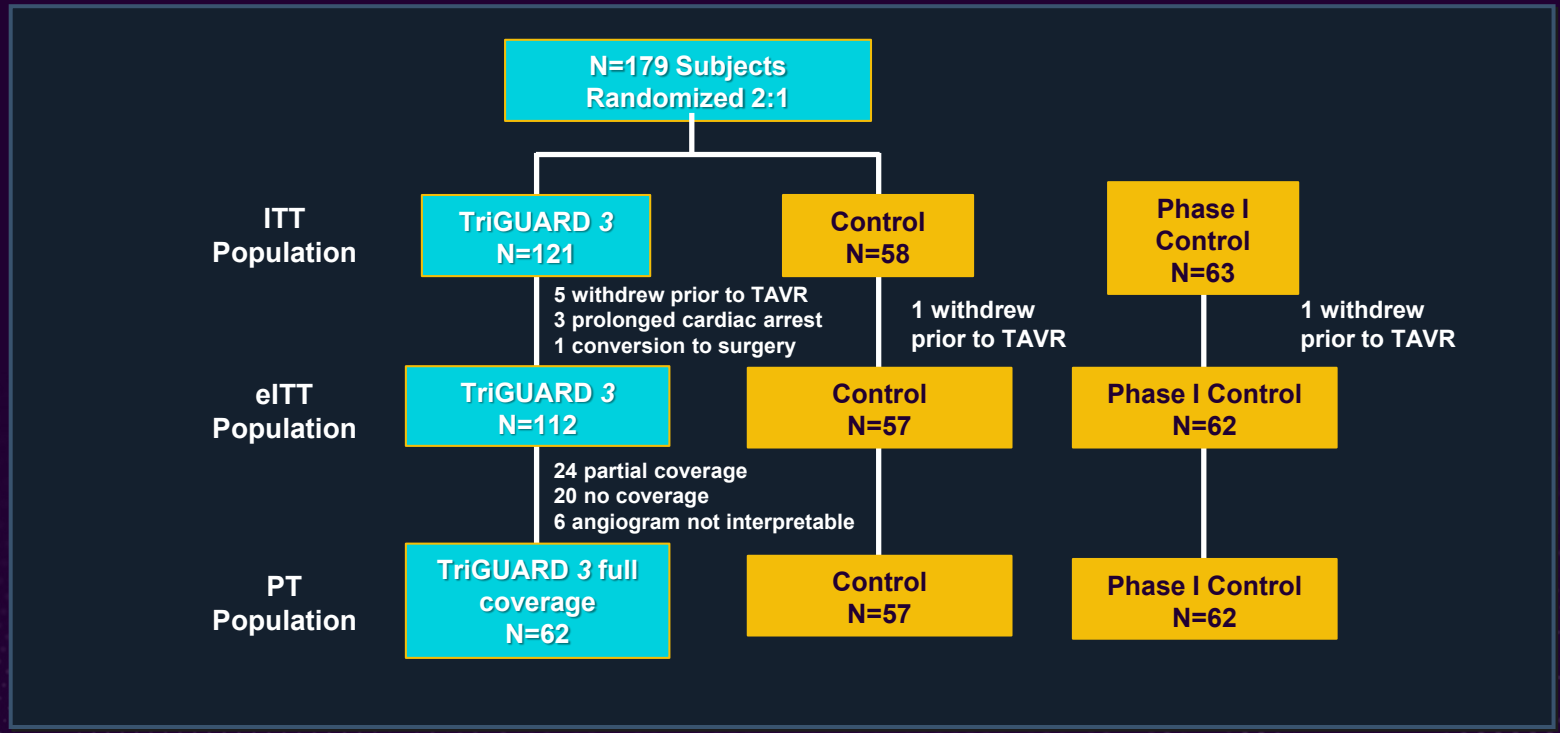
* Prespecified primary safety population was combined TG3 (randomized + roll-in)

Stroke Timing: In-Hospital vs 30 days



* 1 undetermined stroke in TG3

Efficacy Cohort Patient Flow



The study was prospectively designed to leverage previously collected data from Control patients enrolled in the REFLECT Trial Phase I of the prior generation TriGuard HDH device. Phase I controls remained blinded and met poolability criteria with phase 2

Efficacy Endpoints: TG vs Control

	TriGUARD *3*	Pooled Controls	*P* value
Primary Outcomes	112	119	
Primary Efficacy Score	-8.58 ± 120.76	8.08 ± 116.51	0.857
Win percentage, %	45.7	54.3	–
Component event rates			
All-cause mortality or any stroke at 30 days, %	9.8	6.7	0.475
NIHSS worsening predischarge, %	14.1	7.6	0.176
Cerebral ischemic lesions, %	85.0	84.9	1.000
Total cerebral lesion volume, mm^3, Median (IQR)	215.39 (68.13, 619.71)	188.09 (52.08, 453.12)	0.405

Prespecified primary efficacy population was randomized TG3 vs pooled controls
Win percentage= wins/wins+losses (removes ties)

Secondary Imaging Efficacy Endpoints (eITT and PT)

	eITT		PT	
	TriGUARD *3*	Pooled Controls	TriGUARD *3*	Pooled Controls
Cerebral ischemic lesions, (%)	85.0	84.9	79.6	84.9
Cerebral ischemic lesions, mean ± SD	6.0 ± 8.3	4.6 ± 5.9	3.9 ± 4.8	4.6 ± 5.9
Average volume ischemic lesions, mm^3, Median (IQR)	59.9 (35.7, 90.5)	57.5 (34.0, 90.6)	52.7 (25.0, 83.9)	57.5 (34.0, 90.6)
Single volume ischemic lesions, mm^3, Median (IQR)	31.3 (18.8, 71.4)	35.8 (0.0, 71.4)	35.7 (18.8, 76.5)	35.8 (0.0, 71.4)
Total volume of ischemic lesions, mm^3, Median (IQR)	215.4 (68.1, 619.7)	188.1 (52.1, 453.1)	145.7 (43.8, 444.4)	188.1 (52.1, 453.1)

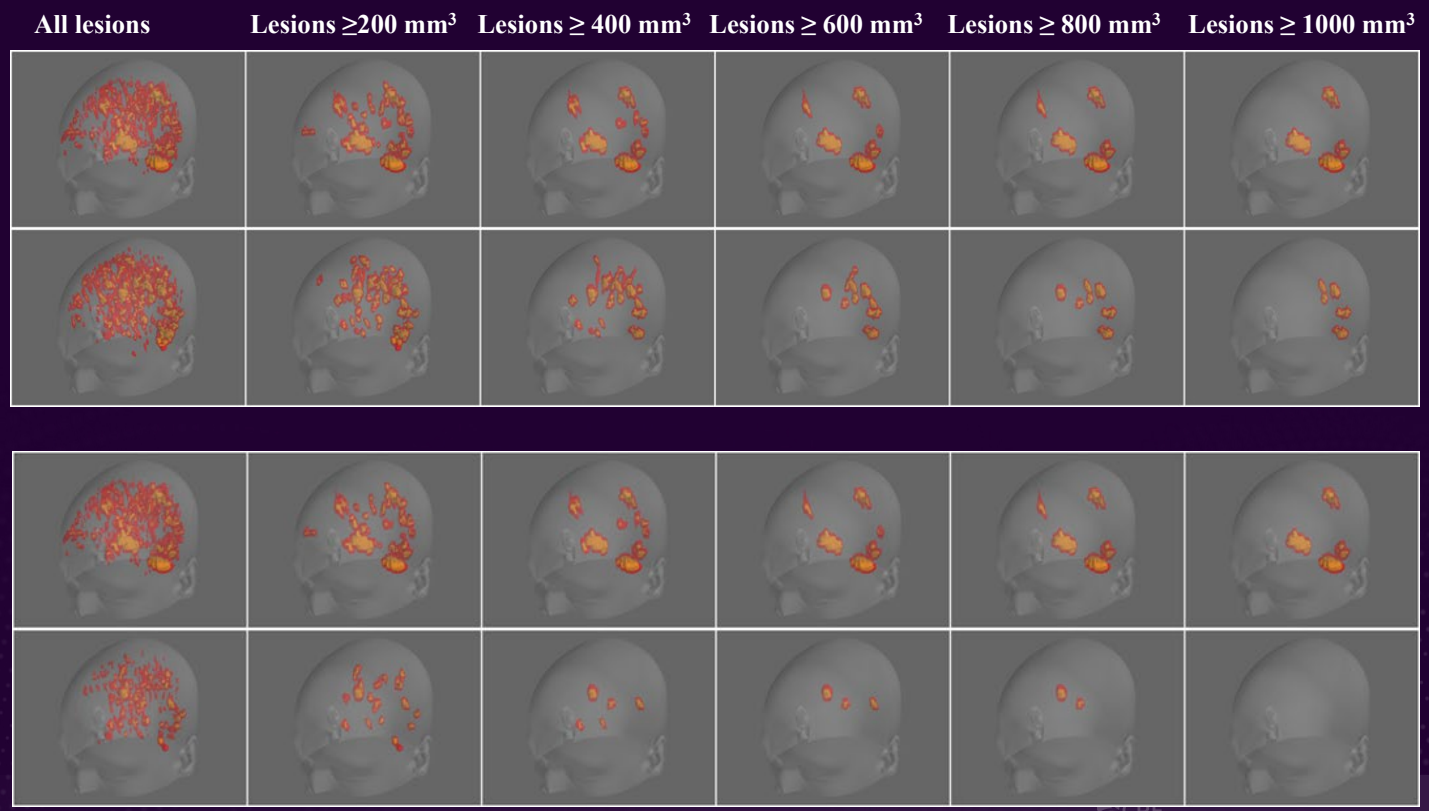
P=NS for all comparisons

Rationale for Post Hoc Analysis

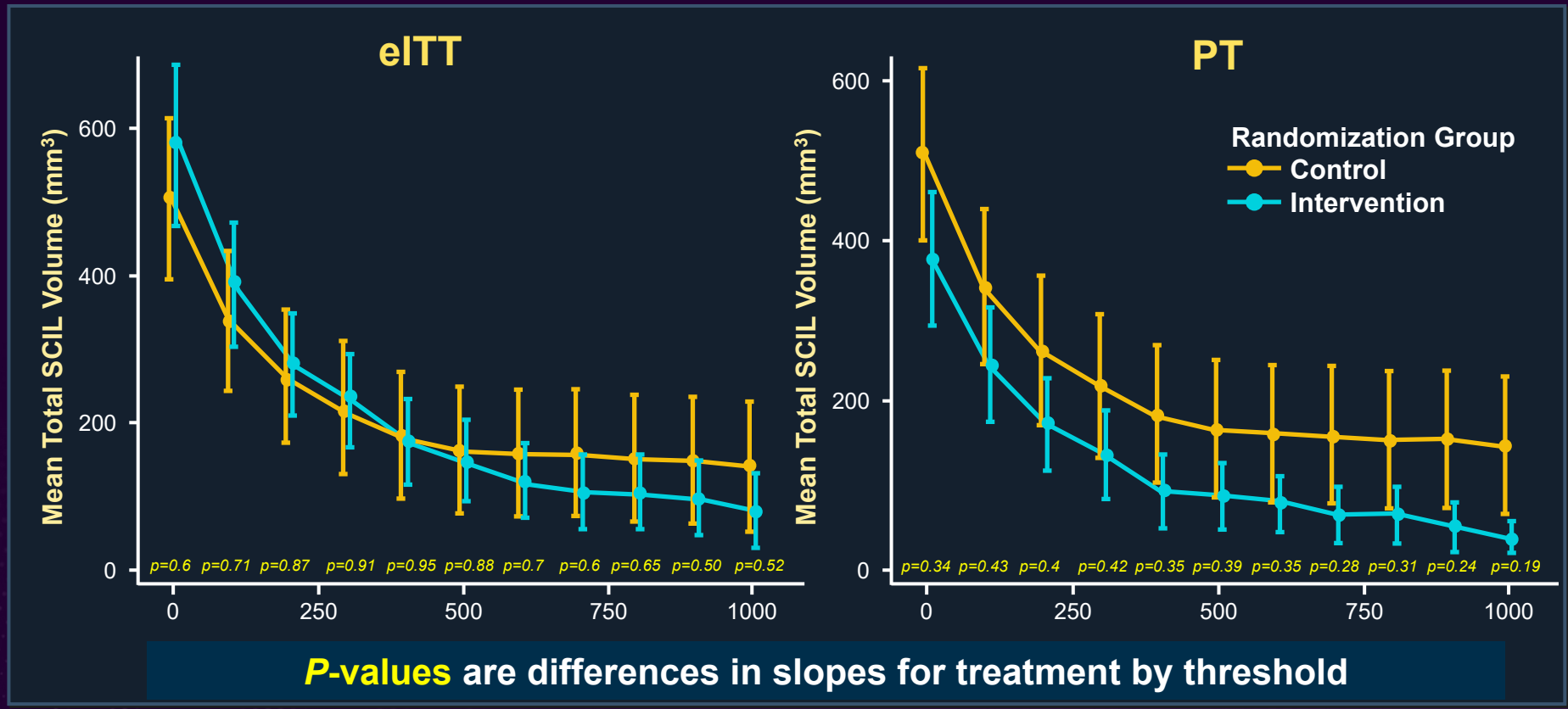
- Numerous studies have demonstrated that lesion size on DW MRI after a procedure is associated with clinical symptoms including stroke and post-operative cognitive decline[18,28-30]
- To evaluate whether TG*3* had a differential impact in preventing different lesion sizes, a multi-threshold, lesion-wise analysis was performed to investigate per-patient supra-threshold cerebral ischemic lesion (SCIL) volume above incremental thresholds from >100mm^3 to >1000mm^3

18. Kapadia SR. *J Am Coll Cardiol*. 2017;69(4):367-377.
28. Messé SR, *Circulation*. 2014;129(22):2253-2261.
29. Giovannetti T,. *Ann Thorac Surg*. 2019;107(3):787-794.
30. Bonati LH, *Lancet Neurol*. 2010;9(4):353-36

Suprathreshold Lesion Volume Analysis in eITT and PT



Average New Super-threshold Lesion Volumes: eITT & PT



***P*-values are differences in slopes for treatment by threshold**

Lesion Size Threshold Analysis

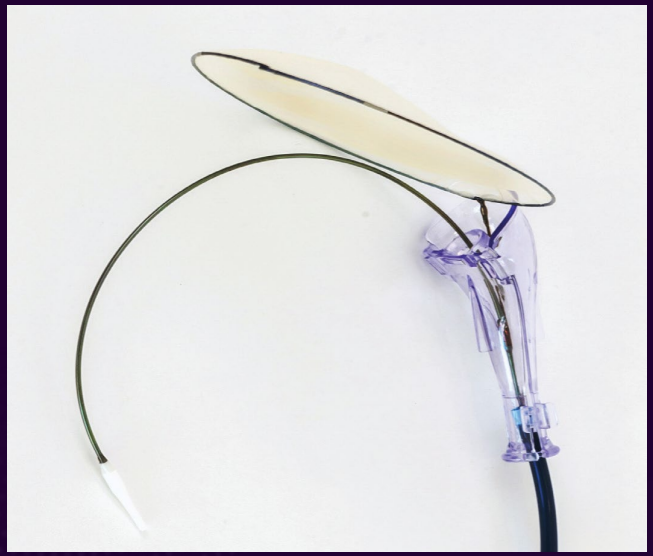
Lesion Size Threshold	eITT			PT		
	TriGUARD (mm^3)	Pooled Controls (mm^3)	Reduction (%)	TriGUARD (mm^3)	Pooled Controls (mm^3)	Reduction (%)
Total, mean (SD)	587.80 (1028.4)	508.22 (1124.0)	+15.7	375.80 (617.7)	508.22 (1124.0)	26.1
>500 mm^3, mean (SD)	146.54 (538.3)	162.21 (901.7)	9.7	79.30 (294.0)	162.21 (901.7)	51.1
>1000 mm^3 mean (SD)	78.22 (476.5)	141.03 (886.9)	44.5	24.15 (177.5)	141.03 (886.9)	82.9

P=NS for all comparisons

Conclusions

- The REFLECT II trial met the primary safety endpoint, demonstrating that the TriGUARD *3* cerebral embolic protection device was safe in comparison with historical TAVR data
- Compared to controls the primary 30-day safety endpoint was higher with TriGUARD 3 due primarily to TAVR related vascular complications
- The study did not demonstrate superiority of TriGUARD *3* compared to pooled controls for the primary hierarchical efficacy endpoint
- Post hoc DW-MRI analysis suggests that TG3 may reduce larger ischemic lesions
- Improved device stability to achieve reliable, complete cerebral coverage might improve outcomes

Post REFLECT Device Update



To maintain coverage and provide the necessary apposition against the aortic arch, the hypotube shaft must be positioned underneath the deflection filter.

- The crimper has been modified to provide a guide for the hypotube shaft to maintain position under the filter.

- In addition, the Instructions for Use and training materials have been updated