U.S. FOOD & DRUG ADMINISTRATION

Premarket Notification 510(k) for Keystone Heart, Ltd's TriGUARD™ 3 Cerebral Embolic Protection Device

Circulatory System Devices Advisory Panel Meeting
August 3, 2021

Presentations By:
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Office of Cardiovascular Devices (OCVD) and Office of Clinical Evidence and Analysis (OCEA)
Office of Product Evaluation and Quality (OPEQ)
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FDA Review Team

Sadaf Toor, MS	- Lead and Engineering
Donna Buckley, MD, MS	- Clinical
Yu Zhao, PhD	- Statistical
Wei-Chen Chen, PhD	- Statistical
Karen Manhart, VMD	- Animal Studies
Girish Kumar, PhD	- Biocompatibility
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Sara Royce, PhD	- Chemistry
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Ankurita Datta, MS	- Engineering

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FDA Presentations

- CDR Sadaf Toor
  - Introduction and Clinical Background
  - Device Description and Proposed Indications for Use
  - Regulatory History
- Dr. Yu Zhao
  - REFLECT Clinical Trial Design and Statistical Considerations
- Dr. Donna Buckley
  - REFLECT Results and Clinical Considerations
- CDR Sadaf Toor
  - Conclusions

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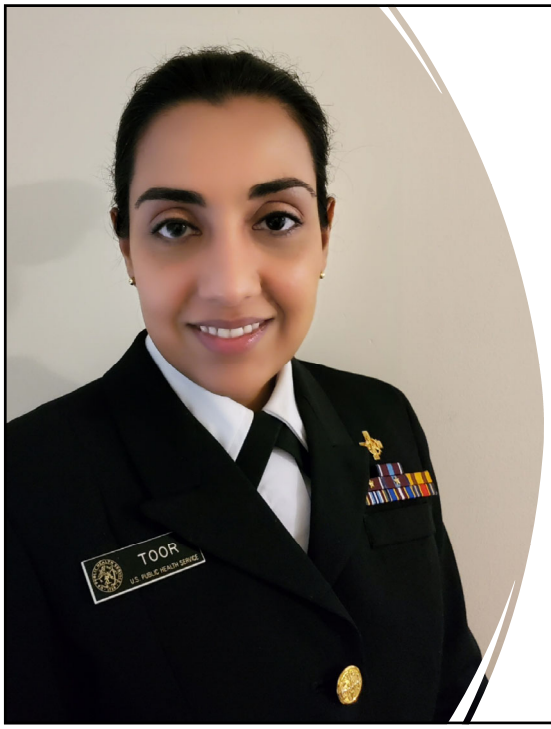

Introduction, Clinical Background, Device Description, and Regulatory History

CDR Sadaf A. Toor, M.S.
Biomedical Engineer
CDRH/OPEQ/OCVD/PIDT

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Meeting Purpose

- The panel is requested to focus discussion on the clinical data and REFLECT study outcomes
- The panel will be asked to discuss the safety and effectiveness of the TriGUARD 3 device as compared to the predicate Boston Scientific Sentinel™ Cerebral Protection System
- There are no outstanding questions about the non-clinical studies

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Clinical and Regulatory Background

- Periprocedural stroke occurs in 2-6% of patients undergoing Transcatheter Aortic Valve Replacement (TAVR)
- Cerebral Embolic Protection Devices (EPDs) for use during TAVR are classified as Class II devices and regulated under 21 CFR 870.1251 (temporary catheter for embolic protection during transcatheter intracardiac procedures)
- For a 510(k) device to receive clearance, it must:
  - demonstrate substantial equivalence to its predicate device
    - as safe and as effective as another legally marketed device with the same intended use
  - meet the general controls of the FD&C Act and any special controls
    - Special controls are outlined in 21 CFR 870.1251

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Regulatory Background (cont.)

21 CFR 870.1251 Special Controls for TAVR EPDs

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

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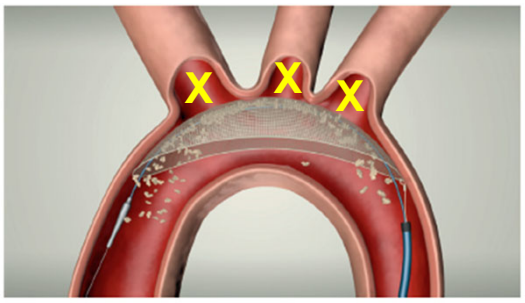
Device Description

TriGUARD 3 is a temporarily placed cerebral EPD delivered transfemorally through an 8F sheath to the aortic arch

- structural nitinol frame and a polymer mesh attached to the frame
- heparin coated to reduce thrombogenicity and increase lubricity
- intended to cover the ostia of all 3 aortic arch great vessels (brachiocephalic, left common carotid, and left subclavian arteries)



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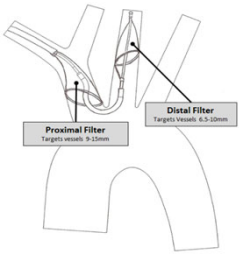
Predicate Device

- Boston Scientific Sentinel™ Cerebral Protection System
  - Currently the only commercially available cerebral EPD in the U.S.
  - Indicated to capture and remove thrombus/debris while performing TAVR procedures
  - Dual filter system that traps embolic debris within the right brachiocephalic and left common carotid arteries



- If cleared, TriGUARD 3 would be the second cerebral EPD commercially available in the U.S.

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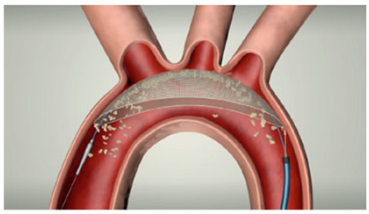
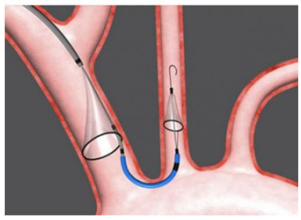
TriGUARD 3 (subject) vs. Sentinel (predicate)



- Positioned in aortic arch
- Designed to protect all 3 arch vessels
- Deflects debris downstream
- Delivered transfemorally (8F)



- Positioned within branch vessels
- Designed to protect 2 of 3 arch vessels (does not cover L. subclavian)
- Captures and removes debris
- Delivered transradially (6F)

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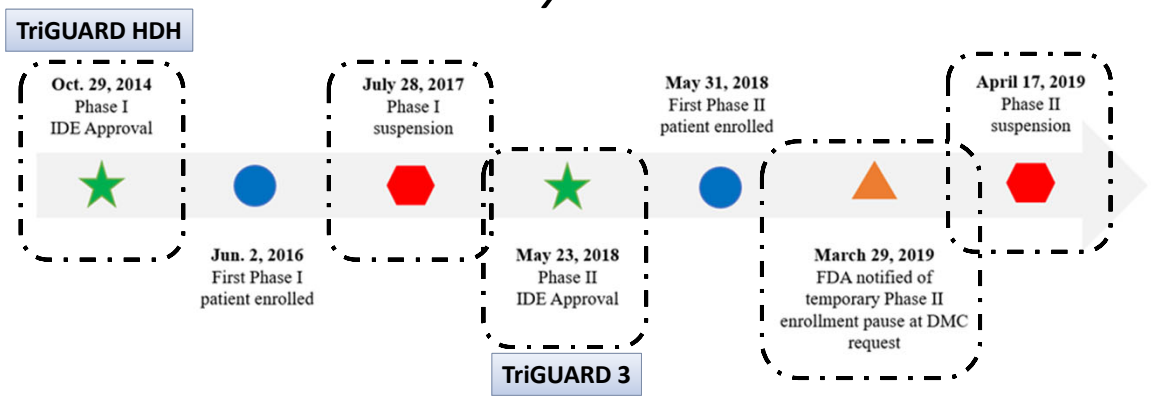
Proposed Indications for Use

The TriGUARD 3 Cerebral Embolic Protection Device is designed to minimize the risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during trans-catheter aortic valve replacement (TAVR).

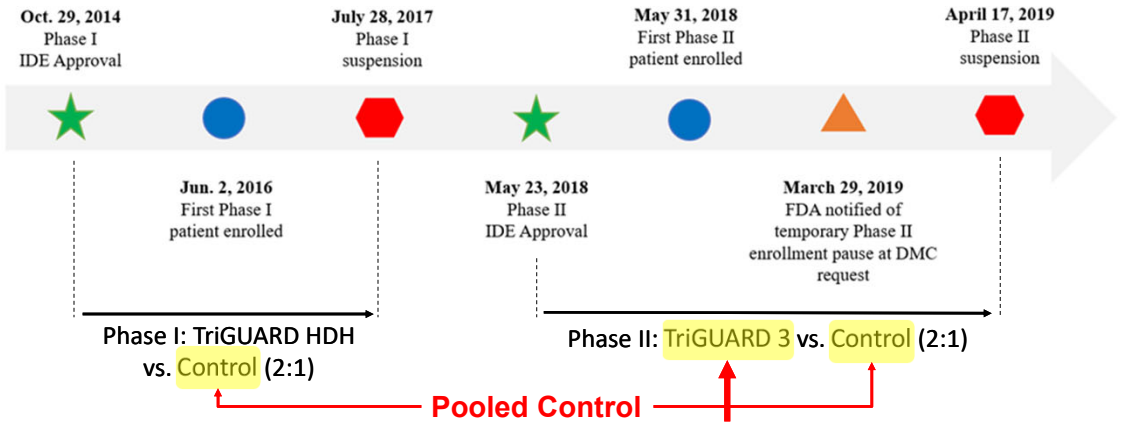
Regulatory History

REFLECT Study IDE Timeline



REFLECT Phase I: TriGUARD HDH device – not proposed for marketing
REFLECT Phase II: TriGUARD 3 device – subject of this 510(k) submission

Regulatory History
REFLECT Study IDE Timeline



REFLECT Phase II was designed to assess TriGUARD 3 and combine control data from Phase I and II into a pooled control group

Device Modifications Following IDE Study

- Crimper - used to load the TriGUARD 3 into the delivery sheath during device preparation.
- Modification was made to crimper to improve preparation and positioning of the TriGUARD 3 device.
- No REFLECT study subjects were treated with the TriGUARD 3 using the modified crimper.
- The sponsor provided real world clinical data from 50 commercial cases of the device with the modified crimper at a single center in the Netherlands to support improved device performance.

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  - Conclusions

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Clinical Trial Design and Statistical Considerations

Yu Zhao, Ph.D.
Statistical Reviewer
CDRH/OCEA/DCEAII

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REFLECT Phase II Study Design

- Prospective, multicenter, single-blind, 2:1 randomized, controlled trial
  - Test group (TriGUARD 3 group): TriGUARD 3 with TAVR
  - Control group: Unprotected TAVR
- Target Enrollment:
  - Up to 225 randomized subjects
  - Up to 50 roll-in (RI) Subjects
  - Phase I control group (total enrollment N=63) would be included in effectiveness assessment if Phase I and Phase II controls were deemed poolable

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Primary Safety Endpoint

Definition: a composite of following safety events at 30 days based on VARC-2 definition:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening or disabling bleeding
- Acute kidney injury – Stage 2 or 3 (including renal replacement therapy)
- Coronary artery obstruction requiring intervention
- Major vascular complication
- Valve-related dysfunction requiring repeat procedure (balloon aortic valvuloplasty, TAVR, or surgical aortic valve replacement)

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Primary Safety Endpoint
Statistical Hypothesis and Analysis

- Hypothesis:

$$H_0: \pi \geq 0.344 \text{ and } H_1: \pi < 0.344$$

where π is the primary safety endpoint event rate for the randomized TriGUARD 3 subjects combined with roll-in subjects.

- Pre-Specified Statistical Analysis:
  - Z test with one-sided alpha = 0.05
  - Primary analysis population: As Treated Safety Population (SP[AT])
    - Including both randomized and roll-in subjects in Phase II study
    - Subjects were analyzed according to actual treatment received

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Primary Effectiveness Endpoint

Definition: a composite according to the following pre-specified hierarchy of adverse outcomes:

- All-cause mortality and/or any stroke (fatal and non-fatal, disabling or non-disabling) [evaluated at 30 days]
- NIH Stroke Scale (NIHSS) worsening (increase from baseline) [evaluated at 2 to 5 days post-procedure]
- Any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure

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Primary Effectiveness Endpoint Statistical Hypothesis

Superiority Hypothesis

$H0$: The hierarchical composite of death/stroke, NIHSS worsening, any cerebral ischemic lesions detected by DW-MRI, and total volume of cerebral ischemic lesions is not different between the TriGUARD 3 and control groups

vs.

$H1$: The TriGUARD 3 group performs better compared to the control group regarding the hierarchical composite of death/stroke, NIHSS worsening, any cerebral ischemic lesions detected by DW-MRI, and total volume of cerebral ischemic lesions

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Primary Effectiveness Endpoint Analysis Method

- The hypothesis test was planned to be conducted using Finkelstein–Schoenfeld method at a one-sided alpha level of 0.025
- Pocock win-ratio and win-percentage were calculated to estimate the treatment effect
  - TriGUARD 3 vs. Control:
    - Win ratio > 1: indicates a treatment effect favoring the TriGUARD 3 group
    - Win ratio < 1: indicates a treatment effect favoring the control group
    - Win percentage > 50%: indicates a treatment effect favoring the TriGUARD 3 group
    - Win percentage < 50%: indicates a treatment effect favoring the control group

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Primary Effectiveness Endpoint Analysis Population

- Primary analysis population: efficacy Intention to Treat Population (eITT)
  - Excluded subjects who underwent conversion to surgery or experienced prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI
  - Excluded subjects who withdrew before TAVR procedure
  - Subjects were analyzed according to randomization assignment
- Control group
  - Pooled control: if Phase I and Phase II controls were deemed poolable
  - Phase II control: if Phase I and Phase II controls were deemed non-poolable

Assessment Strategy of Poolability Between Phase I and Phase II Controls

Per the Statistical Analysis Plan (SAP), the two control groups would be deemed poolable if no statistically significant difference was detected for each of the following 7 baseline characteristics (each at a two-sided alpha level of 0.15)

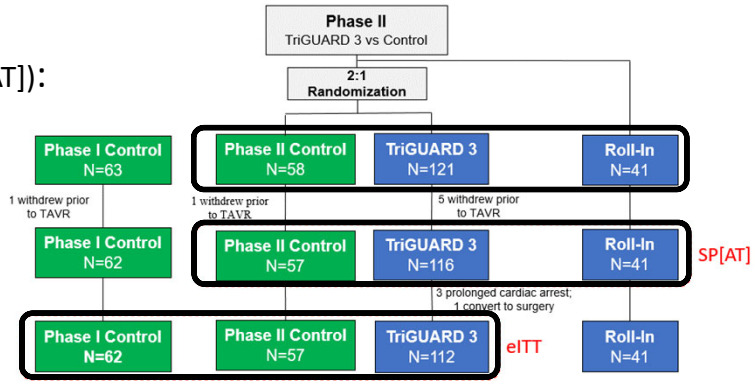
- Age
- Diabetes mellitus
- History of CHF
- Prior cerebral vascular attack (CVA) or transient ischemic attack (TIA)
- NIHSS
- Society of Thoracic Surgeons (STS) score
- Clinical frailty

Study Success Criteria and Secondary Endpoints

- Study success criteria:
  - Both primary safety and effectiveness endpoints need to be met
- Five hypothesis driven secondary endpoints would be tested for superiority at a one-sided 0.025 alpha level in the following pre-specified sequence, only if study success was achieved:
  - All stroke [evaluated at 7 days]
  - NIHSS worsening [evaluated 2 to 5 days post-procedure]
  - Composite of all-cause mortality and all stroke [evaluated at 7 days]
  - Central nervous system (CNS) infarction [evaluated at 30 days]
  - Total volume of cerebral ischemic lesions [evaluated 2 to 5 days post-procedure]

Study Enrollment

- Phase II study enrollment:
  - Randomized subjects: n=179
  - Roll-in group: n=41
- As Treated Safety Population (SP[AT]):
  - Phase II Randomized TriGUARD 3 + Roll-in: n=157
  - Phase II Control: n=57
- eITT population:
  - Phase II Randomized TriGUARD 3: n=112
  - Phase II control: n=57
  - Phase I control: n=62



Primary Safety Endpoint Results

- As Treated Safety Population (SP[AT]):
  - Randomized TriGUARD 3 subjects + roll-in subjects: n=157

	Subjects with Event(s)	Upper 95% Confidence Interval	Performance Goal	P-value
SP[AT]	25/157 (15.9%)	21.3%	34.4%	<0.0001

- The primary safety endpoint was met

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Poolability between Phase I and Phase II Controls

Baseline Characteristics	Phase I Control *N=62*	Phase II Control *N=57*	p-value
Age (yrs)			
Mean±SD (n)	81.6 ± 7.2 (62)	78.1 ± 8.2 (57)	0.01
Median, Range (Min, Max)	82.0, (56.0, 94.0)	79.0, (59.0, 93.0)	
Diabetes Mellitus (DM)	30.6% (19/62)	40.4% (23/57)	0.34
History of Congestive Heart Failure (CHF)	37.7% (23/61)	58.9% (33/56)	0.03
Prior CVA or TIA	11.7% (7/60)	5.3% (3/57)	0.32
NIHSS (NIHSS=0)	83.9% (52/62)	81.5% (44/54)	0.81
STS Score			
Mean±SD (n)	4.8 ± 3.1 (59)	4.5 ± 2.5 (57)	0.57
Median, Range (Min, Max)	4.1, (0.9, 19.5)	3.6, (0.8, 11.8)	
Clinical Frailty	Not consistently collected in Phase I		NA

- Per the strategy specified in the SAP, the two control groups would be deemed non-poolable

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Primary Effectiveness Endpoint Results

- The primary analysis of the primary effectiveness endpoint was based on eITT population with Pooled Controls

Primary Effectiveness Hierarchical Endpoint	TriGUARD 3 vs. Pooled Control	
	N=112	*N=119*
Finkelstein–Schoenfeld test p value	0.857	
Win-ratio	0.84	
Win-percentage	45.7%	

- The primary effectiveness endpoint was not met
- TriGUARD 3 vs. Pooled Control:
  - Observed win ratio = 0.84, *< 1 favors the control group*
  - Observed win percentage = 45.7% , *< 50% favors the control group*

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REFLECT II Study Statistical Conclusions

- The study success criteria were not met
  - Primary safety endpoint was met
  - Primary effectiveness endpoint was not met
- No secondary endpoints were formally tested

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Tipping Point Analyses for Primary Effectiveness Endpoint Components

- REFLECT Phase II Study enrollment was stopped early
- FDA conducted tipping point analyses to evaluate potential impact of early stopping of study enrollment on the primary effectiveness endpoint components
- Unlikely for TriGUARD 3 to be better than control under full enrollment regarding 30-day death/stroke, NIHSS worsening and total lesion volume

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REFLECT Phase II Study Statistical Summary

- The primary safety endpoint was met
- The primary effectiveness endpoint was not met
  - Win ratio <1, numerically favored Control group
- Poolability of Phase I and Phase II Control groups questionable
- Tipping point analyses: Unlikely for TriGUARD 3 to be better than control under full enrollment regarding 30-day death/stroke, NIHSS worsening and total lesion volume

Study success criteria not met

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Clinical Data Review

Donna Buckley, M.D., M.S.
Interventional Radiologist/Medical Officer
CDRH/OPEQ/OCVD/PIDT

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Clinical Experience

REFLECT PHASE II PIVOTAL IDE STUDY →

Includes Pooled Control Data from Phases I and II

Study	Description	Patient Enrollment
REFLECT (US Pivotal Study NCT02536196)		
REFLECT Phase I TriGUARD HDH 2016/17	Pivotal 2:1 randomization (TriGUARD HDH: unprotected TAVR) 26 Sites: 20 US, 6 EU	N = 445 planned; 258 actual
REFLECT Phase II TriGUARD 3 2018/19	Pivotal 2:1 randomization (TG3: unprotected TAVR) 18 US sites	N = 275 planned; 220 actual
Real World Evidence		
RWE: Netherlands Heart Registry TriGUARD 3 2020	Single-arm physician-initiated registry Single Center (Utrecht, NL) Includes the modified crimper to aid device positioning	50 consecutive cases

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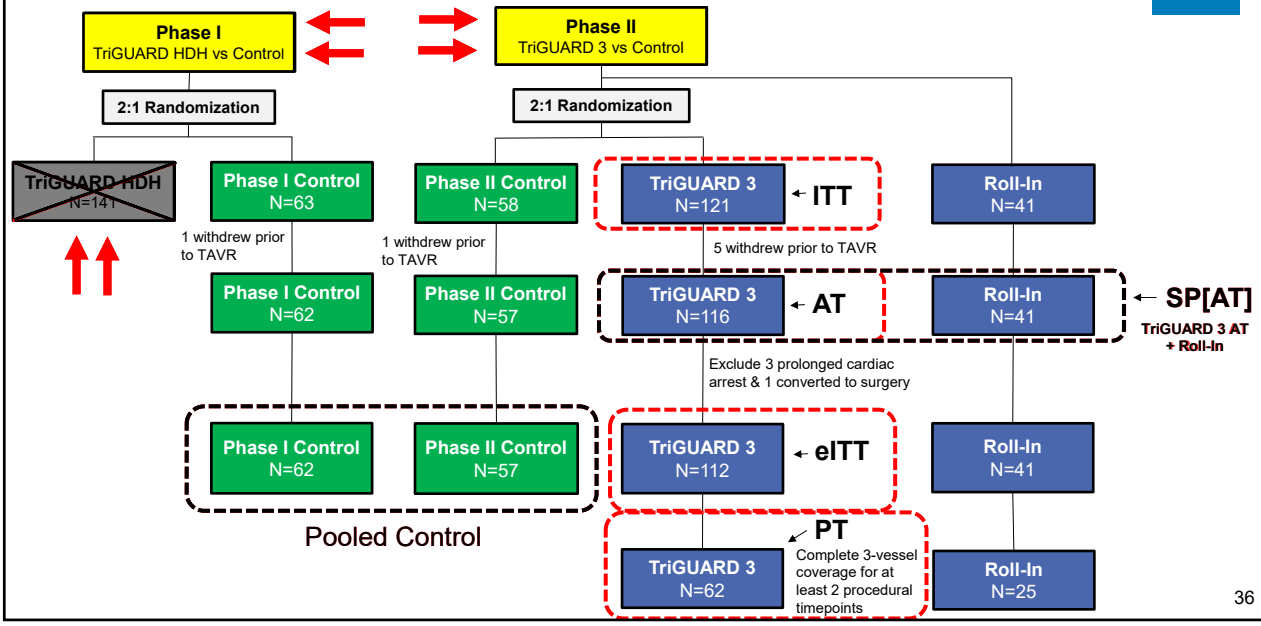
Study & Population Definitions



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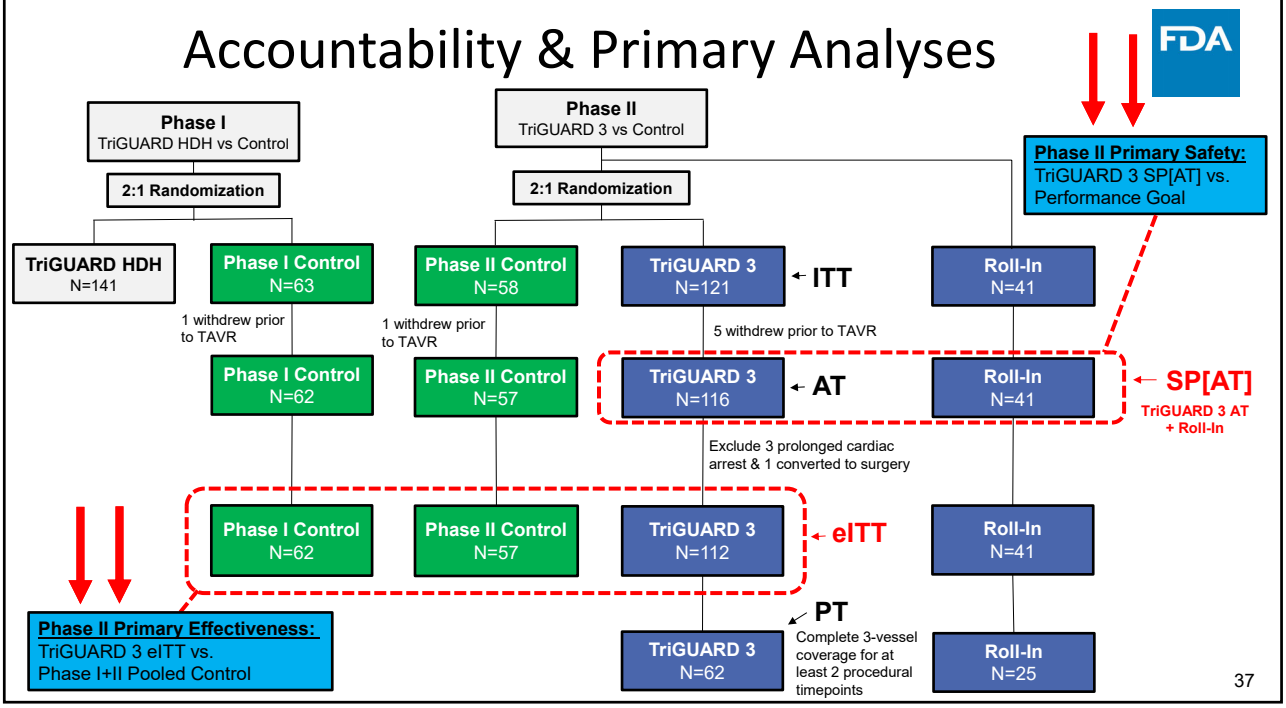
Accountability & Primary Analyses



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Demographics & Baseline Characteristics

FDA

Subject Characteristics eITT Population	TriGUARD 3 *N=112*	Pooled Control *N=119*
Age (years)		
Mean ± SD (n)	79.71 ± 7.96 (112)	79.88 ± 7.84 (119)
Median	80 (55, 98)	81 (56, 94)
Male gender	55.4% (62/112)	64.7% (77/119)
Hispanic or Latino Ethnicity	5.4% (6/112)	4.2% (5/119)
Smoking/Tobacco Usage		
Current within last year	1.8% (2/112)	7.6% (9/119)
Ex-Smoker	40.2% (45/112)	43.7% (52/119)
Never	58.0% (65/112)	48.7% (58/119)
Diabetes Mellitus (DM)	34.8% (39/112)	35.3% (42/119)
Insulin Dependent (IDDM)	15.8% (6/38)	40.0% (16/40)
Diet-controlled	44.7% (17/38)	29.4% (10/34)
Oral hypoglycemic controlled	76.9% (30/39)	57.9% (22/38)
History of Hypertension	93.7% (104/111)	89.9% (107/119)
History of Hyperlipidemia	83.0% (93/112)	79.7% (94/118)
History of Peripheral Vascular Disease	13.5% (15/111)	16.5% (19/115)

Subject Characteristics eITT Population	TriGUARD 3 *N=112*	Pooled Control *N=119*
History of aortic disease (aneurysm)	1.8% (2/112)	0.8% (1/119)
History of treatment/ repair	0.0% (0/2)	0.0% (0/1)
Carotid artery disease	17.6% (19/108)	16.7% (19/114)
Prior cerebral vascular attack (CVA)	10.7% (12/112)	5.1% (6/117)
Prior transient ischemic attack (TIA)	8.3% (9/109)	5.1% (6/117)
Prior CVA or TIA	17.9% (20/112)	8.5% (10/117)
History of anemia requiring transfusion	6.5% (7/107)	4.5% (5/112)
History of renal disease	20.5% (23/112)	23.7% (28/118)
LVEF	96.4% (108/112)	95.8% (114/119)
History of CHF	56.3% (63/112)	47.9% (56/117)
History of atrial fibrillation/atrial flutter	28.6% (32/112)	28.0% (33/118)
History or presence of intracardiac mass, thrombus, or vegetation	0.9% (1/112)	0.0% (0/119)
History of prior coronary artery bypass graft(s) (CABG)	18.8% (21/112)	17.6% (21/119)
History of prior percutaneous coronary intervention (PCI)	32.1% (36/112)	28.2% (33/117)
Chronic Lung disease/ COPD	15.2% (17/112)	19.1% (22/115)
In home Oxygen Use	3.6% (4/112)	2.6% (3/117)
Severe Pulmonary HTN	6.3% (7/112)	3.4% (4/117)

High frequency of co-morbidities, representative of typical patients undergoing TAVR

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Primary Safety Endpoint

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Primary Safety Endpoint

Phase II Primary Safety Endpoint SP[AT] Population	TriGUARD 3 *N=157*	Upper 95% CI
Combined Safety Endpoint within 30 Days	15.9% (25/157)	21.3%
All-Cause Death	2.5% (4/157)	
Stroke (Disabling and Non-Disabling)	8.3% (13/157)	
Life-Threatening or Disabling Bleeding	5.7% (9/157)	
Acute Kidney Injury (Stage 2/3)	2.5% (4/157)	
Coronary Artery Obstruction Requiring Intervention	0.6% (1/157)	
Major Vascular Complication	7.0% (11/157)	
TG3 Access Site-Related	1.9% (3/157)	
TAVR or Other Access Site-Related	4.5% (7/157)	
Secondary Access Site-Related	0.0 (0/157)	
Aortic Vascular Injury	1.3% (2/157)	
Valve Related Dysfunction Requiring Intervention	0.0% (0/157)	

SAFETY – PG COMPARISON (SP[AT] population)

157 (116 RCT; 41 RI)

Observed rate = 15.9%
95% UCL = 21.3%; <PG of 34.4%

SAFETY ENDPOINT MET

Individual event types:
- Stroke 8.3%
- Major vascular complication 7.0%
- Major bleeding 5.7%

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Additional Safety Considerations

Descriptive Safety Endpoint Evaluation

	TriGUARD 3			Phase II Control	Phase I Control	Pooled Control
	RI *N=41*	AT *N=116*	SP(AT) *N=157*	AT *N=57*	AT *N=59*	Phase I + II *N=116*
Combined Safety Endpoint within 30 Days	2.4% (1/41)	20.7% (24/116)	15.9% (25/157)	7.0% (4/57)	8.5% (5/59)	7.8% (9/116)
All-Cause Death	0	3.4% (4/116)	2.5% (4/157)	1.8% (1/57)	0	0.9% (1/116)
Stroke (Disabling and Non-Disabling)	0	11.2% (13/116)	8.3% (13/157)	5.3% (3/57)	6.8% (4/59)	6.0% (7/116)
Life-Threatening or Disabling Bleeding	2.4% (1/41)	6.9% (8/116)	5.7% (9/157)	0	0	0
Acute Kidney Injury (Stage 2/3)	0	3.4% (4/116)	2.5% (4/157)	0	0	0
Coronary Artery Obstruction Requiring Intervention	0	0.9% (1/116)	0.6% (1/157)	0	0	0
Major Vascular Complication	2.4% (1/41)	8.6% (10/116)	7.0% (11/157)	0	1.7% (1/59)	0.9% (1/116)
TriGUARD Access Site-Related	2.4% (1/41)	1.7% (2/116)	1.9% (3/157)	0	0	0
TAVR or Other Access Site-Related	0	6.0% (7/116)	4.5% (7/157)	0	0	0
Secondary Access Site-Related	0	0	0	0	0	0
Aortic Vascular Injury	0	1.7% (2/116)	1.3% (2/157)	0	1.7% (1/59)	0.9% (1/116)
Valve Related Dysfunction Requiring Intervention	0	0	0	0	0	0

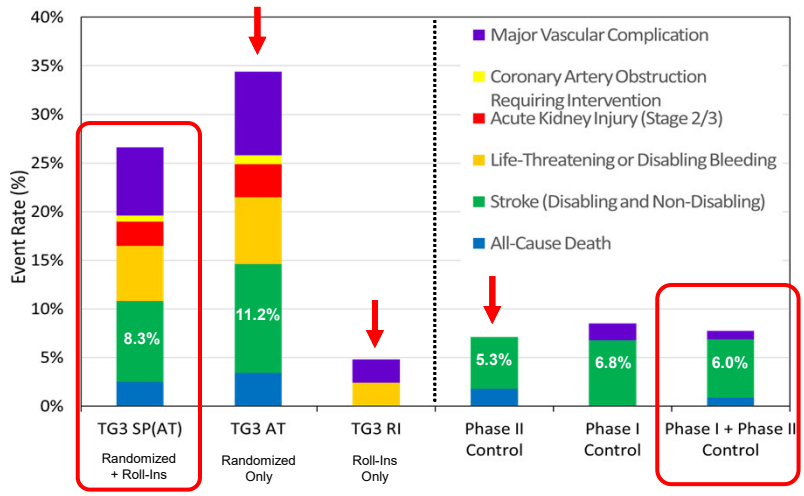
PRIMARY SAFETY ANALYSIS

No statistical analysis planned or performed between TriGUARD 3 and Control

Descriptive observations only

- Roll-in patients had a numerically lower observed complication rate compared to the randomized cohort
- Phase I Control had a slightly numerically higher event rate than the Phase II control
- Individual event rates numerically higher for Phase II randomized cohort - TriGUARD 3 compared to Phase II Control

Descriptive Safety Endpoint Evaluation



PRIMARY SAFETY ANALYSIS POPULATION

No statistical analysis planned or performed between TriGUARD 3 and Control

Descriptive observations only

- Roll-in patients had a lower observed complication rate compared to the randomized cohort
- Phase I Control had a slightly higher event rate than the Phase II control
- Cumulative event rates numerically higher for Phase II randomized cohort - TriGUARD 3 compared to Phase II Control

*Note: some patients may have more than one event.

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Stroke Timing

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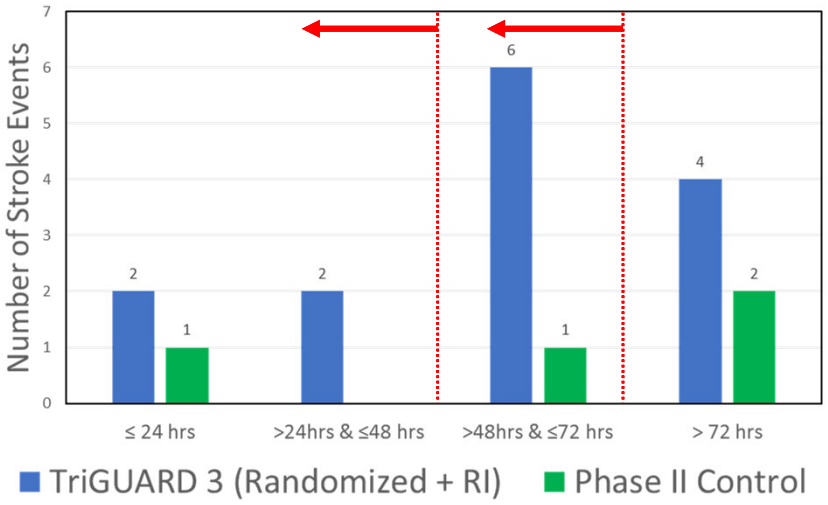
Stroke Timing



TriGUARD 3
- 14 strokes in 13 patients
- Combined randomized and roll-in rate 8.3%

Control
- 4 strokes in 3 patients
- Phase II Control group stroke rate 5.3%

No signal of stroke reduction observed in TriGUARD 3 subjects

*raw numbers should not be compared given differential randomization allocation

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Vascular Complications

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Vascular Complications

	TriGUARD 3			Phase II Control	Phase I Control	Pooled Control
	RI *N=41*	AT *N=116*	SP(AT) *N=157*	AT *N=57*	AT *N=59*	Phase I + II *N=116*
Combined Safety Endpoint within 30 Days	2.4% (1/41)	20.7% (24/116)	15.9% (25/157)	7.0% (4/57)	8.5% (5/59)	7.8% (9/116)
Major Vascular Complication	2.4% (1/41)	8.6% (10/116)	7.0% (11/157)	0	1.7% (1/59)	0.9% (1/116)
TriGUARD Access Site-Related	2.4% (1/41)	1.7% (2/116)	1.9% (3/157)	0	0	0
TAVR or Other Access Site-Related	0	6.0% (7/116)	4.5% (7/157)	0	0	0
Secondary Access Site-Related	0	0	0	0	0	0
Aortic Vascular Injury	0	1.7% (2/116)	1.3% (2/157)	0	1.7% (1/59)	0.9% (1/116)

Panel will be asked to comment on the access site complication risk associated with TriGUARD 3 device use

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Device-Related Events

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TriGUARD Device/Procedure-Related Events

	Pre-Specified Primary Safety Endpoint	Primary Safety Endpoint CEC Adjudication		
		Not related to TG3	Possibly Related to TG3	Related to TG3
Combined Safety Endpoint within 30 Days	15.9% (25/157)	16, 10.2%	10, 6.4%	2, 1.3%
All-Cause Death	2.5% (4/157)	4, 2.5%	--	--
Stroke (Disabling and Non-Disabling)	8.3% (13/157)	5, 3.2%	9, 5.7%	--
Life-Threatening or Disabling Bleeding	5.7% (9/157)	8, 5.1%	1, 0.6%	--
Acute Kidney Injury (Stage 2/3)	2.5% (4/157)	4, 2.5%	--	--
Coronary Artery Obstruction Requiring Intervention	0.6% (1/157)	1, 0.6%	--	--
Major Vascular Complication	7.0% (11/157)	8, 5.1%	1, 0.6%	2, 1.3%
TG3 Access Site-Related	1.9% (3/157)	--	1, 0.6%	2, 1.3%
TAVR or Other Access Site-Related	4.5% (7/157)	7, 4.5%	--	--
Secondary Access Site-Related	0.0% (0/157)	--	--	--
Aortic Vascular Injury	1.3% (2/157)	2, 1.3%	--	--
Valve Related Dysfunction Requiring Intervention	0.0% (0/157)	--	--	--

Events Possibly or Definitely related to the TriGUARD 3 Device or Procedure

- 12 Safety Endpoint Events within 30d
- 9 Strokes
- 1 Life-Threatening Bleeding Event
- 3 TriGUARD 3 Access Site Related Major Vascular Complications

The Panel will be asked to comment on how relatedness should be considered when evaluating benefit and risk.

Primary Effectiveness Endpoint

Primary Effectiveness Endpoint

	TriGUARD 3 *N=112*	Pooled Control *N=119*	p-value
Primary Effectiveness Hierarchical Endpoint			**0.857**
Win-ratio	0.84	1.19	
Win-percentage	45.7%	54.3%	
All-cause mortality or any stroke at 30 days	9.8% (11/112)	6.7% (8/119)	
NIHSS worsening	14.1% (14/99)	7.6% (8/105)	
Cerebral ischemic lesions	85.0% (85/100)	84.9% (90/106)	
Total volume of cerebral Ischemic lesions (mm^3)			
Mean ± SD (n)	587.80 ± 1028.42 (100)	508.22 ± 1123.96 (106)	
Range (Min, Max)	(0.00, 5681.26)	(0.00, 8133.60)	
Median	215.39	188.09	
(Q1, Q3)	(68.13, 619.71)	(52.08, 453.12)	

EFFECTIVENESS – SUPERIORITY HYPOTHESIS (eITT population)

112 TG3 RCT versus 119 Pooled Control

p-value = 0.857

EFFECTIVNESS ENDPOINT WAS NOT MET

win % favored Control: 54.3%
numerically favored control:

- mortality/stroke 9.8% v 6.7%
- NIHSS worsening 14.1% v 7.6%
- mean lesion volume,587 v 508 mm^3

Similar % of patients with cerebral ischemic lesions, ~85% both groups

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Selected Secondary Endpoints

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Performance Endpoints:

1. Coverage – PT Population
2. Technical Success
3. Procedural Success
4. Device Interference

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Aortic Arch Vessel Coverage – PT Population


Complete Coverage


Complete Coverage

"Complete" coverage for at least <u>two</u> timepoints

- **Pre-TAVR**
- **During-TAVR**
- **Post-TAVR**

+


Complete Coverage

OR


Partial Coverage

OR


No Coverage

OR

Angio Missing or Uninterpretable

Any of the following at <u>one</u> timepoint

- **Complete Coverage**
- **Partial Coverage (1 or 2 vessels)**
- **No Coverage**
- **Missing or Uninterpretable Imaging**

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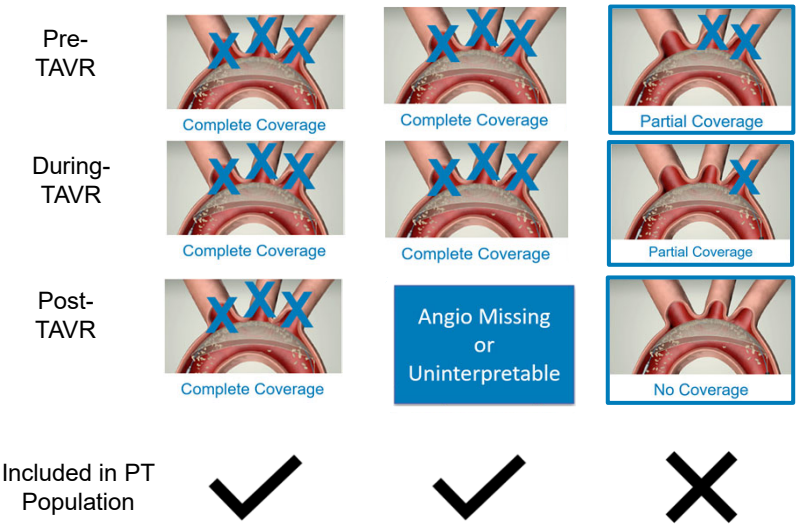
Coverage Examples – PT Population



PT Population = complete coverage for at least 2 procedural timepoints

- Excludes patients (& associated events) with incomplete aortic arch artery coverage
  - 24/112 (21.4%) partial coverage;
  - 20/112 (17.9%) no coverage; and
  - 6/112 (5.4%) uninterpretable angiograms
- Clinical significance of the PT population unclear

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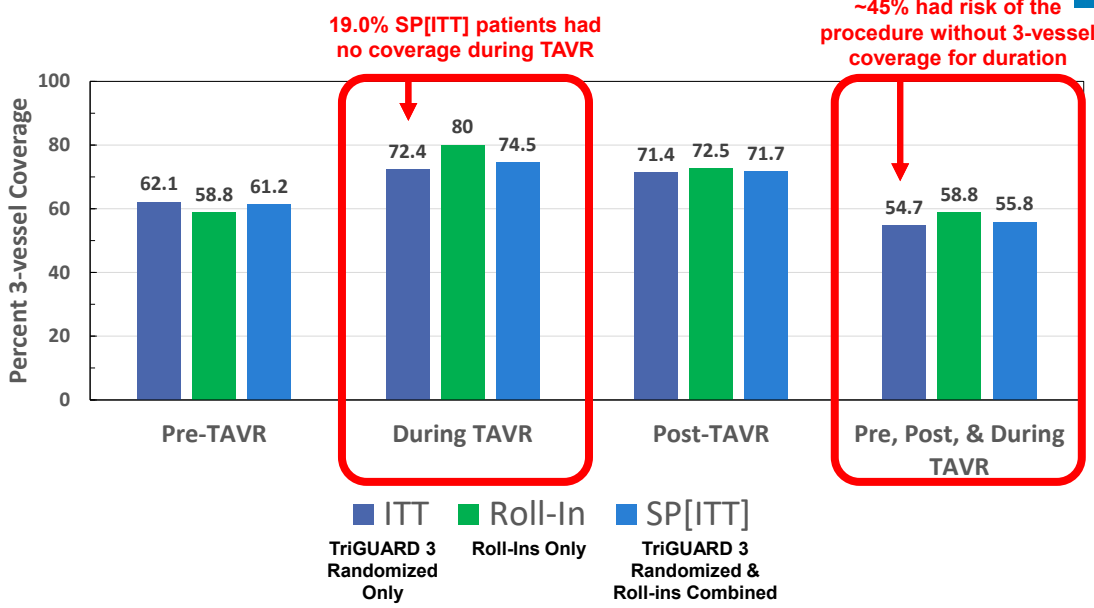
3-Vessel Coverage



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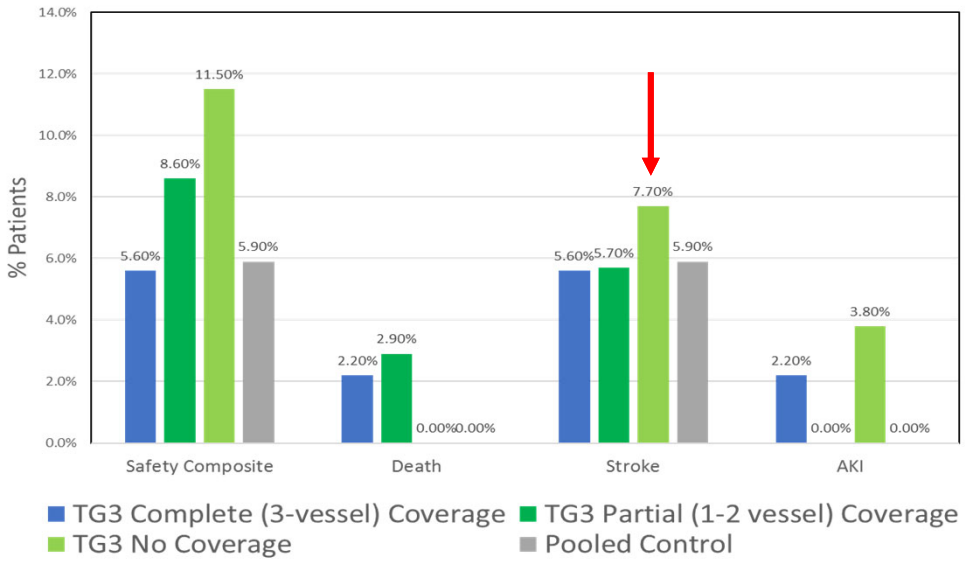
Coverage During 2 of 3 Timepoints



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Technical Success & Procedural Success

	ITT/AT	Roll-In	SP[ITT] ITT+RI
Technical Success	69.5% 73/105	75.0% 30/40	71.0% 103/14
Procedural Success	67.6% 71/105	75.0% 30/40	69.7% 101/145
Device Interference	8.6% 10/116	12.2% 5/41	9.6% 15/157

Additional Secondary Performance Endpoints

- Technical Success: ~70-75%
- Procedural Success: ~70-75%
- Device interference: ~10%

Performance Endpoint Summary

- Lower than expected 3-vessel coverage
  - 54.7% throughout the procedure
  - 19% no coverage during TAVR
- Higher than expected device interference: ~10%

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Imaging & Neurological Endpoints:

Imaging Endpoint Evaluation

Numerical comparison demonstrated TriGUARD 3 favored for:

1. Mean <u>per-patient average</u> single lesion volume as well as maximum of range
2. Mean and median single lesion volume as well as maximum of range
3. Maximum of range for <u>total</u> lesion volume

	TriGUARD 3			Pooled Control
	eITT *N 112*	PT *N=62*	Roll-in *N=41*	eITT *N 119*
Imaging Efficacy (at 1-7 days post-procedure)				
Presence of cerebral ischemic lesions	85.0% (85/100)	79.6% (43/54)	79.4% (27/34)	84.9% (90/106)
Number of cerebral ischemic lesions				
Mean ± SD (n)	6.0 ± 8.3 (100)	3.9 ± 4.8 (54)	5.1 ± 4.7 (34)	4.6 ± 5.9 (106)
Median (Q1, Q3)	3.0 (1.5, 7.0)	2.5 (1.0, 5.0)	5.0 (1.0, 8.0)	2.0 (1.0, 7.0)
Range (Min, Max)	(0, 51)	(0, 23)	(0, 19)	(0, 32)
Per-patient average single cerebral ischemic lesion volume, mm^3				
Mean ± SD (n)	72.8 ± 63.7 (100)	66.9 ± 63.7 (54)	66.1 ± 93.2 (34)	83.3 ± 112.9 (106)
Median (Q1, Q3)	59.9 (35.7, 90.5)	52.7 (25.0, 83.9)	55.1 (31.3, 66.7)	57.5 (34.0, 90.6)
Range (Min, Max)	(0.0, 341.4)	(0.0, 273.2)	(0, 527)	(0.0, 936.9)
Single cerebral ischemic lesion volume (mm^3)				
Mean ± SD (n)	74.9 ± 161.1 (785)	73.3 ± 135.1 (277)	61.9 ± 225.6 (247)	81.4 ± 328.3 (662)
Median (Q1, Q3)	31.3 (18.8, 71.4)	35.7 (18.8, 76.5)	28.4 (0.0, 62.5)	35.8 (0.0, 71.4)
Range (Min, Max)	(0.0, 2037.5)	(0.0, 1304.3)	(0, 3375)	(0.0, 6894.9)
Total volume of cerebral ischemic lesions (mm^3)				
Mean ± SD (n)	587.8 ± 1028.4 (100)	375.8 ± 617.7 (54)	449.5 ± 672.1 (34)	508.2 ± 1124.0 (106)
Median (Q1, Q3)	215.4 (68.1, 619.7)	145.7 (43.8, 444.4)	281.3 (31.6, 610.4)	188.1 (52.1, 453.1)
Range (Min, Max)	**(0.0, 5681.3)**	(0.0, 3519.0)	(0, 3688)	(0.0, 8133.6)

PRIMARY EFFECTIVENESS ANALYSIS POPULATION

Numerical comparison demonstrated Pooled Control favored for:

1. Mean and median number of cerebral ischemic lesions as well as maximum of range
2. Median <u>per-patient average</u> single lesion volume
3. Mean and median <u>total</u> lesion volume

Neurological Endpoint Evaluation

Numerical comparison demonstrated TriGUARD 3 favored for:

- None of the endpoints depicted

	TriGUARD 3			Pooled Control
	eITT *N=112*	PT *N=62*	Roll-in *N=41*	eITT *N=119*
Neurologic Efficacy				
NIHSS worsening				
2-5 days post-procedure/pre-discharge	14.1% (14/99)	13.8% (8/58)	8.3% (3/36)	7.6% (8/105)
30 days (±7 days) post-procedure	7.8% (6/77)	4.9% (2/41)	6.5% (2/31)	3.6% (3/84)
New neurologic impairment				
2-5 days post-procedure	10.0% (9/90)	7.8% (4/51)	3.4% (1/29)	6.4% (6/94)
30 days (±7 days) post-procedure	8.6% (6/70)	5.4% (2/37)	3.7% (1/27)	2.6% (2/78)

PRIMARY EFFECTIVENESS ANALYSIS POPULATION

Numerical comparison demonstrated Pooled Control favored for:

- NIHSS worsening at 2-5 days and 30 days post-procedure
- New neurological impairment at 2-5 days and 30 days post-procedure

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Additional Effectiveness Considerations

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Descriptive Effectiveness Endpoint Comparison

	TriGUARD 3			Control	
				Pooled (Phase I + II)	Phase II only
Endpoint	**eITT** *N=112*	**ITT** *N=121*	**PT** *N=62*	**eITT** *N=119*	**eITT** *N=57*
All-cause mortality or any stroke at 30 days	9.8% (11/112)	12.1% (14/116)	6.5% (4/62)	6.7% (8/119)	7.0% (4/57)
NIHSS worsening (2-5d)	14.1% (14/99)	14.0% (14/100)	13.8% (8/58)	7.6% (8/105)	6.1% (3/49)
Cerebral ischemic lesions (2-5d)	85.0% (85/100)	85.0% (85/100)	79.6% (43/54)	84.9% (90/106)	79.6% (39/49)
Total volume of cerebral ischemic lesions (mm^3)					
Mean ± SD (n)	587.80 ± 1028.42 (100)	587.80 ± 1028.42 (100)	375.80 ± 617.69 (54)	508.22 ± 1123.96 (106)	328.61 ± 496.29 (49)
Range (Min, Max)	(0.00, 5681.26)	(0.00, 5681.26)	(0.00, 3519.00)	(0.00, 8133.60)	(0.00, 2740.24)
Median	215.39	215.39	145.71	188.09	112.50
(Q1, Q3)	(68.13, 619.71)	(68.13, 619.71)	(43.75, 444.44)	(52.08, 453.12)	(26.95, 360.00)

PRIMARY EFFECTIVENESS ANALYSIS

No statistical analysis planned or performed between TriGUARD 3 and Control since primary effectiveness not met

Descriptive comparisons only

PT population
- 3-vessel coverage for at least 2 of 3 timepoints
- Limited to 55.4% (62/112) of eITT population with adequate positioning
- Panel will be asked if there is a signal for benefit of TriGUARD 3 over Control from these data

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Adjunctive Data – Netherlands Heart Registry

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Netherlands Heart Registry

50-patient, single-center, single arm registry to evaluate the safety and performance of the TriGUARD 3 in patients undergoing TAVR in real-world clinical practice

Measure	Stroke or TIA
Primary Safety Endpoint	0% (0/50)

Measure	Successful Deployment	Complete Coverage
Primary Effectiveness Endpoint	100% (50/50)	100% (50/50)

RWE Limitations

- External generalizability (only 1 clinical site and 3 operators) & limited outcome assessments
- Missing data
- Adverse event & neurological assessments
- Common Data Capture
- Data Collection Methods

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Comparison of REFLECT Phase II with SENTINEL Trial Results

When considering hierarchy of valid clinical evidence, FDA believes that the most important comparison is between treatment and control arms within the same randomized study. Comparisons of treatment arms between different studies is considered less robust.

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SENTINEL Study - Safety

Safety Events	ITT Safety Cohort (Safety + Test Groups) *N = 234*	AT Test Group *N 111*	ITT Test Group *N = 117*	Control Group *N 111*
Any MACCE	**7.3% (17/234) (4.3%, 11.4%)**	**6.4% (7/110) (2.6%,12.7%)**	**6.0% (7/117) (2.4%,11.9%)**	**9.9% (11/111) (5.1%, 17.0%)**
Death	1.3% (3/234) (0.3%, 3.7%)	0.9% (1/110) (0.0%, 5.0%)	0.9% (1/117) (0.0%, 4.7%)	1.8% (2/111) (0.2%, 6.4%)
Stroke	5.6% (13/231) (3.0%, 9.4%)	4.6% (5/109) (1.5%, 10.4%)	4.3% (5/116) (1.4%, 9.8%)	9.1% (10/110) (4.4%, 16.1%)
Disabling Stroke	0.9% (2/231) (0.1%, 3.1%)	0% (0.0%,3.3%)	0% (0.0%,3.1%)	0.9% (1/109) (0.0%, 5.0%)
Non-disabling Stroke	4.8% (11/231) (2.4%, 8.4%)	4.6% (5/109) (1.5%,10.4%)	4.3% (5/116) (1.4%,9.8%)	8.2% (9/110) (3.8%, 15.0%)
AKI (Class 3)	0.4% (1/231) (0.0%, 2.4%)	0.9% (1/109) (0.0%,5.0%)	0.9% (1/116) (0.0%,4.7%)	0% (0.0%, 3.3%)

SAFETY – PG COMPARISON
(ITT & ITT w/imputation population)

234 (Safety and Test groups)

Observed rate = 7.3%
95% UCL 10.7% < PG of 18.3%

SAFETY ENDPOINT MET

Individual events numerically lower for Sentinel compared to Control for:
- Death: 1.3% v 1.8%
- Stroke: 5.6% v 9.1%

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TriGUARD 3 REFLECT vs SENTINEL – Safety Endpoint Definition

30 Day Composite Primary Safety Endpoint	Primary Analysis Population	Subjects with Events	95% UCL	PG	P-value
REFLECT Phase II Study					
• All death • All stroke • Life-threatening or disabling bleeding • Stage 2/3 AKI • Coronary artery obstruction requiring reintervention • Major vascular complication • Valve related dysfunction requiring reintervention	SP[AT]	25/157 (15.9%)	21.3%	34.4%	< 0.0001
	AT	24/116 (20.7%)	27.5%	34.4%	0.001
SENTINEL Study					
• All death • All stroke • Stage 3 AKI	ITT, with imputation	18/244 (7.4%)	10.7%	18.3%	< 0.0001
	ITT	17/234 (7.3%)	10.7%	18.3%	< 0.0001

- Different primary safety endpoint definition
- Lower PG threshold
- ITT population (SENTINEL); AT population (REFLECT)

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SENTINEL – Safety Results Compared to REFLECT

REFLECT Phase II Study		
Safety Endpoints AT Population	**TriGUARD 3**	**Control**
All-Cause Death	3.4% (4/116)	1.8% (1/57)
Stroke (Disabling and Non-Disabling)	11.2% (13/116)	5.3% (3/57)
Life-Threatening or Disabling Bleeding	6.9% (8/116)	0
Acute Kidney Injury (Stage 3)	2.6% (3/116)	0
Coronary Artery Obstruction Requiring Intervention	0.9% (1/116)	0
Major Vascular Complication	8.6% (10/116)	0
TG3 Access Site-Related	1.7% (2/116)	0
TAVR or Other Access Site-Related	6% (7/116)	0
Secondary Access Site-Related	0	0
Aortic Vascular Injury	1.7% (2/116)	0
Valve Related Dysfunction Requiring Intervention	0.0% (0/157)	0

TriGUARD 3 component rates numerically favored Control

SENTINEL Study		
Safety Endpoints ITT Population	**Sentinel**	**Control**
All-Cause Death	1.3% (3/234)	1.8% (2/111)
Stroke (Disabling and Non-Disabling)	5.6% (13/231)	9.1% (10/110)
Life-Threatening or Disabling Bleeding	N/A	N/A
Acute Kidney Injury	0.4% (1/231)	0
Coronary Artery Obstruction Requiring Intervention	N/A	N/A
Major Vascular Complication	8.6% (21/244)	5.9% (7/119)
Sentinel Access Site-Related	0.4% (1/244)	N/A
TAVR or Other Access Site-Related	N/A	N/A
Secondary Access Site-Related	N/A	N/A
Aortic Vascular Injury	N/A	N/A
Valve Related Dysfunction Requiring Intervention	N/A	N/A

SENTINEL component rates numerically favored SENTINEL except for AKI and Vascular Complications

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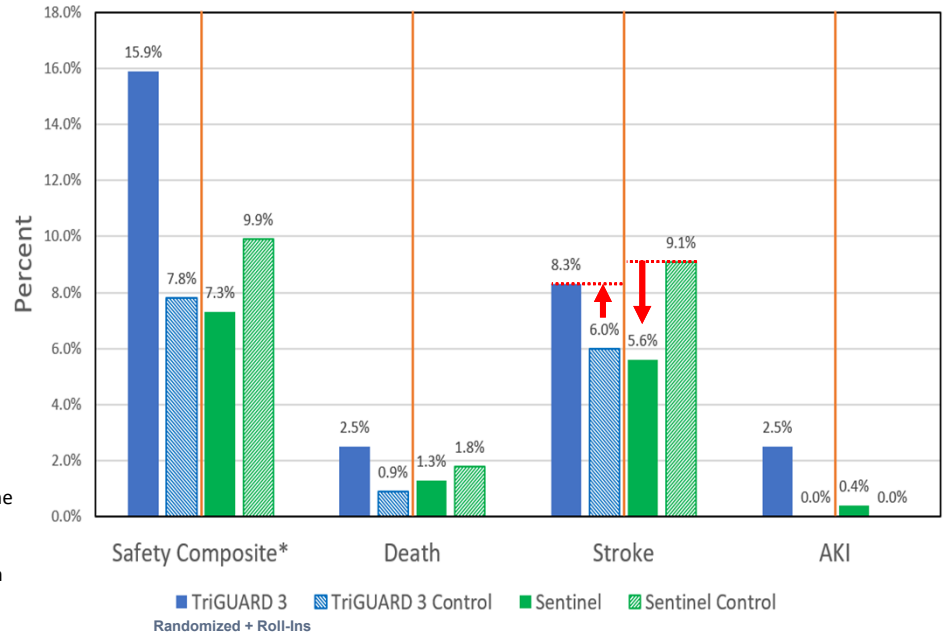
TriGUARD 3 REFLECT vs. SENTINEL - Safety



*Note: The components of the safety composite endpoint are not identical between the REFLECT and SENTINEL trials.

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SENTINEL Study - Effectiveness

Total New Lesion Volume (DW MRI at 2-7 days post-procedure compared to Baseline DW-MRI)				
Population	**Test Group (mm^3)**	**Control Group (mm^3)**	**Observed Treatment Difference (Test - Control)**	**p-value**
Protected Territories				
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
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	-15.8	0.8076

EFFECTIVENESS – SUPERIORITY HYPOTHESIS
(ITT w/ imputation population)

121 Sentinel RCT versus 119 Control

p-value = 0.2354

EFFECTIVNESS ENDPOINT NOT MET

Effectiveness also not met for "all territories"

Numeric results favored Sentinel in:
- Protected territories
- All territories

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TriGUARD 3 REFLECT vs. SENTINEL
Effectiveness Endpoint Definition

Primary Effectiveness Endpoint	Primary Analysis Population
REFLECT Phase II study	
Hierarchical composite determined by pair-wise comparison between all subjects according to the following pre-specified hierarchy of adverse outcomes: • All-cause mortality and/or any stroke (fatal and non-fatal, disabling or non-disabling) [evaluated at 30 days] • NIHSS worsening (increase from baseline) [evaluated at 2 to 5 days post-procedure] • Freedom from any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure • Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure.	eITT
SENTINEL Study	
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 DW-MRI. • Criterion 1: Hypothesis-driven superiority of test vs. control intended 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 2: intended to demonstrate an observed reduction of at least 30% in median new lesion volume for patients with protection with the Sentinel System compared to those without protection To successfully meet the primary effectiveness endpoint the Sentinel device needed to fulfill both criteria.	ITT, with imputation ITT

- Different primary effectiveness endpoint definition
- ITT w/imputation population (SENTINEL); eITT population (REFLECT)
- SENTINEL: 42.2% reduction in median new lesion volume exceeded the 30% reduction goal

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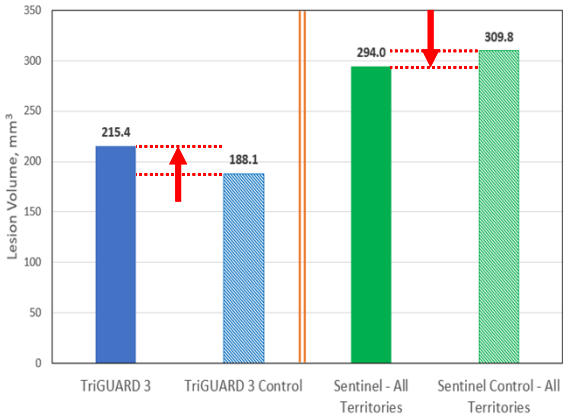
TriGUARD 3 REFLECT vs. SENTINEL - Effectiveness

Population	Test Group (mm^3) median (Q1, Q3) n min, max	Control Group (mm^3) median (Q1, Q3) n min, max	Observed Treatment Difference (Test - Control)
REFLECT Phase II			
eITT	215.39 (68.13, 619.71) n=100 0 min, 5681.26 max	188.09 (52.08, 453.12) n=106 0 min, 8133.60 max	27.3
SENTINEL All Territories analysis			
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



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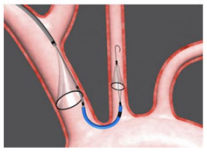
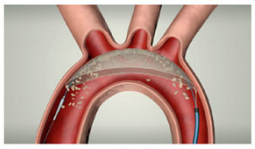
TriGUARD 3 REFLECT vs. SENTINEL - Positioning





	Sentinel	TriGUARD 3
Angiographic evaluation of coverage/positioning	No	Yes (before, during, after TAVR)
3-vessel coverage	Never since left subclavian (and left vertebral artery) not covered; device *intended to* cover carotids bilaterally and right vertebral artery	54.7% throughout procedure
Debris capture	99% from histologic core lab	Intended to primarily deflect; therefore, debris not systematically assessed

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TriGUARD 3 REFLECT Clinical Conclusions - Safety

TriGUARD 3 met the PG for the 30-day composite primary safety endpoint

Observed rate = 15.9%, 95% CI UL 21.3%, <PG of 34.4%

- Key event rates:
  - Stroke 8.3%
  - Major vascular complication 7.0%
  - Major bleeding 5.7%
- Individual component rates numerically higher for TriGUARD 3 Phase II randomized cohort compared to Control
- Roll-in patients - numerically lower observed complication rate compared to the randomized cohort

TriGUARD 3 REFLECT Clinical Conclusions - Safety

- Stroke
  - *Numerical qualitative difference* in strokes for various comparison groups

	TG3 SP[AT] (Randomized + Roll-Ins) Pooled Control	TG3 SP[AT] (Randomized + Roll-Ins) Phase II Control	TG3 AT (Randomized Only) Pooled Control	TG3 AT (Randomized Only) Phase II Control
Observed Stroke Rate	**8.3%-6.0%**	8.3%-5.3%	11.2%-6.0%	11.2%-5.3%
Difference	**2.3%**	3.0%	5.2%	5.9%

- Vascular complications
  - Known/probable risks of 8F arteriotomy
  - 3 major vascular complications were adjudicated as related (2) or possibly related (1) to the TriGUARD 3 device or procedure

TriGUARD 3 REFLECT Clinical Conclusions - Effectiveness

- Primary effectiveness FS endpoint was not met (p = 0.857)
  - Win ratio favored Control: 1.19 (Control) and 0.84 (TriGUARD 3)
  - Win percentage favored Control: 54.3% (Control) and 45.7% (TriGUARD 3)
- Event rates numerically favored Control
  - Mortality/stroke 9.8% vs. 6.7%
  - NIHSS worsening 14.1% vs. 7.6%
  - Mean lesion volume 587 vs. 508 mm3
- Same % in each group had cerebral lesions, ~85%

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TriGUARD 3 REFLECT Clinical Conclusions - Effectiveness

- Performance Endpoints
  - Complete 3-vessel coverage 54.7% throughout the procedure, 19% no coverage during TAVR
  - Device interference ~10%
- Neurological Endpoints (NIHSS worsening, new neurological impairment)
  - Favored Control
- Imaging Endpoints
  - Variably favored TriGUARD 3 or Control Group

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Other TriGUARD 3 REFLECT Clinical Considerations

- Poolability of Phase I and II control groups
- The importance of device-relatedness in assessing safety events in randomized trials
- Impact of baseline characteristics in study interpretation
- The added value and important limitations of real-world data from the Netherlands Registry

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Substantial Equivalence

- In their individual randomized trials, both devices met safety PGs and neither demonstrated superiority for effectiveness vs. respective Control
- REFLECT Phase II: Individual events were numerically higher for TriGUARD 3 compared to its Control for:
  - Death: 2.5% (TriGUARD 3) v 0.9% (Pooled Control)
  - Stroke: 11.2% (TriGUARD 3) v 6.0% (Pooled Control)
- SENTINEL: Individual events were numerically lower for Sentinel compared to its Control for:
  - Death: 1.3% (Sentinel) v 1.8% (Control)
  - Stroke: 5.6% (Sentinel) v 9.1% (Control)

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Substantial Equivalence

- REFLECT Phase II: Effectiveness composite component rates numerically favored Control over TriGUARD 3 for all components
- DWMRI defects not significantly different for either EPD vs. its respective Control
  - Sentinel showed numerically lower rates compared to its Control
  - TriGUARD 3 showed numerical higher rates compared to its Control

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FDA Presentations

- CDR Sadaf Toor
  - Introduction and Clinical Background
  - Device Description and Proposed Indications for Use
  - Regulatory History
- Dr. Yu Zhao
  - REFLECT Clinical Trial Design and Statistical Considerations
- Dr. Donna Buckley
  - REFLECT Results and Clinical Considerations
- CDR Sadaf Toor
  - Conclusions

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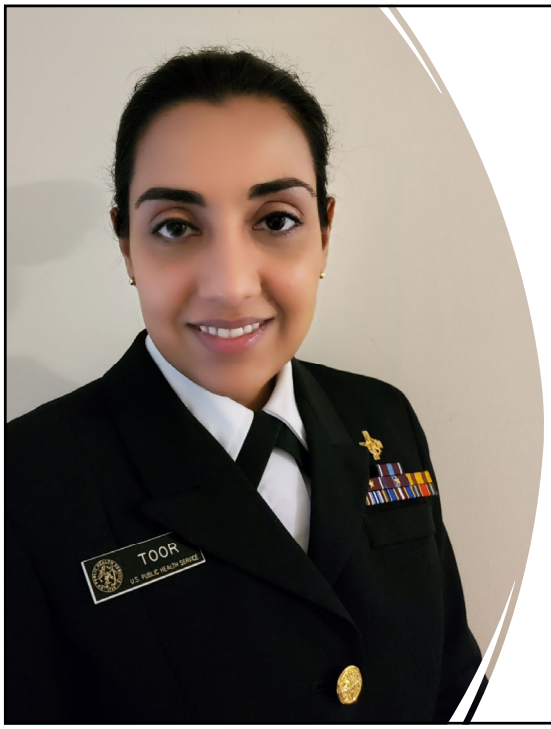

Conclusions

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CDRH/OPEQ/OCVD/PIDT

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Summary of REFLECT study

- REFLECT: a prospective, multicenter, 2:1 randomized, controlled trial, TriGUARD 3 used during TAVR (test group) vs. standard unprotected TAVR (control group)
  - Phase II enrolled 179 of the planned 225 randomized subjects
- REFLECT Phase II results:
  - TriGUARD 3 met the pre-specified performance goal for the primary safety endpoint at 30 days
  - The primary effectiveness endpoint was not met

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REFLECT Phase II FDA Perspectives

- Components of the primary safety and primary effectiveness endpoints favored the control group vs. the TriGUARD 3 group
- Numerically higher stroke rate observed in the TriGUARD 3 group compared to the control noteworthy given the primary aim of this device to prevent ischemic cerebral injury by reducing embolic material from entering the cerebral circulation
- Unclear if the added risks of AKI and vascular complications are offset by a cerebral circulation protection benefit

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Device Positioning and Real-World Evidence

- Achieving optimal positioning of the TriGUARD 3 device appears to be challenging
  - Coverage of all 3 aortic arch vessels for the entire TAVR procedure was confirmed in 54.7% of cases
- Commercial use of the TriGUARD 3 device with modified crimper at a single center in the Netherlands (N=50)
  - There are limitations with the robustness and generalizability of these data regarding stable device positioning resulting in full aortic arch vessel coverage throughout the TAVR procedure

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Conclusions

- The data presented in the subject 510(k) submission are intended to support substantial equivalence of the TriGUARD 3 device to the predicate Sentinel Cerebral Protection System.
- The Panel will be asked to assess the significance of the clinical results presented for TriGUARD 3 vs. its control in the REFLECT Phase II study as compared to Sentinel vs. its control in the SENTINEL study and comment on the benefit-to-risk profile of the TriGUARD 3 used during TAVR procedures.

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Thank you!

Questions?

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