FDA Executive Summary

Prepared for the August 3, 2021 Meeting of the
Circulatory System Devices Panel
to be held Virtually

Premarket Notification [510(k)] for
Keystone Heart, Ltd
TriGUARD 3 Cerebral Embolic Protection Device

Office of Cardiovascular Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
Food and Drug Administration

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1 Introduction

This is FDA's Executive Summary of the premarket notification submitted by Keystone Heart, Ltd (Keystone or "the sponsor") for the TriGUARD™ 3 Cerebral Embolic Protection Device (hereinafter referred to as TriGUARD 3 or TG3). Keystone is requesting clearance for their device in order to market the TriGUARD 3 for use in patients undergoing transcatheter aortic valve replacement (TAVR). The sponsor proposes an indication of "designed to minimize the risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during trans-catheter aortic valve replacement (TAVR)." This Advisory Committee meeting is being held for the Panel to discuss and make recommendations regarding the clinical data submitted to support substantial equivalence of the TriGUARD 3 device to the predicate Boston Scientific Sentinel™ Cerebral Protection System (hereinafter referred to as Sentinel). This document includes a brief clinical review of cerebral Embolic Protection Devices (EPDs), a description of the TriGUARD 3 device, regulatory history associated with this device, and the clinical data provided in the 510(k) application.

2 Background

Transcatheter Aortic Valve Replacement (TAVR) is an important therapy for the treatment of severe symptomatic aortic stenosis. Despite recent advances in TAVR technology, periprocedural stroke remains a complication of TAVR procedures and is associated with increased morbidity and mortality [3]. In TAVR, most periprocedural strokes likely occur secondary to embolism of calcific debris from the aortic valve and atheroembolism from the ascending aorta and arch[2]. Periprocedural stroke occurs in approximately 2%-6% of patients undergoing TAVR procedures [4]. Cerebral EPDs are designed to capture and/or deflect plaque debris during TAVR procedures and have a potential role in reducing stroke incidence and ischemic brain injury.

The Boston Scientific Sentinel™ Cerebral Protection System is currently the only commercially available cerebral EPD in the United States and is indicated to capture and remove thrombus/debris during TAVR procedures. The Sentinel device is a dual-filter system that traps embolic debris within the right brachiocephalic and left common carotid arteries, protecting their vascular territories.

The TriGUARD 3 device is designed to be positioned in the aortic arch during TAVR procedures to protect the brachiocephalic, left common carotid, and left subclavian arteries by deflecting debris downstream, away from the cerebral circulation. If cleared, the TriGUARD 3 device would be the second commercially available cerebral EPD in the United States. The Panel will be asked whether sufficient clinical evidence has been provided for the TriGUARD 3 device to support a determination of substantial equivalence to the Sentinel device for the proposed indications for use.

3 Regulatory Background

Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I (low risk devices) to Class III (high risk device), and device classification regulation defines the regulatory requirements for a general device type. Most Class II devices require Premarket Notification 510(k). For a 510(k) device to receive clearance for marketing/commercialization, it should demonstrate substantial equivalence to its predicate device, meaning it should demonstrate that it is as safe and as effective as another legally marketed device with the same intended use. All 510(k) devices must also meet the general controls of the FD&C Act, and in some cases, additional special controls are established for specific device types. Cerebral 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).

The first cerebral EPD to request marketing in the United States was the Sentinel™ Cerebral Protection System. Sentinel was the first device of this type, and therefore was reviewed under the De Novo pathway.

Upon granting of the De Novo submission for the Sentinel device, FDA established Special Controls for devices used for embolic protection during transcatheter intracardiac procedures, as outlined in 21 CFR 870.1251. Special controls are regulatory requirements for Class II devices and can include non-clinical and clinical data requirements. In order to meet regulatory requirements to receive marketing clearance, a 510(k) submission should include sufficient information to (1) demonstrate substantial equivalence to a predicate device in terms of both safety and effectiveness and (2) demonstrate that all controls (general and any specific for that product type) are met.

In combination with the general controls of the FD&C Act, any device used for embolic protection during transcatheter intracardiac procedures is subject to the following special controls:

1. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   i. Simulated-use testing in a clinically relevant bench anatomic model to assess the following:
      A. Delivery, deployment, and retrieval, including quantifying deployment and retrieval forces, and procedural time
      B. Device compatibility and lack of interference with the transcatheter intracardiac procedure and device
   ii. Tensile strengths of joints and components, tip flexibility, torque strength, torque response and kink resistance
   iii. Flow characteristics
      A. The ability of the filter to not impede blood flow
      B. The amount of time the filter can be deployed in position and retrieved from its location without disrupting blood flow
   iv. Characterization and verification of all dimensions

2. Animal testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be assessed:

i. Delivery, deployment, and retrieval, including quantifying procedural time
ii. Device compatibility and lack of interference with the transcatheter intracardiac procedure and device
iii. Flow characteristics
    A. The ability of the filter to not impede blood flow
    B. The amount of time the filter can be deployed in position and retrieved from its location without disrupting blood flow
iv. Gross pathology and histopathology assessing vascular injury and downstream embolization

3. All patient contacting components of the device must be demonstrated to be biocompatible.

4. Performance data must demonstrate the sterility of the device components intended to be provided sterile.

5. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

6. Labeling for the device must include:
    i. Instructions for use;
    ii. Compatible transcatheter intracardiac procedure devices;
    iii. A detailed summary of the clinical testing conducted; and
    iv. A shelf life and storage conditions.

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.

FDA Comment 1: FDA will request that the Panel discuss whether the clinical data meet special controls 7iii (secure positioning and stability throughout the TAVR procedure) and 7iv (evaluation of all event rates) to support substantial equivalence of the TriGUARD 3 device to the Sentinel device.

4 Summary

If cleared, the TriGUARD 3 device would be the second commercially available cerebral EPD in the US.

The TriGUARD 3 Premarket Notification 510(k) request is based upon the results of the **R**andomized **E**valuation o**F** the TriGUARD HDH Cerebral Embolic Protection and the TriGUARD 3 Cerebral Embolic Protection Device to Reduce the Impact of Cerebral Embolic **LE**sions after Trans**C**atheter Aortic Valve Implan**T**ation (REFLECT) trial, which was a clinical

study conducted under IDE (b)(4) . The purpose of the REFLECT trial was to assess the safety and effectiveness of the TriGUARD HDH (the first generation device) and TriGUARD 3 embolic deflection devices in patients undergoing TAVR compared to a control group of patients undergoing TAVR without the use of an EPD(also referred to as unprotected TAVR).

The REFLECT study was initiated in October 2014, initially designed to assess the safety and effectiveness of the TriGUARD HDH when used during TAVR versus TAVR alone. The portion of the study using the TriGUARD HDH device was later termed "Phase I" of the REFLECT study. Phase I of the study was suspended at the recommendation of the study Data Monitoring Committee (DMC) after their review of unblinded data and modeling for conditional powering and potential outcomes. The study was later reinitiated with the next generation TriGUARD 3 device. This portion of the REFLECT study using the TriGUARD 3 device is referred to as "Phase II." As discussed in Section 7.1.4, Phase II of the study was also suspended at the recommendation of the DMC after discussion with the FDA. *The Panel is being asked to discuss and make recommendations regarding the clinical data presented for only the TriGUARD 3 device as it compares to the clinical performance data of the Sentinel™ Cerebral Protection System (predicate device).*

The sponsor is seeking marketing clearance for the TriGUARD 3 device only. The earlier version, TriGUARD HDH, is not a subject of this submission. For this reason, FDA will focus on the Phase II study. Phase I study results are included in Section 20 (Appendix I).

FDA Comment 2: The Panel will be asked to assess the clinical data from a perspective of substantial equivalence in comparison to the proposed predicate device. In addition, the Panel will be asked to assess whether the special controls for this device type have been met by the TriGUARD 3 device under the 510(k) regulatory framework.

The primary safety endpoint for Phase II of the REFLECT study was a composite of all-death, all-stroke, life-threatening or disabling bleeding, Stage 2/3 acute kidney injury (AKI), coronary artery obstruction requiring intervention, major vascular complications, and valve related dysfunction requiring repeat procedure at 30 days compared against a performance goal of 34.4%. The primary safety endpoint *was met*.

The primary effectiveness endpoint for Phase II of the REFLECT study was a hierarchical composite of all-cause mortality and/or stroke at 30 days, NIH Stroke Score (NIHSS) worsening evaluated between days 2-5 post-procedure, cerebral ischemic lesions detected by diffusion weighted magnetic resonance imaging (DW-MRI) evaluated between days 2-5 post-procedure, and the total volume of cerebral ischemic lesions detected by DW-MRI evaluated between days 2-5 post-procedure. The TriGUARD 3 group was compared to the control group for superiority testing. The primary effectiveness endpoint *was not met*.

This executive summary highlights the following key issues for which FDA requests Panel input:

Safety

- Although the primary safety endpoint met the prespecified performance goal, numerical rates of several important individual components of the safety composite were higher in the TriGUARD 3 group vs. the control group. Specifically, the stroke rate at 30 days for the randomized TriGUARD 3 group was 11.2% compared to 5.3% for the Phase II control group. The death rate at 30 days for the randomized TriGUARD 3 group was 3.4% compared to 1.8% for the Phase II control group. The Panel will be asked to provide input on TriGUARD 3 safety considering the primary safety composite endpoint results and individual components of the composite.

- Differences in baseline characteristics were observed between the TriGUARD 3 and control patient groups including prior stroke or TIA and insulin-dependent diabetes (IDDM). The Panel will be asked to provide their clinical interpretation of the impact of observed imbalances on study results.

- The sponsor asserts that CEC-adjudicated relatedness of adverse events to the device should also be considered to understand the risk attributable to the accessory device along with the prespecified primary safety endpoint that includes all events. Of note, the analyses used for the predicate device included all safety events. The Panel will be asked to provide input on clinical interpretation of device relatedness when considering adverse events.

- The sponsor asserts that outcomes associated with the TriGUARD 3 in Phase II of the REFLECT study versus outcomes associated with the Sentinel device in the SENTINEL study should be prioritized over the comparison of the TriGUARD 3 and the Sentinel devices versus their respective control groups. The Panel will be asked to provide input on the appropriateness and meaningfulness of comparing the two test groups (TriGUARD 3 and Sentinel) from the two different randomized controlled trials, and whether the data support substantial equivalence of the TriGUARD to the predicate in terms of safety.

- The TriGUARD 3 is introduced through an 8F access sheath located contralateral to TAVR device access. Although standard TAVR also commonly utilizes a contralateral sheath to accommodate pressure catheters, a smaller 6F sheath is typically employed for this use. The Panel will be asked to provide input on the clinical significance of an increased risk of vascular complications associated with an 8F puncture.

Effectiveness

- The prespecified primary effectiveness endpoint was not met. The sponsor presents analyses on secondary imaging endpoints including but not limited to per patient average single cerebral ischemic lesion (SCIL) volume and SCIL volume in the eITT group compared to the control. The Panel will be asked to provide input on the clinical interpretation of these analyses

- In some cases, the sponsor considers effectiveness analyses limited to a patient subgroup in whom device positioning was considered successful for the duration of the TAVR procedure (i.e., 3-vessel coverage during at least 2 of the 3 procedural time points, pre-, during, or post-TAVR). The Panel will be asked to provide input on the clinical relevance of these analyses as they pertain to the entire intended patient population, and whether these analyses support substantial equivalence to the predicate device.

Ability of the device to maintain stable positioning

- The TriGUARD 3 achieved 3-vessel coverage during at least 2 of the 3 procedural time points (pre-, during, or post-TAVR) in 59.3% (89/150) of randomized TriGUARD 3 and roll-in REFLECT Phase II subjects.

- The TriGUARD 3 achieved complete 3-vessel coverage for all 3 procedural timepoints in 54.7% (52/95) randomized TriGUARD 3 subjects, 58.8% (20/34) roll-in, and 55.8% (72/129) combined TriGUARD 3 and roll-in REFLECT Phase II subjects.

- The sponsor proposed device modifications intended to improve positioning and presented real-world clinical evidence to support whether the device can achieve and maintain stable positioning.

The Panel will be asked to provide their clinical interpretation of these data as they relate to stable positioning and the ability of the device to reduce the risk of stroke and cerebral injury.

Poolability of Phase I and II control groups

- The REFLECT study was designed to pool control subjects from Phase I and Phase II for the evaluation of the primary and secondary effectiveness endpoints if the two control groups were deemed poolable. However, the poolability criteria specified in the Statistical Analysis Plan (SAP) were not met. The Panel will be asked to provide input on Phase I and Phase II control group poolability and whether the pooled control group or the Phase II control group should be considered the primary comparator in assessing device effectiveness.

Substantial Equivalence and Special Controls

- The sponsor proposed the Boston Scientific Sentinel Cerebral Protection System (granted under De Novo submission DEN160043 on June 1, 2017) as the predicate device for determination of substantial equivalence under the 510(k) regulatory pathway.

The Panel will be asked to review the totality of the data and provide recommendations regarding whether the TriGUARD 3 has demonstrated substantial equivalence to the predicate Sentinel device with respect to both safety and effectiveness and whether TriGUARD 3 has met cerebral EPD Special Controls.

5 Proposed Indications for Use

The indications for use as proposed by the sponsor in the 510(k) submission is:

"*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*)."

6 Device Description

6.1 Subject Device: TriGUARD 3

The TriGUARD 3 device is a temporarily placed cerebral EPD delivered transfemorally through an 8F sheath to the aortic arch (Figure 1). The device is available in a single size (74 mm x 98 mm) and is composed of a structural nitinol frame and a polymer mesh attached to the frame. The device is heparin coated to reduce thrombogenicity and increase lubricity.

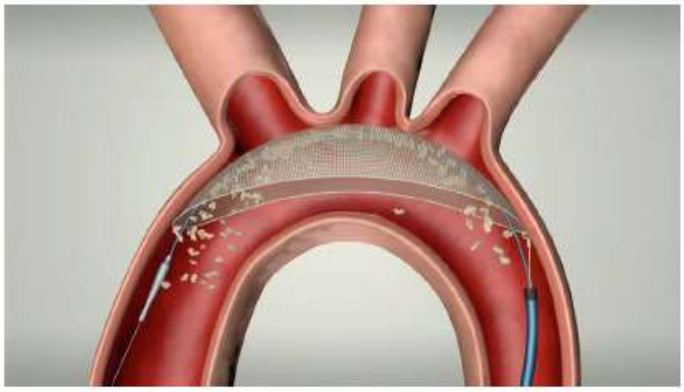

Figure 1. Keystone TriGUARD 3 Cerebral Embolic Protection Device

The TriGUARD 3 device is intended to cover the ostia of all 3 aortic arch great vessels (brachiocephalic, left common carotid, and left subclavian arteries) and is designed to maintain position in the aortic arch via circumferential pressure and support of the nitinol frame. The device is intended to *divert* emboli and particulate matter away from the cerebral circulation downstream to the descending aorta. This mechanism of action differs from the Sentinel device which *captures and removes* emboli and particulate matter from the body.

6.2 Predicate Device: Sentinel Cerebral Protection System

The Sentinel™ Cerebral Protection System is a temporarily placed cerebral EPD delivered via the right radial or brachial artery through a 6F sheath (Figure 2).

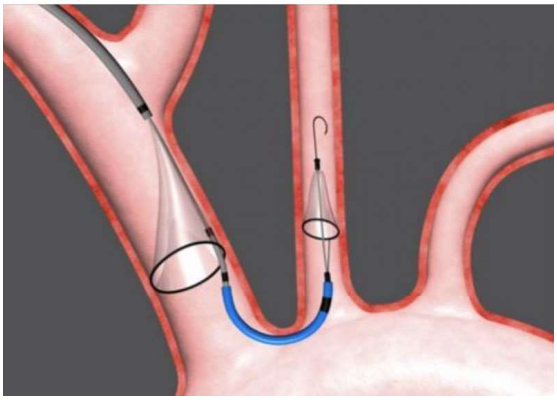

Figure 2. Boston Scientific Sentinel™ Cerebral Protection System

The Sentinel system is composed of two embolic filters made of nitinol and polyurethane film. The Proximal Filter is delivered to the brachiocephalic artery and is 15 mm in diameter, and the Distal Filter is deployed to the left common carotid artery and is 10 mm in diameter.

The Sentinel Cerebral Protection System is indicated for use as an embolic protection device to capture and remove thrombus/debris during transcatheter aortic valve replacement procedures. The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 – 10 mm in the left common carotid.

7 Regulatory History

7.1 Changes During the Course of the IDE Investigation

7.1.1 Initiation of Phase I of the REFLECT trial with the first generation TriGUARD HDH device

An Investigational Device Exemption (IDE) application for the first-generation (TriGUARD HDH) device was first submitted to FDA under (b)(4) , and FDA approved the IDE to initiate the REFLECT Phase I study on October 29, 2014.

The REFLECT Phase I study was approved for a total of 285 randomized subjects (2:1 TAVR with TriGUARD HDH: unprotected TAVR) and an additional 90 roll-in subjects.

The primary safety endpoint was a composite of all-cause death, stroke, life threatening or disabling bleeding, stage 2 or 3 Acute Kidney Injury (AKI), coronary artery obstruction requiring intervention, major vascular complications, and aortic valve-related dysfunction requiring repeat procedure evaluated at 30 days.

The primary effectiveness endpoint was a hierarchical composite of all-cause mortality or any stroke at 30 days, NIH Stroke Score (NIHSS) worsening from baseline evaluated at 2-5 days post-procedure or Montreal Cognitive Assessment (MoCA) worsening (decrease of 3 points or more

from baseline) at 30 days, cerebral ischemic lesions detected by DW-MRI evaluated between days 2-5 post-procedure, and the total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) evaluated at 2-5 days post-procedure. An interim analysis was planned to be performed after 90 subjects completed 30-day follow up.

On June 23, 2017, FDA approved a modification to the REFLECT Phase I study sample size to 355 randomized subjects (70 additional subjects) to allow for continued enrollment while the independent DMC reviewed the interim analysis.

7.1.2 Suspension of Phase I of the REFLECT Study

On August 1, 2017, Keystone informed FDA of a suspension of enrollment in the REFLECT Phase I study based on DMC recommendation after their review of unblinded data and modeling for conditional powering and potential outcomes. Keystone remained blinded to the trial results with the intent to modify the trial design and continue enrollment with a next generation device. A total of 258 subjects (204 randomized subjects; 141 TriGUARD HDH, 63 control and 54 roll-ins) had been enrolled in Phase I at the time of suspension.

7.1.3 Design Modification and Initiation of Phase II with TriGUARD 3 device

Keystone implemented design changes to the first generation TriGUARD HDH device and developed the second generation TriGUARD 3 device. The notable differences in the TriGUARD 3 design are:

- removal of the upper and lower stabilizer arms,
- use of a polymer mesh as opposed to a nitinol mesh,
- increase in filter area (from 21 cm^2 to 59 cm^2), and
- modification to the delivery sheath from 9F to 8F

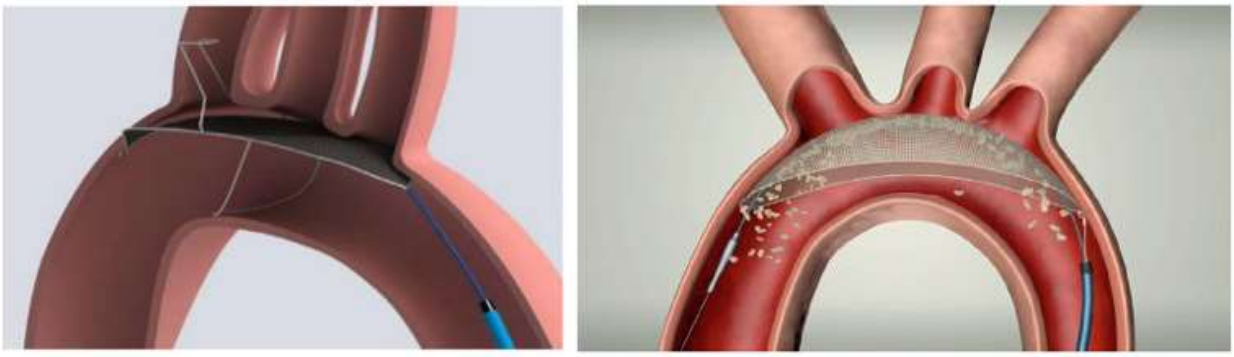

Figure 3. TriGUARD HDH device (left) and TriGUARD 3 device (right)

The sponsor submitted an IDE application for the second generation TriGUARD 3 device and FDA approved the application on May 23, 2018 to initiate the REFLECT Phase II study.

The REFLECT Phase II study was initially approved for a total of 225 randomized subjects (2:1, TriGUARD 3 used during TAVR vs. unprotected TAVR) and 50 roll-in subjects.

The primary safety endpoint was a composite of all-cause mortality, all stroke (disabling and non-disabling), life threatening or disabling bleeding, Stage 2 or 3 AKI, coronary artery obstruction requiring intervention, major vascular complications, and aortic valve related dysfunction requiring repeat procedure at 30 days.

The primary effectiveness endpoint was a hierarchical composite evaluated in the following order:

1. All-cause mortality and/or any stroke at 30 days;
2. NIH Stroke Score (NIHSS) worsening evaluated between days 2-5 post-procedure;
3. Cerebral ischemic lesions detected by DW-MRI evaluated between days 2-5 post-procedure; and
4. Total volume of cerebral ischemic lesions detected by DW-MRI evaluated between days 2-5 post-procedure.

On August 31, 2018, the sponsor implemented a modification to Phase II to incorporate an adaptive design into the study. Under this revision, an interim analysis would be performed when 50% of the randomized Phase II cohort reached 30-day follow-up to determine if a sample size increase would be necessary to adequately power the study.

On December 4, 2018, the sponsor requested an expansion of the REFLECT Phase II study sample size to 295 randomized subjects (70 additional subjects) to prevent a delay in enrollment in the event that the interim analysis determined that additional subjects were required to ensure adequate study power.

7.1.4 Suspension of Phase II of the REFLECT Study

On the recommendation of the DMC, during their scheduled interim review of 30-day data on the first 125 patients, study enrollment was paused on February 12, 2019 due to a discrepancy identified in the tabulation of safety events reported to the sponsor by the CEC. At the time of the enrollment suspension, there were 178 randomized subjects enrolled. The sponsor responded to the DMC that trial enrollment would be limited to the originally planned sample size of 225 randomized patients (corresponding to 47 additional randomized subjects), and there would be no interim analysis for sample size readjustment. On March 22, 2019, the DMC recommended that enrollment could resume.

FDA was notified of the enrollment pause on March 29, 2019. On April 16, 2019, after discussion with FDA regarding the available data, the DMC issued a letter to Keystone recommending a resuspension in enrollment. The REFLECT Phase II enrollment was suspended on April 17, 2019. The final REFLECT Phase II sample size included 179 randomized subjects (121 TriGUARD 3, 58 control) and 41 roll-in subjects.

7.2 IDE Timeline Summary

The timeline for the major points in the pivotal IDE study is shown in Figure 4.

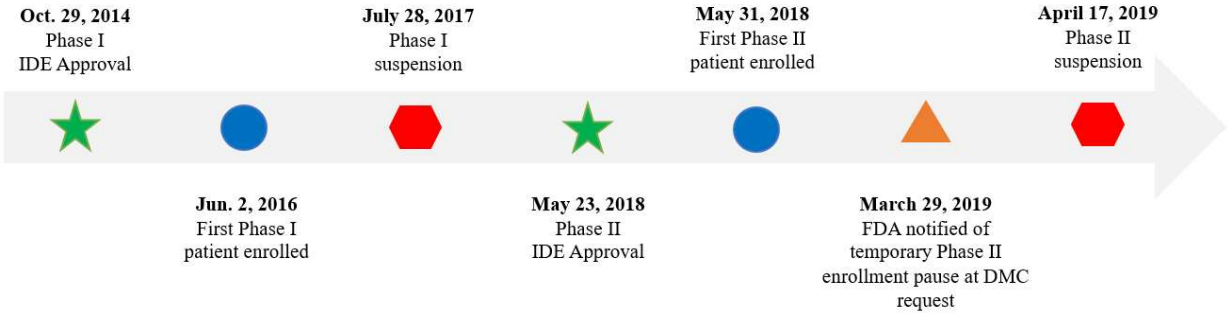

Figure 4. IDE Timeline Summary

7.3 Modifications to the investigational device compared to 510(k) device: Crimper component

After Phase II study suspension, and in response to observations and physician feedback during the IDE Study, the sponsor modified the device's crimper component, which is used to load the TriGUARD 3 into the delivery sheath during device preparation. This modification was made to improve preparation and positioning of the TriGUARD 3 device. For this change, FDA reviewed engineering (simulated use bench testing and evaluation of loading, deployment, and retrieval forces) and biocompatibility testing.

No subjects in either phase of the REFLECT study were treated with the TriGUARD 3 with the modified crimper component. However, 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 (see Section 9.2.1).

7.4 510(k) Timeline Summary

FDA received the TriGUARD 3 510(k) submission on September 24, 2020. To support the 510(k) application, Keystone provided the available data from the Phase II study totaling 220 subjects (41 roll-in subjects, 121 randomized subjects treated with TriGUARD 3, and 58 control subjects) and control data from the Phase I study (N=63, to be pooled with Phase II control data). Section 9 includes the important primary and secondary analyses of these data. On March 25, 2021, the sponsor provided additional information in response to questions from FDA.

During FDA's review of the sponsor's response, FDA determined that external expertise was needed. FDA requested that an FDA Advisory Panel Meeting be convened to provide input on the clinical data submitted to support substantial equivalence of the TriGUARD 3 device to the Sentinel device and whether the TriGUARD 3 device meets Special Controls for cerebral EPDs.

8 Non-Clinical Studies

The TriGUARD 3 device underwent appropriate non-clinical testing as outlined in 21 CFR 820.1251.

FDA Comment 3: There are no outstanding questions about the non-clinical studies, and the Advisory Panel is requested to focus its discussion on the clinical data and the REFLECT study outcomes

9 Clinical Investigations

This section summarizes the clinical data included in the 510(k) application for the TriGUARD 3 device. Phase II of the pivotal clinical study, the REFLECT study, is the primary dataset intended to support clearance and provides the most meaningful data to evaluate the TriGUARD 3 (Section 9.1; NCT02536196). The following sections present analyses that were pre-specified in the REFLECT Phase II protocol intended to assess the substantial equivalence of the TriGUARD 3 to Sentinel. The complete Phase II clinical study report is provided in Section 19 (Appendix H). A summary of the Phase I dataset is provided in Section 20 (Appendix I) and additional more recent real-world data is also included as an adjunctive dataset in Section 9.2.

The REFLECT pivotal study included two phases: Phase I and Phase II. Phase I compared the first-generation TriGUARD HDH device used during TAVR (test) to unprotected TAVR (control). REFLECT Phase II compared the second generation TriGUARD 3 device used during TAVR (test) to unprotected TAVR (control). The REFLECT study was originally intended as a single-phase study with the TriGUARD HDH device; however, the study was suspended based on DMC recommendations. Following the suspension period, the sponsor introduced a modified device called the TriGUARD 3 device. When the study was resumed, the portion of the study conducted using the TriGUARD HDH device was called 'Phase I' and the portion of the study that was newly enrolling patients was called 'Phase II.' To support clearance of the TriGUARD 3 device, Keystone compared the TriGUARD 3 test group to pooled Phase I and II control data in the primary analyses (Figure 5). Following least-burdensome principles, FDA agreed to pooling Phase I and II control data contingent on a successful poolability assessment. Additional details on Phase I and II of the REFLECT pivotal study are provided in Sections 20 and 9.1, respectively.

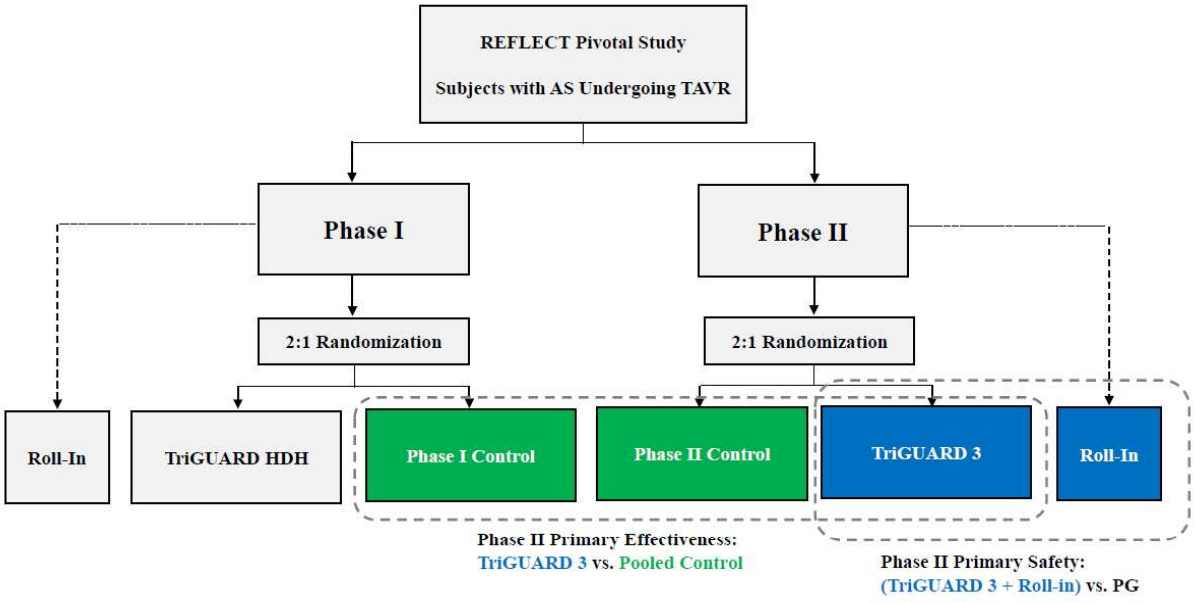

Figure 5. Pivotal REFLECT Study Flowchart

An overview of the clinical experience with the TriGUARD HDH and TriGUARD 3 devices (REFLECT Phase I and Phase II, respectively) is summarized in Table 1: Please note that the TriGUARD HDH is not the subject of this Panel review and has not been submitted for marketing clearance consideration.

A comprehensive summary of clinical experience with TriGUARD 3 and the first-generation TriGUARD HDH is provided in Section 12 (Appendix A).

Table 1: Overview of Clinical Experience

Study	Description	Patient Enrollment
REFLECT (US Pivotal Study NCT02536196)		
REFLECT Phase I [1] TriGUARD HDH used during TAVR vs. unprotected TAVR Enrollment: June 2016 – July 2017	Pivotal 2:1 randomization (TriGUARD HDH: unprotected TAVR) 26 Sites: 20 US, 6 EU	N = 445 planned enrollment; 355 randomized, 90 roll-in N actual enrollment = 258
REFLECT Phase II TriGUARD 3 used during TAVR vs. unprotected TAVR Enrollment: May 2018 – March 2019	Pivotal 2:1 randomization (TG3: unprotected TAVR) 18 US sites	N = 275 planned enrollment; 225 randomized, 50 roll-in N actual enrollment = 220
Real World Evidence		
RWE: Netherlands Heart Registry TriGUARD 3 Enrollment: July 2020 – December 2020	Single-arm physician initiated registry Single Center (Utrecht, NL) Includes the modified crimper to aid device positioning.	50 consecutive cases

[1]The DMC recommended stopping Phase I after their review of unblinded data and modeling for conditional powering and potential outcomes. Blinding was maintained to facilitate pooling of Phase I and Phase II control data to support a future marketing application for the TriGUARD 3 device.

9.1 REFLECT IDE - Phase II Pivotal Study

The REFLECT Phase II study was a prospective, multicenter, single-blind, 2:1 randomized, controlled trial comparing the TriGUARD 3 used during TAVR (test group) vs. unprotected TAVR (control group).

A total of 179 randomized subjects, 121 in the test group and 58 in the control group, and 41 roll-in subjects were enrolled at 18 sites in the US. The primary study objectives were to demonstrate safety compared to a pre-specified PG and superior effectiveness of the TriGUARD 3 device used during TAVR compared to unprotected TAVR. The following sections present details regarding the study design, subject demographics and baseline characteristics, and study results.

9.1.1 Study Population

The REFLECT Phase II study population included subjects with severe aortic stenosis undergoing TAVR via the transfemoral approach with an FDA-approved TAVR device.

9.1.2 Eligibility Criteria

9.1.2.1 Key Inclusion Criteria

- The patient is a male or non-pregnant female ≥18 years of age
- The patient meets indications for TAVR.

9.1.2.2 Key Exclusion Criteria

- Patients undergoing TAVR via the trans-apical, trans-axillary, trans-subclavian, or trans-aortic route
- Patients with a previously implanted prosthetic aortic valve (i.e., planned valve-in-valve TAVR)
- Patients with contraindication to cerebral MRI

9.1.3 Study Design

Subjects were randomized 2:1 to TriGUARD 3 during TAVR or unprotected TAVR.

9.1.4 Blinding

Patients, core laboratories, the sponsor, and the CEC were blinded to study group assignment. The operator was not blinded to treatment. Site personnel administering neurological evaluations were blinded to treatment group assignment and DW-MRI results.

9.1.5 Analysis Populations

The sponsor performed analyses on the following pre-defined populations: efficacy intention-to-treat (eITT), intention-to-treat (ITT), as treated (AT), per treatment (PT), roll-in (RI), and safety (SP) populations. These populations are defined as follows:

- *Intention-to-Treat (ITT) population*: All randomized subjects analyzed regardless of treatment received. The ITT population was the primary analysis population for the *secondary performance* endpoints.
- *Efficacy Intention-to-Treat (eITT) population*: All randomized subjects analyzed regardless of treatment received and who did not undergo conversion to surgery or experience prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI. The eITT population was the primary analysis population for the *primary effectiveness* endpoint, the *hypothesis driven-secondary endpoints,* and the *secondary effectiveness endpoints.*
    - In the primary effectiveness analysis, the control group was intended to be pooled control data from Phase I and Phase II of the study, if the two control groups were deemed poolable (see Section 9.1.9.2.2). Otherwise, the Phase II control group was intended to be used as the comparator.

- *As Treated (AT) population*: All randomized subjects analyzed according to actual treatment received.
    - Subjects in whom vascular access in the contralateral femoral artery was established for deployment of the TriGUARD 3 device, were analyzed as part of the TriGUARD 3 group.
    - Subjects in whom the TAVR procedure was initiated, but vascular access for intended deployment of TG3 was not established, were analyzed as part of the Control group.
- *Safety Population (SP[AT] or SP[ITT])*: Includes all subjects (randomized and roll-in) analyzed according to actual treatment received (SP[AT]) or according to randomization assignment (SP[ITT]). The SP(AT) population was the primary analysis population for the primary and secondary safety outcomes.
- *Per Treatment (PT) population*: Subjects in test group in whom device positioning achieved complete 3-vessel coverage for at least 2 of 3 procedural timepoints, pre-, during, or post-TAVR. The PT population is a subset of the eITT population in that it also excludes those who underwent conversion to surgery or experienced prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI.
- *Roll-in (RI) population*: Subjects who underwent TAVR with the TriGUARD 3 prior to enrollment of the first randomized subject at each investigational site. RI subjects were combined with randomized TriGUARD 3 subjects for analyses using the SP[AT] population.

FDA Comment 4:
The SAP and REFLECT Phase II study protocol define the PT population as "subjects in the Intervention group in whom device positioning is maintained until final procedure with complete cerebral coverage." The definition of the PT population used in the final analyses was defined in the angiography core laboratory charter further, defining the PT as subjects where 3-vessel coverage was achieved in at least 2 of 3 procedural timepoints rather than complete cerebral coverage at 3 procedural timepoints. The sponsor has noted that, in some cases, the camera was not following the accessory device, but rather following the index procedure.

In some cases, the sponsor proposed to limit the analysis to the PT population. FDA notes that limiting the analysis to this patient group may not be representative of the entire intended population to be treated and may exclude data important to understanding the device's overall safety and effectiveness. FDA also notes that the clinical relevance of defining this group as those with complete coverage in at least any 2 of the 3 procedural timepoints is unclear.

The sponsor utilized the SP(AT) population for the primary safety endpoint analysis as specified in the protocol and SAP. This population includes RI subjects. In most clinical trials, it is customary to exclude roll-in subjects from the primary analyses. Section 9.1.10.1.1 provides a qualitative assessment of differences between the RI and randomized groups.

Table 2 summarizes the key analyses conducted on each of the analysis populations defined above.

Table 2: Key Analyses per various Analysis Populations

Endpoint	eITT	ITT	SP(eITT)	SP(AT)	PT
Primary Safety				✓	
Primary Effectiveness	✓	•			•
Hypothesis Driven Secondary Effectiveness	✓		•		•
Secondary Safety				✓	
Secondary Effectiveness	✓	•			•
Secondary Performance		✓			

Note: The blue (✓) indicates the primary analysis population, and the green (•) indicates secondary or supportive analysis populations.

9.1.6 Primary and Secondary Analyses

9.1.6.1 Primary Safety Endpoint (randomized TriGUARD 3 and Roll-in Subjects Compared to a Performance Goal)

The primary safety endpoint was the composite of the following events at 30 days (based on the 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
- Aortic valve-related dysfunction requiring repeat procedure (BAV, TAVR, or SAVR)

9.1.6.2 Primary Effectiveness Endpoint (Superiority of TriGUARD 3 to the Pooled Phase I and II Control)

The primary effectiveness endpoint was a 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]
- **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.

9.1.6.3 Hypothesis-Driven Secondary Endpoints

If *both* the primary safety and primary effectiveness endpoints were met, sequential tests for superiority of the test group to the control group for the following secondary hypothesis-driven endpoints were planned:

- **All stroke** [evaluated at 7 days in the efficacy intention to treat (eITT) population]
- **NIHSS worsening**, defined as any NIHSS score increase from baseline [evaluated at 2 to 5 days post-procedure in the eITT analysis population]. A sensitivity analysis will further compare >2 points NIHSS worsening [evaluated at 2-5 days post-procedure in the eITT analysis population]
- **Composite of all-cause mortality and all stroke** [evaluated at 7 days in the eITT population]
- **CNS Infarction** (NeuroARC-defined) [evaluated at 30 days in the eITT population]
- **Total volume of cerebral ischemic lesions detected by DW-MRI**, [evaluated 2 to 5 days post-procedure in the eITT population]

9.1.6.4 Secondary Endpoints (Descriptive)

Numerous additional secondary endpoints were prospectively planned to be captured and results presented descriptively. These secondary endpoints include those for safety, effectiveness (neurologic and imaging), and performance (see Section 14, Appendix C). Results for select descriptive secondary endpoints are shown in Section 9.1.10.3.

9.1.7 Statistical Methodology

9.1.7.1 Background

The approved Phase II protocol included an initial randomized cohort of up to 225 subjects. The sponsor later modified their study to incorporate an adaptive design for sample size re-estimation to ensure adequate study power. An interim look was planned to occur when 50% of the initial randomized cohort reached 30-days follow-up. FDA approved a study expansion to 295 subjects to prevent a delay in enrollment in the event that the interim analysis determined that additional subjects would be necessary. Ultimately, the sponsor did not conduct the planned interim look before enrollment suspension and data unblinding.

9.1.7.2 Primary Safety Endpoint Analysis

The pre-specified hypothesis test of the primary safety endpoint was as follows:

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

where π is the primary safety endpoint event rate for the randomized TriGUARD 3 subjects combined with roll-in subjects, compared to a literature-based performance goal (PG) of 34.4%. The PG was calculated from a literature-reported 25% expected rate of VARC-2 complications for the control (Medtronic CoreValve Evolut R and Evolut PRO and Edwards SAPIEN 3 TAVR) + a margin of 9.4% (37.5% relative risk compared to the expected rate). The test was planned to be conducted at a one-sided 0.05 alpha level based on a z-test. Only subjects who had at least 23 days (30 days minus the allowable 7-day visit window) of follow-up or who did not have at least 23 days of follow-up but experienced a safety endpoint were included in the analyses.

9.1.7.3 Primary Effectiveness Endpoint Analysis

The primary effectiveness hypotheses were as follows:

> H_0: The hierarchical composite of death/stroke, NIHSS worsening, any cerebral ischemic lesions detected by DW-MRI, and total cerebral ischemic lesion volumes is not different between the TriGUARD 3 and control groups
>
> vs.
>
> H_1: 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 cerebral ischemic lesion volumes

The primary effectiveness endpoint was analyzed using the Finkelstein-Schoenfeld (FS) method [1]. The TriGUARD 3 test group would be determined superior to the control if the one-sided p-value of the above hypothesis test is <0.025.

In the FS method, each subject in the analysis population is compared to every other subject in the analysis population, based on the pre-specified hierarchy of death/stroke, NIHSS worsening, any new cerebral ischemic lesions, and total new cerebral ischemic lesion volume as illustrated in Figure 6. Then the comparison of the two treatment groups will be conducted based on the results of these pairwise comparisons using the test statistic derived by Finkelstein-Schoenfeld. A summary of the FS method is provided in Section 13 (Appendix B), and further details of this method are in the original paper by Finkelstein-Schoenfeld[1].

Since the FS method does not provide a point estimate for the treatment effect between two study groups, the Pocock win ratio was used to measure the treatment effect between the TriGUARD 3 and control groups with regard to the primary effectiveness endpoint [5]. In the win ratio method, each subject in the TriGUARD 3 group is compared to each subject in the control group based on the pre-specified hierarchy of death/stroke, NIHSS worsening, any new lesions, and total lesion volume. For each comparison, the subject that does better receives a score of +1 while the other subject receives a score of -1; if the two subjects are tied, then they both receive a score of 0. The rule by which the scores are assigned to each subject in each comparison is represented in Figure 6. Within each pair-wise comparison, the subject who scores "+1" is considered a "winner" and the subject who scores "-1" is considered a "loser".

The win ratio is calculated as the total number of "winners" divided by the total number of "losers" among all TriGUARD 3 subjects across all pair-wise comparisons. For the TriGUARD 3 group, a *win ratio greater than 1 favors the TriGUARD 3 group, and a win ratio less than 1 favors the control group*. The win percentage is calculated as the total number of "winners" in the TriGUARD 3 group divided by the total number of "winners" plus the total number of "losers" in the TriGUARD 3 group. *For the TriGUARD 3 group, a win percentage greater than 50% favors the TriGUARD 3 group and a win percentage less than 50% favors the control group*. The win ratio and win percentage of the control group were calculated and interpreted analogously.

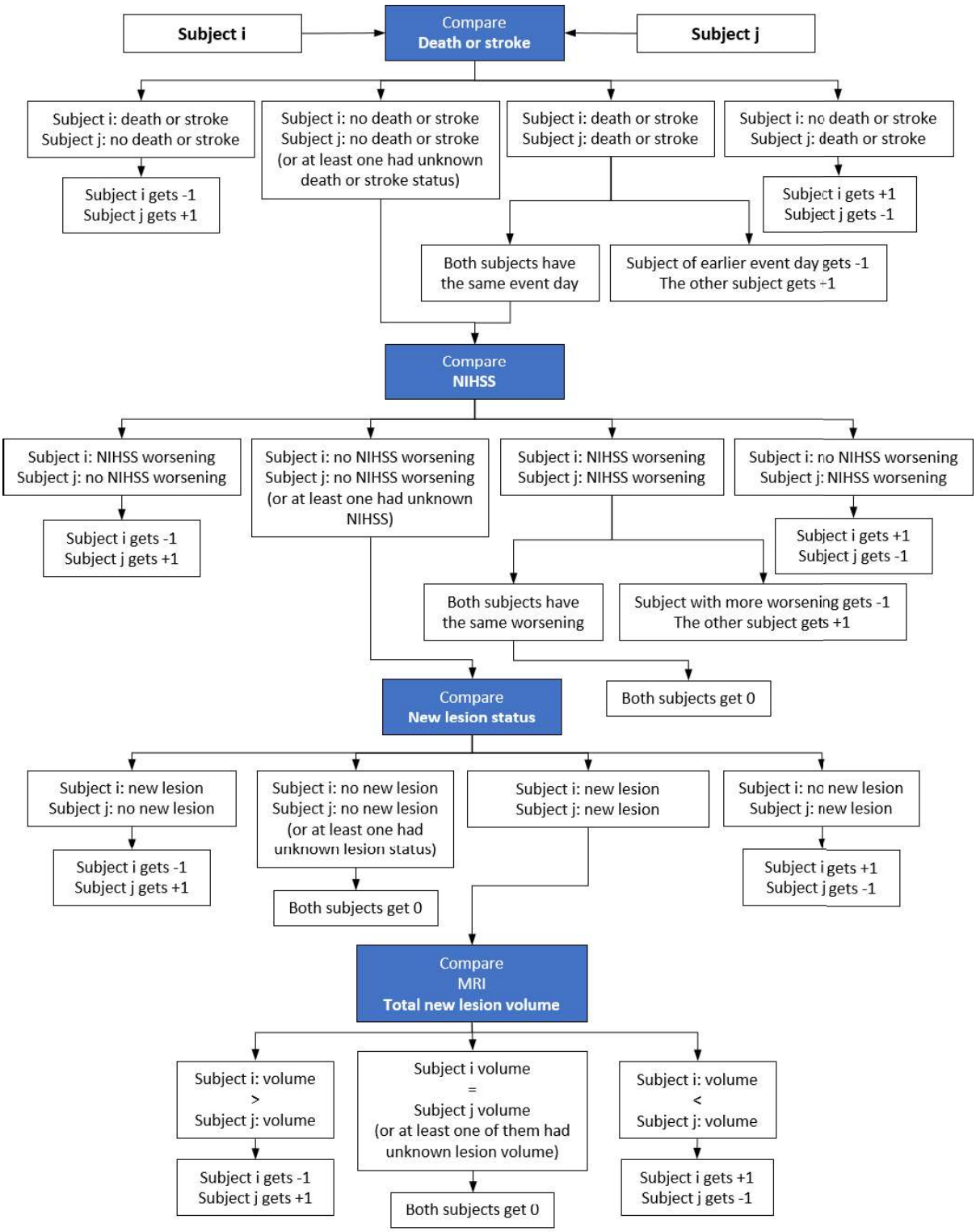

Figure 6. FS Algorithm*

* FDA notes that this is not the conventional implementation of the FS algorithm. However, the reported primary effectiveness results using this implementation are nearly identical to those generated by FDA using the conventional implementation.

9.1.7.4 Study Success Criteria

The trial would be deemed a success if both primary safety and effectiveness endpoints were met.

9.1.7.5 Hypothesis-Tested Secondary Endpoint Analyses

If the study reached overall success for both primary safety and effectiveness, the five pre-specified hypothesis tests shown in Table 3 below were to be conducted. These secondary endpoints would be tested in the pre-specified sequence, each at the 0.025 one-sided alpha level if all previous tests reach statistical significance.

Table 3: Hypothesis Tested Secondary Endpoints

Sequence	Endpoint	Null and Alternative Hypothesis	Definition
1	All stroke	$H_0: \pi_{STRK-I} \geq \pi_{STRK-C}$ vs. $H_1: \pi_{STRK-I} < \pi_{STRK-C}$	π_{STRK-I} = TG3 true stroke rate π_{STRK-C} = control true stroke rate
2	NIHSS worsening	$H_0: \pi_{NIHSS-I} \geq \pi_{NIHSS-C}$ vs. $H_1: \pi_{NIHSS-I} < \pi_{NIHSS-C}$	$\pi_{NIHSS-I}$ = TG3 true NIHSS worsening rate $\pi_{NIHSS-C}$ = control true NIHSS worsening rate
3	Composite of all-cause mortality and all stroke	$H_0: \pi_{COMP-I} \geq \pi_{COMP-C}$ vs. $H_1: \pi_{COMP-I} < \pi_{COMP-C}$	π_{COMP-I} = TG3 true all-cause death and all stroke rate π_{COMP-C} = control true all-cause death and all stroke rate
4	CNS infarction	$H_0: \pi_{CNS-I} \geq \pi_{CNS-C}$ vs. $H_1: \pi_{CNS-I} < \pi_{NCNS-C}$	π_{CNS-I} = TG3 true CNS infarction rate π_{CNS-C} = control true CNS infarction rate
5	Total volume of cerebral ischemic lesions	$H_0: \pi_{TLV-I} \geq \pi_{TLV-C}$ vs. $H_1: \pi_{TLV-I} < \pi_{TLV-C}$	π_{TLV-I} = TG3 true total cerebral ischemic lesions π_{TLV-C} = control total cerebral ischemic lesions

9.1.8 Follow-up Schedule

The follow-up schedule for REFLECT Phase II subjects is shown in Table 4.

Table 4: Phase II Follow-up Schedule

	Visit Window				
Follow-up Event	**Screening/ Baseline**	**Procedure** *Day 0*	**Post-Procedure**	**30-Day** *± 7 days*	**90-Day** *± 14 days*
Written Informed Consent	✓				
Medical History	✓				
Physical Examination	✓		✓	✓	
Review of Eligibility Criteria	✓	✓			

	Visit Window				
Follow-up Event	**Screening/ Baseline**	**Procedure** *Day 0*	**Post-Procedure**	**30-Day** *± 7 days*	**90-Day** *± 14 days*
Clinical Frailty Scale	✓				
12-lead ECG	✓		✓		
Concomitant Medications	✓	✓	✓	✓	
Pregnancy Test	✓				
Hematology/Chemistry	✓		✓		
Cardiac Enzymes	✓		✓		
CT Imaging	✓				
Cerebral DW-MRI			✓		
NIH Stroke Scale	✓		✓	✓	
Modified Rankin Scale	✓		✓	✓	
TAVR		✓			
Echocardiography (SOC)			✓		
Device deployment		✓			
Adverse Events		✓	✓	✓	
Phone call to assess mortality/stroke					✓

9.1.9 Subject Characteristics

9.1.9.1 Subject Disposition Accountability

Subject disposition, accountability (rates of withdrawal, death, and lost-to-follow-up), randomization, and study flow are shown in Figure 7. The 510(k) was submitted with data on a total of 283 subjects:

- 220 Phase II subjects
  - 41 TriGUARD 3 roll-in,
  - 121 randomized TriGUARD 3, and
  - 58 randomized control
- 63 Phase I randomized control subjects.

Please see Section 16 (Appendix E) for FDA's tipping point analysis of the primary effectiveness endpoint components, which simulates potential outcomes under different scenarios if the Phase II study had completed the planned full enrollment of 225 randomized subjects.

Subject follow-up compliance, defined as subjects with expected visits who completed all required follow-up documentation, was similar between groups and was approximately 85% post-procedure, 92% at 30 days, and 99% at 90 days for both the TriGUARD 3 and Phase I and II

Control groups. Missing MRI follow-up data were also similar between groups (13.6% TriGUARD and 13.8% control).

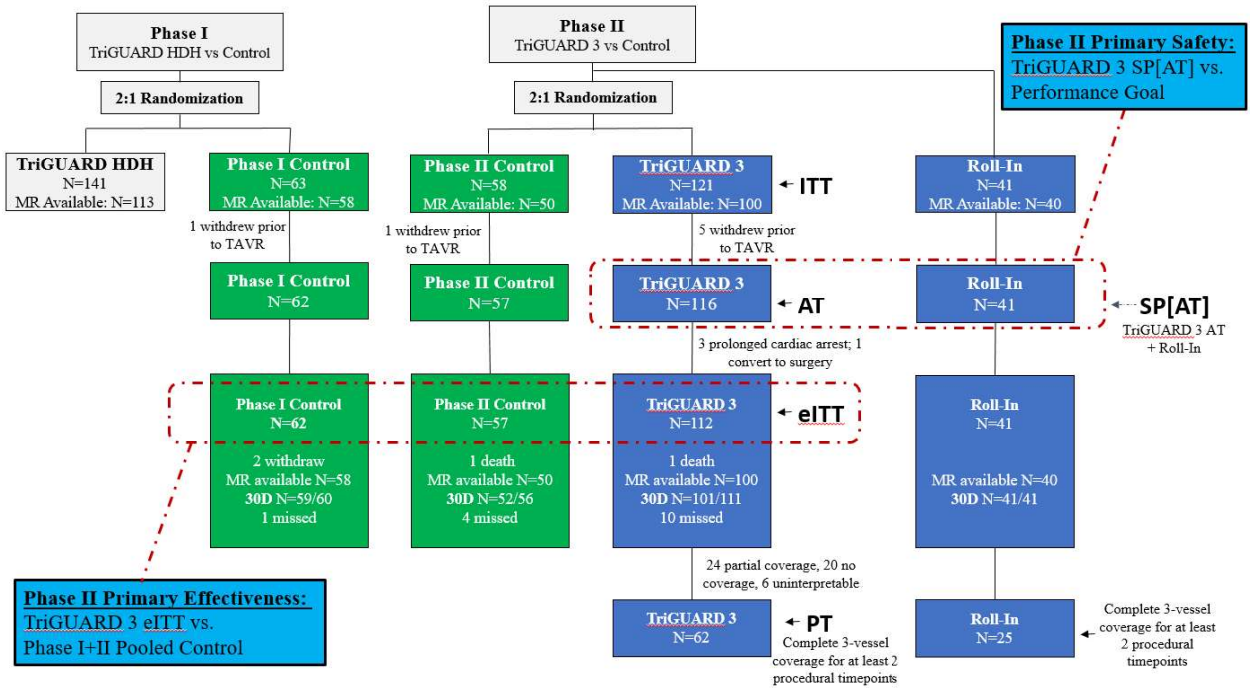

Figure 7. Randomization and Study Flow Chart

9.1.9.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics were collected prior to the procedure and are shown in Table 5. The average age was 80 years in both treatment groups, and the study population had a high frequency of co-morbidities, representative of typical patients undergoing TAVR for critical AS.

9.1.9.2.1 Primary Effectiveness eITT Population

With regards to baseline medical history and pre-existing conditions, the following differences were noted in the eITT population between the TriGUARD 3 group and the Phase I and Phase II Pooled Control group (Table 5):

- The frequency of diabetes was similar in the TriGUARD 3 and pooled control group (34.8% vs. 35.3%, respectively), but among diabetic subjects, insulin-dependent diabetes (IDDM) was less common in the TriGUARD 3 group vs. the pooled control group (5.4% vs. 13.7%, respectively).
- The TriGUARD 3 group had a higher prevalence of prior stroke or TIA compared to the pooled control group (17.9% vs. 8.5%, respectively).
- Keystone performed a post-hoc imaging analysis evaluating T2 lesions to assess baseline lesion burden prior to the procedure. The sponsor reported that in patients with available DW-MRIs, the frequency of baseline cerebral infarcts was higher in TriGUARD 3 subjects

compared to pooled control subjects (mean T2 lesion volume 9820 mm^3 vs. 7780 mm^3, respectively).

Table 5: Demographic Characteristics and Medical History

Subject Characteristics eITT Population	TriGUARD 3 *N=112*	Pooled Control *N=119*
Demography		
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)	**5.4% (6/111)**	**13.7% (16/117)**
Diet-controlled	15.3% (17/111)	9.0% (10/111)
Oral hypoglycemic controlled	26.8% (30/112)	19.1% (22/115)
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 (PVD)	13.5% (15/111)	16.5% (19/115)
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 assessed	96.4% (108/112)	95.8% (114/119)
History of congestive heart failure (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)

FDA Comment 5: FDA notes that there are differences in baseline characteristics between treatment groups. While the rate of prior stroke or TIA was higher for patients in the TriGUARD 3 group, the rate of IDDM was higher for patients in the control group. The panel will be asked to comment on the clinical significance of these between group differences.

9.1.9.2.2 Phase I and II controls

Section 12.4.3 of the clinical investigational plan specified that a pooled control consisting of Phase I and Phase II control group data would serve as the comparator in the analyses of the primary and secondary effectiveness endpoints if the two control groups were deemed poolable and given that blinding was maintained for the Phase I study. In the event that Phase I and II control groups were deemed not poolable, the control data for the primary and secondary effectiveness endpoint analyses was to be limited to the Phase II control group.

Per the poolability assessment strategy specified in the Statistical Analysis Plan (SAP), the poolability of Phase I and II controls was to be assessed by comparing 7 baseline characteristics between the two control groups, and the groups would be deemed poolable if no statistically significant difference was detected regarding any of these 7 characteristics (each tested at a two-sided alpha level of 0.15): age, diabetes mellitus, history of congestive heart failure (CHF), prior CVA or TIA, NIHSS, Society of Thoracic Surgeons (STS) score, and clinical frailty.

The results of the poolability assessment are shown in Table 6, and the poolability assessment following the strategy specified in the SAP are identified by bolded rows. Note that the pre-specified comparison between the two control groups regarding clinical frailty was not conducted, since Phase I did not have complete data for this baseline assessment. In addition, the sponsor also provided comparisons between the two control groups regarding some additional baseline characteristics to facilitate the poolability assessment, the results of which are also summarized in Table 6 (unbolded rows).

Per the pre-specified SAP strategy, *the Phase I and II control groups are non-poolable*, since the two groups were different regarding age (81.6±7.2, n=62 vs. 78.1±8.2, n=57, p=0.01) and a history of CHF (37.7%, 23/61 vs. 58.9%, 33/56, p=0.03) for Phase I vs. Phase II, respectively.

Table 6: Poolability Analysis of Control Subjects from Phase I and Phase II

Baseline Characteristics	Phase I Control *N=62*	Phase II Group *N=57*	p-value[b]
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)**	
Gender (Male)	67.7% (42/62)	61.4% (35/57)	0.57
Ethnicity (Not Hispanic or Latino)	100.0% (60/60)	90.6% (48/53)	0.02
Smoker Status (Never)	54.8% (34/62)	42.1% (24/57)	0.34

Baseline Characteristics	Phase I Control *N=62*	Phase II Group *N=57*	p-value[b]
Diabetes Mellitus (DM)	**30.6% (19/62)**	**40.4% (23/57)**	**0.34**
Diet-controlled diabetes mellitus	9.7% (6/62)	7.0% (4/57)	0.75
History of coronary artery disease (CAD)	10.3% (6/58)	23.2% (13/56)	0.08
History of COPD	16.9% (10/59)	21.4% (12/56)	0.64
History of Congestive Heart Failure (CHF)	**37.7% (23/61)**	**58.9% (33/56)**	**0.03**
History of renal disease	18.0% (11/61)	29.8% (17/57)	0.19
Prior CVA or TIA	**11.7% (7/60)**	**5.3% (3/57)**	**0.32**
History of PCI	30.0% (18/60)	26.3% (15/57)	0.69
History of severe pulmonary HTN	1.7% (1/60)	5.3% (3/57)	0.36
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)**	
T2 Lesion Volume [a]			
Mean±SD (n)	8951.0 ± 13107.5 (56)	6447.7 ± 10804.5 (49)	0.07
Median, Range (Min, Max)	4860.5, (199.7, 72758.3)	2870.5, (55.0, 52073.4)	

a. Total volume of T2 cerebral lesions was cube root transformed for calculation of the p-value.
b. P-values are from two-sided Fisher's exact tests or t-tests, as appropriate.
* Bolded rows were included in the poolability assessments of Phase I and II controls specified in the SAP.

The sponsor states that the observed differences regarding age and history of CHF were of limited clinical relevance, since there are no studies that establish a linkage between these two clinical characteristics that have a significant impact on TAVR outcomes. Therefore, despite the statistical analysis, the sponsor asserts that Phase I and II controls were poolable. The primary analyses of the primary and secondary effectiveness endpoints were based on the eITT population with Pooled Controls.

FDA Comment 6: The sponsor asserts the two control groups to be poolable, but their poolability assessment did not follow methods pre-specified in the SAP. FDA perspectives on the poolability assessment are provided in Section 9.4.1 below. The panel will be asked to discuss the validity of the specified poolability criteria and the poolability of Phase I and Phase II controls.

9.1.10 REFLECT Phase II Study Results and Analyses

9.1.10.1 REFLECT Phase II Primary Safety Results

The primary safety endpoint is based on the VARC-2 definition of the composite of all-cause mortality, all stroke (disabling and non-disabling), life threatening or disabling bleeding, AKI (Stage 2 or 3, including renal replacement therapy), coronary artery obstruction requiring intervention, major vascular complication, and aortic valve-related dysfunction requiring repeat procedure (BAV, TAVR, or SAVR) at 30 days in the TriGUARD 3 group.

The primary analysis of the primary safety endpoint was evaluated in the SP(AT) population which was comprised of 116 randomized AT and 41 RI subjects who received TriGUARD 3 for a total of 157 subjects. Of the 121 randomized TriGUARD 3 subjects, 5 subjects withdrew before the TAVR procedure, resulting in 116 TriGUARD 3 subjects in the AT population.

The TriGUARD 3 group had a combined primary safety endpoint rate of 15.9%, with a one-sided 95% upper confidence limit of 21.3%, which was lower than the pre-specified PG of 34.3%. The primary safety endpoint was met with a p-value <0.0001 (Table 7). Table 8 summarizes event rates for individual components of the primary safety endpoint.

Table 7: REFLECT Phase II Primary Safety Result

	Subjects with Event(s)	Upper 95% Confidence Interval	Performance Goal	P-value
SP[AT] [1]	25/157 (15.9%)	21.3%	34.4%	< 0.0001
AT [2]	24/116 (20.7%)	27.5%	34.4%	0.001[3]

[1] Phase II CSR, Table 14a. The SP[AT] population is the prespecified primary analysis population.
[2] Keystone AINN Response, Table 18
[3] The reported p value is based on a post-hoc analysis without multiplicity adjustment

Table 8: Primary Safety Endpoint through 30 Days (Phase II SP[AT] Population)

Phase II Primary Safety Endpoint SP[AT] Population	TriGUARD 3 *N=157*	95% CI[1]
Combined Safety Endpoint within 30 Days	15.9% (25/157)	[11.0%, 22.5%]
All-Cause Death	2.5% (4/157)	[1.0%, 6.4%]
Stroke (Disabling and Non-Disabling)	8.3% (13/157)	[4.9%, 13.7%]
Life-Threatening or Disabling Bleeding	5.7% (9/157)	[3.0%, 10.5%]
Acute Kidney Injury (Stage 2/3)	2.5% (4/157)	[1.0%, 6.4%]
Coronary Artery Obstruction Requiring Intervention	0.6% (1/157)	[0.1%, 3.5%]
Major Vascular Complication	7.0% (11/157)	[4.0%, 12.1%]
TG3 Access Site-Related	1.9% (3/157)	[0.7%, 5.5%]
TAVR or Other Access Site-Related	4.5% (7/157)	[2.2%, 8.9%]
Secondary Access Site-Related	0.0 (0/157)	[0.0%, 2.4%]
Aortic Vascular Injury	1.3% (2/157)	[0.4%, 4.5%]
Valve Related Dysfunction Requiring Intervention	0.0% (0/157)	[0.0%, 2.4%]

[1] Confidence interval is the Wilson score interval. The reported confidence intervals are not based on pre-specified hypothesis tests and without multiplicity adjustment.

9.1.10.1.1 Qualitative Safety Comparison Between Various Groups/Populations

A *numerical* comparison of patients randomized to either the TriGUARD 3 group or Phase II control group indicated numerically higher rates of death (3.4% vs 1.8%), stroke (11.2% vs 5.3%), bleeding (6.9% vs 0), AKI (3.4% vs 0), coronary artery obstruction (0.9% vs 0%), major vascular complications (7.0% vs 0%) and aortic vascular injury (1.7% vs 0%) in the TriGUARD 3 group compared to the control (**Table 9** and **Figure 8)**. In addition, RI subjects receiving the TriGUARD 3 device had a substantially lower rate of safety events compared to randomized TriGUARD 3 subjects. If RI patients are excluded from the Primary Safety Analysis (comparing AT vs. SP[AT] in Table 9), the primary safety endpoint event rate in the TriGUARD 3 group increases from 15.9% (25/157) to 20.7% (24/116).

Table 9: Primary Safety Endpoint and individual components (Supplemental Analysis Populations)

	TriGUARD 3			Phase II Control	Phase I Control	Pooled Control
	RI[1] *N=41*	AT[2] *N=116*	SP(AT)[3] *N=157*	SP(AT)[4] *N=57*	SP(AT)[5] *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

[1] Phase II CSR, Table 14c
[2] Keystone AINN Response, Table 18; in a post-hoc analysis the combined 30-day rate excluding roll-ins was 20.7% (95% CI UL of 27.5%)
[3] Phase II CSR, Table 14a & 14b
[4] Phase II CSR, Table 18
[5] Phase I CSR, Table 12.2

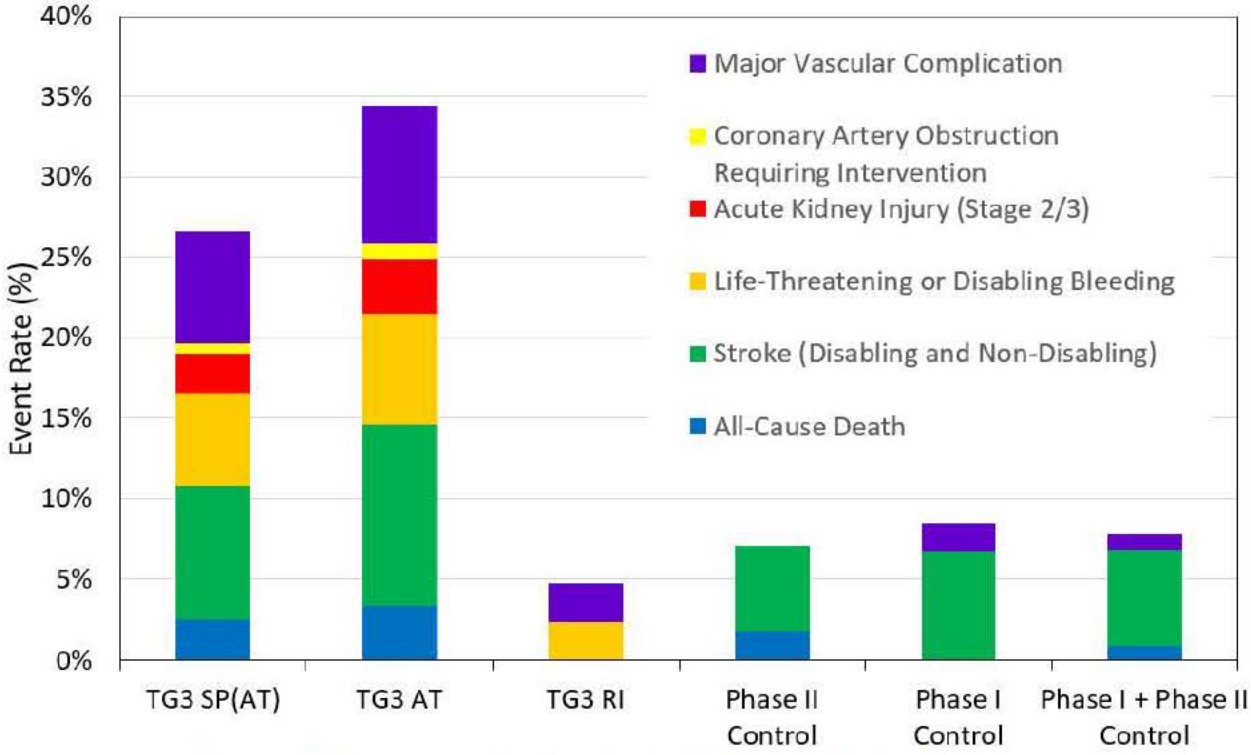

Figure 8. Primary Safety Endpoint Rates for Various Cohorts
*Note, some patients may have more than one event.

Note that the event rates in the ITT and SP[ITT] populations were identical to the AT primary analysis (SP[AT]), because all 5 subjects who were included in the ITT population but excluded from the AT population withdrew prior to TAVR and therefore were not evaluable for the primary safety endpoint.

FDA Comment 7: FDA notes that the individual safety component event rates are consistently numerically greater for the TriGUARD 3 group compared to the control. Specifically, FDA notes the numerically higher stroke rate (8.3% TriGUARD 3 SP[AT] group vs. 5.3% Phase II control) given the primary purpose of the TriGUARD 3 to reduce the potential of embolic debris from entering the cerebral circulation during TAVR.

Observed stroke rates are further discussed and compared to those observed in the Phase II control group in Figure 9 below.

The panel will be asked to discuss the clinical relevance of the observed differences in individual safety component event rates.

Additionally, RI subjects had substantially lower event rates vs. subjects randomized to the TriGUARD 3. FDA's perspective on these observations are provided in Section 9.4.

The panel will be asked to comment on the inclusion of RI subjects in the primary safety endpoint analysis.

9.1.10.1.2 Comparison of Stroke Timing

In the TriGUARD 3 group, there were 14 strokes in 13 patients (8.3%), and in the Phase II control group, there were 4 strokes in 3 patients (5.3%). In the Phase II Roll-In group, the 2 non-disabling strokes occurred >72 hours post-procedure. The CEC-adjudicated timing of stroke events is shown in Figure 9 (excerpted from Appendix E-5 of the Phase II Clinical Study Report). Ten of the 14 strokes observed in patients receiving the TriGUARD 3 occurred within 72 hours of the TAVR procedure, and 2 of the 4 strokes observed in the control patients occurred within the same time period.

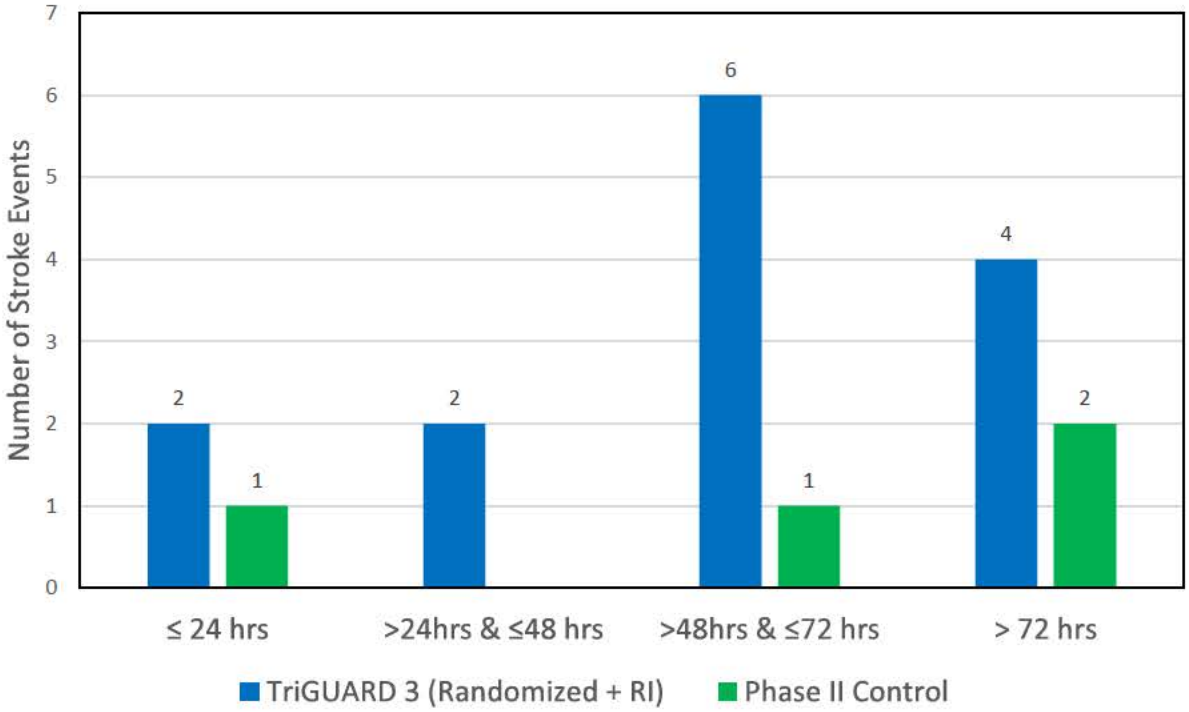

Figure 9: Timing of Stroke Events (Phase II SP[AT] Population)
*Note, randomization was 2:1 (TriGUARD 3:control).

9.1.10.1.3 Vascular Complications

The TriGUARD 3 device is placed via femoral arterial access contralateral to the TAVR femoral arterial access. Note that contralateral femoral access is often used during routine TAVR procedures for diagnostic imaging and hemodynamic monitoring and may be performed with a 5F or 6F sheath. However, a larger, 8F contralateral access required for the TriGUARD 3. Despite this difference, information was not provided to confirm the contralateral arteriotomy sizes that were used for the patients in the REFLECT trial control group.

There were 3 major vascular complications related (n=2) and possibly related (n=1) to the TriGUARD 3 yielding a major vascular complication rate attributable to the TriGUARD 3 of 1.9% (3/157). See Table 10.

Table 10: TriGUARD 3 Major Vascular Complications Related or Possibly Related to the TriGUARD 3

Event	Adjudication	Narrative
(b) (6)	Possibly Related	On post-procedure Day 1, CT angiography of the chest, abdomen and pelvis was reported to have shown multifocal extravasation from the distal right iliac artery and right common femoral artery resulting in an 11cm x 7.9 cm right retroperitoneal hematoma and right iliac pseudoaneurysm. Arteriotomy closed by AngioSeal.
(b) (6)	Related	TAVR procedure was successful and TriGUARD 3 was deployed successfully into position on first attempt. TriGUARD 3 and TAVR delivery sheath were successfully removed. A Perclose vascular closure device was deployed in the left femoral artery but closure was unsuccessful. At this point, oozing from around the left 8 Fr arterial sheath insertion site was noted. An attempt to close the left femoral arterial access with another Perclose device was made, which was unsuccessful. Manual pressure was applied and conversion to surgical repair of the artery was performed.
(b) (6)	Related	TriGUARD 3 and valve placement were successful through left and right groin accesses, respectively. Post hemostatic closure, the patient developed progressive hypotension and tachycardia. There was concern for pelvic/retroperitoneal bleeding so two units of blood were administered as access was re-established in the left femoral artery. No contrast extravasation was noted following bilateral selective lower extremity angiography and flow in both vessels appeared to be uncompromised. The patient was diagnosed with a left flank hematoma believed to have caused the transient instability.

In addition, minor vascular complications were reported for the TriGUARD 3 and Phase II Control groups. There were 18 events in the TriGUARD 3 group and 6 events in the Control group (note, 2:1 randomization). Of the TriGUARD 3 minor vascular complication events, there were 5 events related to the device or procedure. CEC adjudicated minor vascular complications are provided in Section 17 (Appendix F)

FDA Comment 8: FDA's perspective on the use of a larger contralateral access sheath for TriGUARD 3 is provided in Section 9.4.8. The panel will be asked to discuss the risks of a larger sheath when considering the overall benefits and risks of the TriGUARD 3.

9.1.10.1.4 Device-Related Events

The proposed 510(k) device is an accessory device to be used in a TAVR procedure. The goal of randomization was to evaluate for potential improvement/benefit of the accessory device in the background of events that may be attributable to TAVR. The CEC determined first whether an event occurred and second whether the event was related to the TriGUARD 3 device or the procedure.

The pre-specified primary safety endpoints for the REFLECT and SENTINEL trials were not limited to events judged to be attributed to the test devices. Despite this point, the sponsor proposed to limited safety events to those possibly or definitely related to the TriGUARD 3. The sponsor provided post-hoc analyses wherein they excluded events from the safety endpoint analysis that were CEC-adjudicated as not related to the TriGUARD 3 (n=16) and included only those events that were possibly (n=10) or definitely related (n=2) to the TriGUARD 3.

Table 11: CEC-Adjudicated Safety Events Regarding Relationship to TriGUARD 3 Device or Procedure (SP[AT] population)

	Pre-Specified Primary Safety Endpoint Rates[1]	CEC-Adjudicated Relationship to TriGUARD 3 Device or Procedure [2]		
Primary Safety Endpoint/Component		Not related	Possibly Related	Related
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%
TriGUARD 3 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)	--	--	--

[1] Number of subjects who experienced the respective safety endpoint at least once.
[2] If the relationship to TriGUARD 3 Device is different than the relationship to TriGUARD 3 Procedure, then the most related of the two is considered for evaluation.

See Table 31 for secondary safety endpoints regarding relationship to TriGUARD 3.

FDA Comment 9: It should be noted that comparing rates in different randomized trials and surmising "device-relatedness" requires clinical judgement. Note that the CEC-adjudicated events in the Sentinel study were not limited to potential relatedness to the Sentinel device. FDA believes a similar approach, considering all events is important when considering the substantial equivalence framework used to compare the subject and predicate devices. In addition, because data for the predicate and subject devices were collected within randomized studies, the context of device relatedness may be accounted for when comparing against "no protection" controls.

9.1.10.2 REFLECT Phase II Primary Effectiveness Results

The primary effectiveness endpoint was a hierarchical composite determined by a pair-wise comparison between all subjects in the TriGUARD 3 group and the control group according to the following pre-specified hierarchy:

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

Although the protocol specified that MRI was to be performed at 2 to 5 days post procedure, in the final analyses, the sponsor included all MRI data collected between 1 and 7 days post-procedure (inclusive) in all effectiveness analyses to maximize the amount of data available for analysis.

The primary effectiveness endpoint was evaluated in the eITT population which included 112 TriGUARD 3 patients; of 121 TriGUARD 3 patients enrolled, 5 patients withdrew before the TAVR procedure, 1 patient was converted to surgery, and 3 patients had a cardiac arrest. There were 119 Phase I and II pooled control subjects available for the primary effectiveness endpoint analysis; of 121 enrolled control subjects, 1 Phase I control patient and 1 Phase II control patient withdrew before the TAVR procedure. Note that the sponsor conducted the primary effectiveness

endpoint analysis based on the eITT population with pooled controls and considered it as the primary analysis. Please see section 9.1.9.2.2 regarding considerations for pooling control data.

For the primary effectiveness endpoint (Table 12), the Finkelstein and Schoenfeld method resulted in a one-sided p-value of 0.857, greater than the pre-specified one-sided 0.025 significance level; **therefore, the primary effectiveness endpoint was not met.**

In addition, the observed Pocock win ratio (the ratio of the number of wins to the number of losses in treatment-versus-control pairs, with higher number representing better outcome) was 0.84 in the TriGUARD 3 group indicating an unfavorable treatment effect for the TriGUARD 3 group. The win percentage (the number of wins divided by the sum of the number of wins and losses) favored the pooled control group: 45.7% in the TriGUARD 3 group and 54.3% in the pooled control group (Table 12).

When comparing outcomes for individual components of the primary effectiveness endpoint, the TriGUARD 3 group had a numerically higher rate of all-cause mortality or stroke at 30 days (9.8% TriGUARD 3 vs. 6.7% control), higher rate of NIHSS worsening at 2 to 5 days post-procedure (14.1% TriGUARD 3 vs. 7.6% control), and higher mean total volume of cerebral ischemic lesions (mean 587.80 mm3 TriGUARD 3 vs. 508.22 mm3 control) compared to the pooled control group. The frequency of cerebral ischemic lesions was similar between the two groups (85.0% vs. 84.9%).

Table 12: Primary Effectiveness Endpoint (eITT population with Pooled Controls)[1]

	TriGUARD 3 *N=112*	**Pooled Control** *N=119*	**p-value [2]**
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)	

[1] Phase II CSR, Table 20a
[2] p-value calculated using FS method

FDA Comment 10: The clinical components of the effectiveness endpoint numerically favor the control, and all imaging measures favor the control with the exception of the maximum range of total volume of cerebral ischemic lesions (5681.26 mm^3 TriGUARD 3 compared to 8133.60 mm^3 Control) despite the mean and medians favoring the control.

Embolic protection devices are designed to prevent embolic material from entering the cerebral circulation, and the REFLECT primary hierarchical effectiveness endpoint was used to assess the ability of TriGUARD 3 to perform this function. The panel will be asked to discuss the primary effectiveness results within the context of the primary purpose of the device, and how these results are considered within the substantial equivalence framework.

9.1.10.2.1 Qualitative Effectiveness Comparison Between Various Groups/Populations

Several additional *qualitative* post-hoc comparisons of different analysis populations were performed by the sponsor and summarized in Table 13. Of note, the sponsor presented data on the PT population which represents subjects in the TriGUARD 3 eITT group in whom 3-vessel coverage is achieved in at least 2 of the 3 procedural timepoints (pre-TAVR, during TAVR, and post-TAVR). This population is limited to 55.4% (62/112) of the TriGUARD 3 eITT subjects and excludes patients who did not have adequate device positioning (24 partial coverage; 20 no coverage; 6 uninterpretable angiograms).

Table 13: REFLECT Phase II Primary Effectiveness Endpoint Components in Supplemental Analysis Populations

	TriGUARD 3			Control	
				Pooled (Phase I + II)	Phase II only
Endpoint	**eITT[1]** *N=112*	**ITT[2]** *N=121*	**PT[3]** *N=62*	**eITT[4]** *N=119*	**eITT[5]** *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	14.1% (14/99)	14.0% (14/100)	13.8% (8/58)	7.6% (8/105)	6.1% (3/49)
Cerebral ischemic lesions	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

	TriGUARD 3			Control	
				Pooled (Phase I + II)	Phase II only
Endpoint	**eITT[1]** *N=112*	**ITT[2]** *N=121*	**PT[3]** *N=62*	**eITT[4]** *N=119*	**eITT[5]** *N=57*
(Q1, Q3)	(68.13, 619.71)	(68.13, 619.71)	(43.75, 444.44)	(52.08, 453.12)	(26.95, 360.00)

[1]Phase II CSR, Table 20a, eITT: all randomized subjects analyzed regardless of treatment received and who do not have conversion to surgery or prolonged cardiac arrest
[2]Phase II CSR, Table 20b, ITT: all randomized subjects analyzed regardless of treatment received
[3]Phase II CSR, Table 20c, PT: Subjects in the eITT group in whom device positioning maintains 3-vessel coverage in at least 2 of three procedural timepoints
[4]Phase II CSR, Table 20a and 20b
[5]FDA Generated

FDA Comment 11: Of the TriGUARD 3 analysis cohorts, the PT population yielded the most favorable outcomes for the device group. However, the PT population excludes TriGUARD 3 patients (and associated events) where complete aortic arch artery protection did not occur.

As discussed in Section 9.1.5, there is uncertainty regarding the clinical relevance of this analysis population and whether this analysis biases results in favor of the TriGUARD 3 device by omitting events occurring in a entirety of the target population.

9.1.10.3 Select Secondary Endpoint Results

9.1.10.3.1 Hypothesis-Driven Secondary Effectiveness Results

The SAP specified that hypothesis-driven secondary endpoints would only be formally tested in the event of a positive outcome of the primary endpoints. Despite the primary effectiveness endpoint not being met, the sponsor opted to conduct tests on the secondary hypothesis-driven effectiveness endpoints in an exploratory manner. Section 14 (Appendix C) provides descriptive statistics for the five pre-specified secondary endpoints. In the eITT population, the TriGUARD 3 group performed numerically worse for all five endpoints compared to the pooled control group.

9.1.10.3.2 Secondary Safety Results

Numerous secondary safety endpoints were planned to be conducted using the AT population (only randomized). In the final analysis of the secondary safety endpoints, the sponsor opted to use the SP[AT] population of subjects (i.e., including Roll-ins), rather than the pre-specified AT population. The sponsor noted this was for consistency with the primary analysis population for the primary safety endpoint. The sponsor also did not present the pre-specified secondary analysis in the ITT population of evaluable subjects. Pre-specified analyses of secondary safety endpoints in the RI population are reported. Results for the secondary safety endpoints are presented in Section 15 (Appendix D) and generally indicate that RI subjects perform better than subjects randomized to receive the TriGUARD 3, and TriGUARD 3 subjects in the SP(AT) perform worse than control despite the favorable results observed for RI subjects.

9.1.10.3.3 Secondary Imaging and Neurologic Effectiveness Endpoints

The SAP included numerous planned analyses to descriptively assess secondary imaging effectiveness endpoints and secondary neurologic effectiveness endpoints (Table 14). The sponsor reported analyses of all secondary imaging and neurologic effectiveness endpoints using pooled controls rather than the protocol-specified Phase II control group only.

The sponsor also conducted a comparison of the PT population, (subjects with complete TriGUARD 3 3-vessel coverage for at least 2 of 3 timepoints throughout the procedure and without conversion to surgery or prolonged cardiac arrest prior to the post-procedure DW-MRI), to the Pooled Control group.

For all secondary *clinical* neurological endpoints for all analysis patient populations, the TriGUARD 3 performed numerically worse than the control group. The TriGUARD 3 performed numerically better for two secondary imaging endpoints, notably per-patient single cerebral ischemic lesion volume (72.8 ± 63.7 mm^3 vs. 83.3 ± 112.9 mm^3) and average single cerebral ischemic lesion volume (74.9 ± 161.1 mm^3 vs. 81.4 ± 328.3 mm^3). Numerical benefit was also enhanced when the PT population was analyzed; however, the numerical benefit is limited to those cases where successful positioning (3-vessel coverage) was maintained in any 2 of 3 procedural timepoints. It is important to note that assessments of these endpoints were to be conducted as descriptive analyses and not for hypothesis testing.

Table 14: Secondary Imaging and Neurologic Effectiveness Endpoints

	TriGUARD 3			Pooled Control
	eITT[1] *N=112*	PT[2] *N=62*	Roll-in[3] *N=41*	eITT[4] *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[7]				
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)[4]				
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)

	TriGUARD 3			Pooled Control
	eITT[1] *N=112*	PT[2] *N=62*	Roll-in[3] *N=41*	eITT[4] *N=119*
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) [8]				
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)
Neurologic Efficacy				
NIHSS worsening [5]				
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[6]				
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 [2]	8.6% (6/70)	5.4% (2/37)	3.7% (1/27)	2.6% (2/78)

[1] Worsening of NIHSS score is defined as a higher NIHSS score at the time of assessment than at baseline.
[2] Defined as NIHSS worsening accompanied by the presence of cerebral ischemic lesions. Endpoints evaluated at 30 days post-procedure are based on NIHSS collected at 30 days and MRI results collected at post-procedure.
[3] Number of lesions is transformed with a square root for p-value calculations.
[4] Volume=0 is assigned to patients without cerebral ischemic lesions. Endpoint is transformed with a cubic-root for p-value calculations.

The results presented for the primary and secondary effectiveness endpoints in the eITT population presented in Table 13 and Table 14 indicate the following:

- The Control group had an observed numerical advantage with regard to:
  - All-cause mortality or any stroke at 30 days
  - NIHSS worsening (at 2-5 days and 30 days post-procedure)
  - Presence of cerebral ischemic lesions
  - Total volume of cerebral ischemic lesions (with exception of the maximum volume within the range)
  - New neurological impairment
  - Number of cerebral ischemic lesions

- The TriGUARD 3 had an observed numerical advantage with regard to:
  - Mean (but not median) per-patient average single cerebral ischemic lesion volume
  - Single lesion volume

Multiple additional post-hoc DW-MRI analyses were conducted by the sponsor in order to further assess DW-MRI findings between groups. Key sponsor conclusions are as follows:

- The TriGUARD 3 group had higher rates of baseline clinical CVA/TIA and higher baseline T2 lesion volume;
- In the subset of patients with complete coverage during at least 2 of the procedural timepoints (PT), the TriGUARD 3 group had smaller total number and volume of new cerebral ischemic lesions, as well as smaller individual lesion sizes (per-patient average and maximum single cerebral ischemic lesion volumes);
- In the subset of patients who experienced stroke, the TriGUARD 3 group had smaller lesions (per-patient average single and maximum cerebral ischemic lesion volumes); and
- The sponsor identified a more pronounced impact as the lesion volume threshold increased (i.e., reduction in lesion volume was more pronounced when considering all lesions larger than a particular size).

Additional findings and details are outlined in Section 9.6 of the Phase II CSR (Section 19 Appendix H).

FDA Comment 12: It's unclear to FDA whether the use of the PT population in effectiveness analyses represents the intended patient population. Additionally, the clinical significance of the select secondary imaging endpoints where the TriGUARD 3 showed numerical improvement over the Control is unclear within the context of benefit to patients.

FDA's perspective on the use of the PT population is provided in Section 9.4.3. FDA's perspective on secondary imaging endpoint findings is provided in Section 9.4.9.

9.1.10.3.4 Secondary Performance Endpoints

The sponsor prespecified numerous secondary performance endpoints to evaluate the technical performance of the device (see Section 15.3, Appendix D). Select secondary performance endpoints related to successful device positioning are presented in Table 15. For secondary performance endpoints, the secondary AT analysis is identical to the primary ITT population results because all 5 subjects that were included in the ITT population but not the AT population withdrew prior to the procedure, and therefore do not have device performance data. FDA also reports post-hoc rates for subjects with complete 3-vessel TriGUARD 3 coverage for all 3 procedural timepoints in Table 15 and Figure 10. The presented data for this analysis is limited to patients with interpretable angiography at all three timepoints.

Of note, in the "During TAVR" procedural timepoint, 72.4% of ITT subjects had complete 3-vessel coverage and 19.0% of ITT subjects had no coverage. Additionally, 3-vessel coverage during all three procedural timepoints was achieved in 55.8% of randomized TriGUARD 3 and roll-in subjects with available angiograms to evaluate positioning success.

Table 15: Select TriGUARD 3 Secondary performance endpoints [1, 2]

	ITT/AT [3]	Roll-In	SP[ITT] ITT+RI
Device Positioning Pre-TAVR			
Complete (3 vessel)	62.1% (59/95)	58.8% (20/34)	61.2% (79/129)
Partial (1 or 2 vessel)	15.8% (15/95)	26.5% (9/34)	18.6% (24/129)
No vessel coverage	22.1% (21/95)	14.7% (5/34)	20.2% (26/129)
Device Positioning During TAVR			
Complete (3-vessel)	72.4% (76/105)	80.0% (32/40)	74.5% (108/145)
Partial (1 or 2 vessel)	8.6% (9/105)	7.5% (3/40)	8.3% (12/145)
No vessel coverage	19.0% (20/105)	12.5% (5/40)	17.2% (25/145)
Device Positioning Post-TAVR [4]			
Complete (3 vessel)	71.4% (80/112)	72.5% (29/40)	71.7% (109/152)
Partial (1 or 2 vessel)	12.5% (14/112)	15.0% (6/40)	13.2% (20/152)
No vessel coverage	16.1% (18/112)	12.5% (5/40)	15.1% (23/152)
Coverage during any 2 of 3 timepoints			
Complete (3 vessel)	58.2% (64/110)	62.5% (25/40)	59.3% (89/150)
Coverage during all 3 timepoints [5]			
Complete (3 vessel)	54.7% 52/95	58.8% 20/34	55.8% 72/129
Device Interference [6]	8.6% 10/116	12.2% 5/41	9.6% 15/157
Technical Success [7]	69.5% 73/105	75.0% 30/40	71.0% 103/145
Procedural Success [8]	67.6% 71/105	75.0% 30/40	69.7% 101/145

[1] Phase II CSR, Table 28a

[2] Subjects with Coverage = N/A (due to indiscernible angiograms) are not included in the denominator.

[3] Five (5) TG3 randomized subjects did not undergo the TAVR procedure and were not followed, and therefore are not included in the denominators. The ITT and AT populations are the same in this case.

[4] Post-TAVR: After any additional post-dilatation or valve implantations have been completed, and the TAVR delivery system has been removed.

[5] This is not a prespecified secondary endpoint in the study protocol.

[6] Device interference: Interaction of the TriGUARD 3 device with the TAVR system leading to (1) inability to advance or manipulate the TAVR delivery system or valve prosthesis, OR (2) inability to deploy the TAVR valve prosthesis, OR (3) inability to retrieve the valve prosthesis or delivery system.

[7] Technical success: Successful device deployment, device positioning for complete coverage during TAVR, and successful device retrieval in the absence of device interference.

[8] Procedure success: Technical success in the absence of any investigational device-related or procedure-related in-hospital procedural safety events.

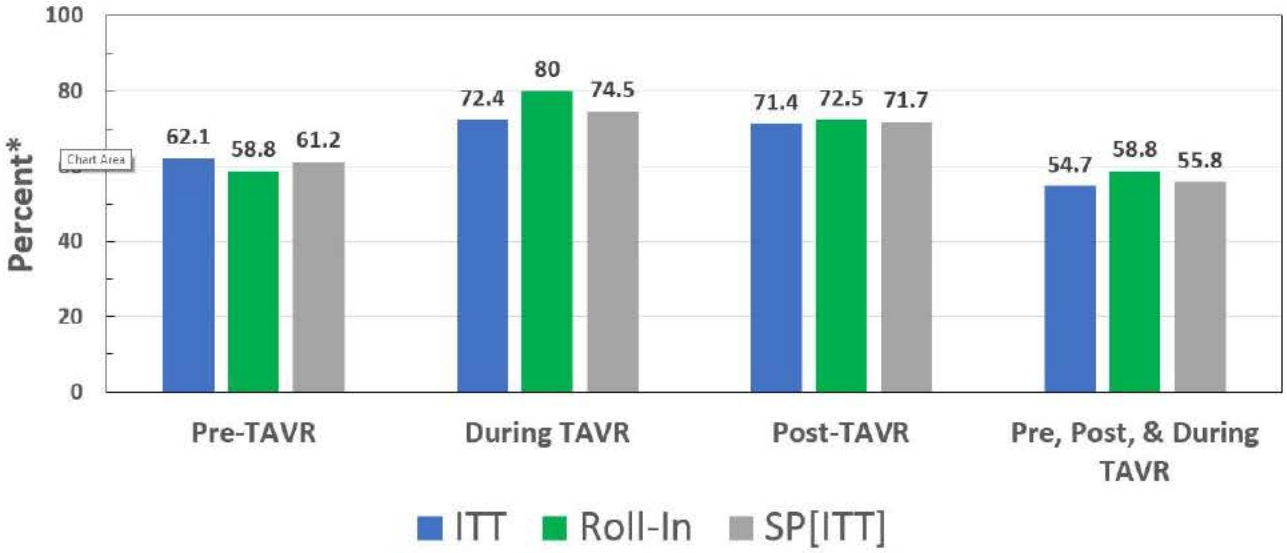

Figure 10. Percent of subjects with complete 3-vessel coverage at various timepoints
*Note, this analysis was conducted on patients with evaluable imaging.

<u>FDA Comment 13</u>: FDA perspectives on the coverage/positioning assessment of the device are provided in Section 9.4.10 below. The Panel will be asked to comment on the observed vessel coverage rates as they relate to special control 7(iii) for ability to maintain stable positioning.

Key safety endpoints were evaluated by vessel coverage during at least 2 of 3 procedural timepoints and stratified by coverage: full coverage (3-vessel), partial coverage (1 or 2 vessel), or no coverage (Figure 11). The observed ischemic stroke rate in the REFLECT Phase II TriGUARD 3 subjects was numerically highest (7.7%) in patients with no coverage.

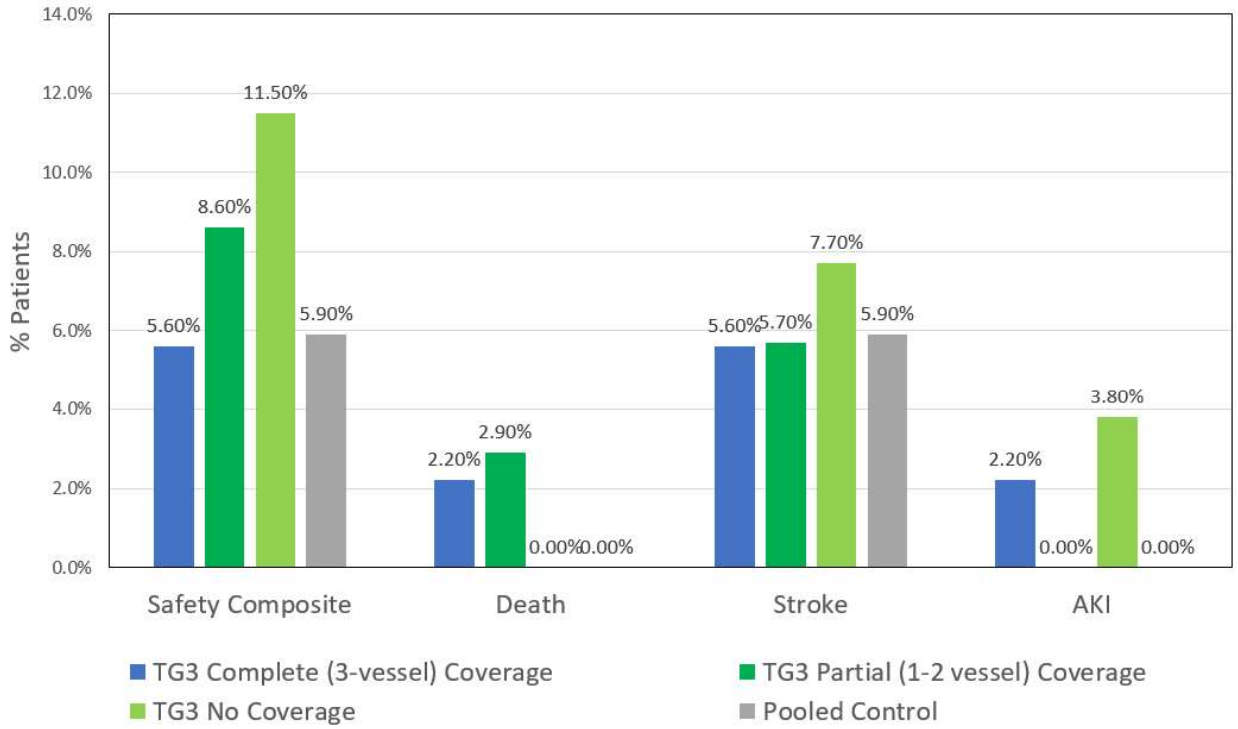

Figure 11: Comparison of key safety outcomes for patients with complete, partial, and no Coverage, for TriGUARD 3 SP(AT) subjects and Phase I and II Pooled Control Subjects.
*Note, this analysis was conducted on patients with evaluable imaging. Data was limited to those patients with coverage in at least 2 of 3 timepoints.

9.1.11 REFLECT Phase II Incomplete Enrollment: FDA Tipping Point Analysis on Primary Effectiveness Endpoint Components

Enrollment of the Phase II study was suspended after recommendations from the DMC and FDA based on a review of unblinded interim safety data. At the time of trial suspension, enrollment in the Phase I randomized cohort was 121 TriGUARD 3 subjects and 58 control subjects, 46 subjects fewer than the target enrollment of 225 subjects (Figure 12). FDA conducted tipping point analyses to assess the potential impact of early study enrollment suspension on the evaluation of the primary effectiveness endpoint components.

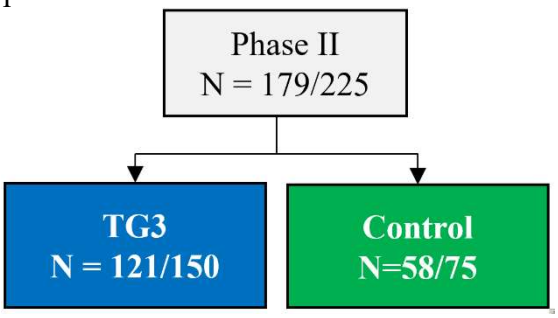

Figure 12. REFLECT Phase II enrollment (N = actual enrollment/assumed total)

In the tipping point analyses, FDA simulated all possible outcome scenarios regarding each primary effectiveness endpoint component for the 46 future subjects who would have been enrolled in the study if the study had enrolled to completion. Given the 2:1 randomization scheme, for simplicity, FDA assumed that 29 subjects out of the 46 future subjects would be randomized to the TriGUARD 3 group and 17 subjects would be randomized to the control group; the final enrollment would consist of 150 TriGUARD 3 subjects and 75 control subjects. Tipping point analyses were conducted based on the eITT population with Pooled Controls, the observed results of which are based on the actual enrollment as summarized in Table 12.

Tipping point analyses were conducted for each primary effectiveness endpoint component to evaluate the scenario(s) where the treatment effect estimate would numerically favor the TriGUARD 3 group. Key results are summarized below.

- **Assuming that the future subjects perform similarly to the enrolled subjects in both study groups,** the observed 30-day death or stroke rate, NIHSS worsening rate, and mean total volume of cerebral ischemic lesions would be numerically higher in the TriGUARD 3 group compared to the control group based on the target enrollment of 225 subjects; while cerebral ischemic lesion rate in the TriGUARD 3 group would be generally similar to the control group.

- **Assuming that the future 29 TriGUARD 3 subjects perform similarly to the enrolled TriGUARD 3 subjects**, to observe a treatment effect favoring the TriGUARD 3 group for each component based on the target enrollment, the 17 future *control* subjects need to have a much higher event rate for 30-day death or stroke, NIHSS worsening, and total volume of cerebral ischemic lesions compared to the observed rate among the actually enrolled control group (Table 16). FDA believes the likelihood of this scenario occurring is very low.

Table 16: Minimum Event Rates among the 17 Future Control Subject Required to Observe Treatment Effects Favoring TriGUARD 3 Group Regarding Primary Effectiveness Endpoint Components

Endpoint	Minimum Required Event Rate among the 17 Future Control Subjects	Observed Event Rate of Enrolled Control Subjects
Mortality/Stroke @ 30D	35.3% (6/17)	6.7%
NIHSS Worsening	58.8% (10/17)	7.6%
Cerebral Ischemic Lesions	88.2% (15/17)	84.9%
Total volume of cerebral ischemic lesions (mean)	1084.01 mm^3	508.22 mm^3

- **Assuming that the future 29 TriGUARD 3 subjects are event free for 30-day death or stroke and NIHSSS worsening,** to observe a treatment effect favoring the TriGUARD 3 group regarding each component based on the target enrollment, the 17 future control subjects need to have a much higher event rate for 30-day death or stroke and NIHSS worsening compared to the corresponding observed rates among the actually enrolled control group (Table 17). FDA believes the likelihood of this scenario occurring is very low.

Table 17: Minimum 30-day Death or Stroke Rate and NIHSSS Worsening Rate among the 17 Future Control Subject Required to Observe Treatment Effects Favoring TriGUARD 3 Group Regarding These Two Components

Endpoint	Required Event Rate for future control subjects	Observed Event Rate of control subjects
Mortality/Stroke @ 30D	17.6% (3/17)	6.7%
NIHSS Worsening	35.3% (6/17)	7.6%

- **Assuming that the future 17 control subjects perform similarly to the enrolled control subjects,** it would not be possible to observe a treatment effect favoring the TriGUARD 3 group regarding mortality/stroke and NIHSS worsening based on the target enrollment. For total volume of cerebral ischemic lesions, to observe a treatment effect favoring the TriGUARD 3 group under a similar assumption, the observed mean total volume of cerebral ischemic lesions among the future 29 TriGUARD 3 subjects needs to be less than 233.81 mm^3, which is less than half of the observed mean total volume of cerebral ischemic lesions among the enrolled TriGUARD 3 group (587.80 mm^3).

FDA also conducted an additional set of tipping point analyses for each primary effectiveness component to evaluate the scenario(s) where there would be a statistically significant treatment effect favoring the TriGUARD 3 group at a one-sided alpha level of 0.15 based on the target enrollment if the future 46 subjects had evaluable primary effectiveness endpoint data. Section 16.3 (Appendix E) includes the full results of the two sets of FDA's tipping point analyses.

9.2 Adjunctive Data Provided in the 510(k)

9.2.1 Real-world data from the Netherlands Heart Registry

The sponsor provided real-world clinical data from commercial use of the TriGUARD 3 device with the modified crimper (see Section 7.3) collected in the Netherlands Heart Registry (NHR). These data were provided to address issues related to the 55.8% rate for successful positioning (complete 3-vessel coverage in all 3 procedural timepoints) observed for the randomized TriGUARD 3 and roll-in patients in the REFLECT Phase II study.

Please note that a full dataset, with patient-level data and statistical code, wase not provided to FDA.

9.2.1.1 Study Design

This is a single-center, single arm, real-world registry to evaluate the safety and performance of the TriGUARD 3 in patients undergoing TAVR in real-world clinical practice. A total of 50 consecutive patients were enrolled at 1 site at the University Medical Center Utrecht in Utrecht, Netherlands. The primary safety endpoint was evidence of neurological symptoms (clinical stroke or TIA) within 72 hours post-TAVR procedure or at hospital discharge (whichever came first). The primary device performance endpoint was successful deployment and complete coverage of the aortic arch branches (brachiocephalic, left carotid, subclavian) during device positioning (defined as the ability to position the TriGUARD 3 device in the aortic arch) and ability of TAVR system components to cross under the TriGUARD 3 device.

9.2.1.2 Study Results

No patient was diagnosed with primary clinical symptoms (Stroke or TIA), within 72 hours post-TAVR or at hospital discharge (Table 18).

Table 18: RWE Primary Safety Endpoint Results

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

The TriGUARD 3 device was successfully deployed with correct orientation on the first attempt and complete cerebral coverage was achieved in all patients (Table 19).

Table 19: RWE Primary Effectiveness Endpoint Results

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

<u>FDA Comment 14</u>: The real world study follow-up was limited to immediately post-procedure and 72-hours post-procedure. Other study limitations include uncertainty regarding external generalizability (only 1 clinical site and 3 operators) and limited outcome assessments. Specifically, imaging was missing in 16 of 50 patients during TAVR implantation, and no pre-TAVR or post-TAVR images were provided. Therefore, it is unclear whether the device maintained stable positioning throughout the entire TAVR procedure (pre-TAVR, during TAVR, and post-TAVR). There was also uncertainty regarding:

(1) the expertise of those who evaluated the primary safety and performance endpoints, as neurological assessments were not performed by a neurologist unless there were clinical findings of neurological symptoms or overt stroke, and adverse events were reported without independent review;

(2) whether the common data capture form included appropriate detail and adequate data elements to provide consistency among cases; and
(3) whether the study design and data collection methods (including imaging) provided sufficient granularity to assure complete adverse event ascertainment for all enrolled patients.

The Panel will be asked to comment on the RWE and its potential value in the evaluation of the TriGUARD 3 performance in the context of Special Control 7(iii).

Limitations with the RWE make it challenging to assess events and draw conclusions regarding whether the data support that the crimper and labeling modifications result in improved device positioning in support of Special Control 7(iii).

9.3 Comparison of REFLECT Phase II with SENTINEL Trial Results

9.3.1 SENTINEL RESULTS: Primary Endpoint Composite and Components

- **Safety**: The primary safety endpoint of 30-day MACCE (ITT) was met (MACCE = 7.3% with 95% CI UL of 10.7% which was less than the PG of 18.3%; $p<0.0001$). Similar to the REFLECT Study, the SENTINEL study was not powered to show a difference in adverse event rates between the test and control groups. Note that the definition of safety differed between the SENTINEL and REFLECT studies. In the SENTINEL study, MACCE was defined as all death, all stroke, and acute kidney injury (AKI) class 3. Because there were fewer components in the primary Sentinel composite, the SENTINEL trial had a lower PG rate (i.e., 18.3% for the SENTINEL compared to 34.4% for the TriGUARD in REFLECT), precluding a direct comparison of the composite 30-day MACCE rate. Considering the individual components, excluding AKI, component event rates numerically favored the Sentinel group compared to its control. In particular, the 30-day stroke rate was lower in the Sentinel Arm (5.6%; combining the Test and Safety arms) compared to the control arm (9.1%). Also, the ITT population was used for the SENTINEL Study primary analysis whereas the AT population was used for the REFLECT primary analysis (see Table 20).

Table 20: Components of the Sentinel Predicate Safety Results: MACCE at 30-Days (Combined Safety and Test Arms) – ITT Population

Safety Events	ITT Safety Cohort[1] (Safety + Test Groups) *N = 234*[2]	AT Test Group *N = 111*[3]	ITT Test Group *N = 117*[4]	Control Group *N = 111*[5]
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%)

[1] In the 1:1:1 randomized SENTINEL study, the Safety and Test arms received TAVR + the Sentinel device, and Control subjects received unprotected TAVR. The Safety arm was not included for imaging analysis (Safety subjects did not have DW-MRI); the Test and Control subjects did have imaging (DW-MRI) for effectiveness assessment.
[2]Sentinel Executive Summary, Table 8
[3]Sentinel Executive Summary, Table 11
[4]Sentinel Executive Summary, Table 11
[5]Sentinel Executive Summary, Table 11

<u>FDA Comment 15</u>: Similar to the TriGUARD 3 device, the Sentinel device met its primary safety endpoint. The individual components of the primary safety endpoint differ between the REFLECT and SENTINEL studies (see Table 22). However, when considering individual components of the primary safety endpoint, the SENTINEL trial showed that rates numerically favored the Sentinel device vs. no protection (Table 20), in contrast to the REFLECT trial which showed that numerical rates favored the control group vs. the TriGUARD 3 group (see Table 9). The Panel will be asked to provide input on the clinical relevance of the individual components of the primary safety endpoint as they relate to substantial equivalence between TriGUARD 3 and Sentinel.

- **Effectiveness:** In the SENTINEL study, the primary effectiveness endpoint was 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 diffusion weighted MRI (DW-MRI). Two assessments were designed to evaluate DW-MRI infarct

lesion volume between patients with and without protection (see Table 24). In the SENTINEL Study, superiority was not demonstrated for the pre-specified endpoint, and there was not a significant reduction in median total new ischemic lesion volume in protected territories. Note that the primary analysis excluded cerebral territories attributed to embolic debris from the left vertebral artery which is unprotected by the Sentinel device. Superiority was also not demonstrated when all cerebral territories were considered. The Sentinel device showed a numerical improvement in median total new lesion volume for the ITT population with and without imputation for protected and all territories. It is also notable that when all territories are considered, the numerical improvement is attenuated (Table 21).

Table 21: Effectiveness Results - Reduction in median total new lesion volume in between the Test and Control Arms as assessed by DW-MRI at Day 2-7 post-procedure.

Population[1]	Test Group (mm^3)	Control Group (mm^3)	Observed Treatment Difference (Test - Control)	p-value[2]
Protected Territories				
ITT with Imputation[3]	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
All Territories				
ITT with Imputation[4]	247.2 (97.6, 572.2), n=121 0 min, 14179 max	311.1 (110.7, 848.4), n=119 0 min, 24300 max	-63.9	0.5794
ITT	294 (69.2, 786.4) n=91 0 min, 14179 max	309.8 (105.5, 859.6) n=98 0 min, 24300 max	-15.8	0.8076

[1]FDA Sentinel Executive Summary; Tables 9 and 14

[2]Based on two-sided Wilcoxon test. P-values for the All Territories analysis is for reference only and should not be used to make inference since no formal statistical tests were pre-specified for this secondary analysis.

[3]Missing lesion volume was imputed using Multiple Imputation.

[4]Although not pre-specified for the secondary All Territories analysis, missing lesion volume was imputed using Multiple Imputation and results for the ITT with Imputation population are presented for reference.

Similarly, the TriGUARD 3 effectiveness endpoints for clinical and imaging endpoints were not met as discussed in Section 9.1.10.2, but select secondary imaging endpoints were identified to favor the TriGUARD 3 over the control, namely per-patient single cerebral ischemic lesion volume

(72.8 mm3 vs. 83.3 mm3) and average single cerebral ischemic lesion volume (74.9 mm3 vs. 81.4 mm3) as discussed in Section 9.1.10.3.3.

A qualitative comparison of the DW-MRI results for TriGUARD 3 and Sentinel compared to their respective control groups within the individual studies is presented in Table 26 and Figure 14 below.

FDA Comment 16: Effectiveness results from the SENTINEL study indicated that superiority was not demonstrated for the pre-specified endpoint, and there was not a significant reduction in median total new lesion volume in protected territories. However, the Sentinel device showed a numerical reduction in median total new lesion volume for the ITT population with and without imputation for protected and all territories. A similar trend was not observed for the TriGUARD 3 device, and the clinical relevance of secondary descriptive endpoints is uncertain. The Panel will be asked to discuss the primary effectiveness endpoint results from the REFLECT study and how they compare to those of the SENTINEL study in determining effectiveness equivalence.

FDA regulatory considerations regarding the class II designation of embolic protection devices require the TriGUARD 3 to be substantially equivalent to the predicate device and to meet the special controls. In evaluating the substantial equivalence of the TriGUARD 3 device, FDA believes that the key analyses assess the TriGUARD 3 vs. its REFLECT trial randomized control group compared with the Sentinel device vs. its SENTINEL trial randomized control group. Sections 9.3.2 – 9.3.4 present these informative analyses. However, FDA acknowledges that there are limitations when comparing results of separate studies.

9.3.2 Comparison of REFLECT and SENTINEL Primary Safety Endpoints

The REFLECT Phase II and SENTINEL trials both used 30-day primary safety composite endpoints compared to a PG; however, the components of the composite endpoints differed between the two randomized studies. The endpoints components and outcomes are shown for both trials in Table 22.

Table 22: REFLECT Phase II vs. SENTINEL 30-Day Composite Primary Safety Endpoint

30 Day Composite Primary Safety Endpoint	Primary Analysis Population	Subjects with Events	UL 95% CI	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

In order to establish substantial equivalence per Special Control 7(iv), individual safety events were assessed for the two randomized trials and presented in Table 23 and Figure 13.

FDA Comment 17: Given that the information consists of data from two separate randomized trials, drawing conclusions from a comparison of the TriGUARD 3 and Sentinel outcomes is challenging. However, qualitative comparisons of TriGUARD 3 vs. its randomized control in the REFLECT study and Sentinel vs. its randomized control in the SENTINEL study is illustrative. Note that data presented below for the REFLECT Phase II study is on the As Treated population and does not include Roll-in subjects that were prespecified to be included for the primary safety analysis. Data for the SENTINEL study ITT population also does not include Roll-in subjects.

Table 23: REFLECT Phase II vs. SENTINEL Safety Comparison

REFLECT Phase II Study[1]			SENTINEL Study[2]		
Safety Endpoints AT Population	**TriGUARD 3**	**Control**	**Safety Endpoints ITT Population**	**Sentinel**	**Control**
All-Cause Death	3.4% (4/116)	1.8% (1/57)	All-Cause Death	1.3% (3/234)	1.8% (2/111)
Stroke (Disabling and Non-Disabling)	11.2% (13/116)	5.3% (3/57)	Stroke (Disabling and Non-Disabling)	5.6% (13/231)	9.1% (10/110)
Life-Threatening or Disabling Bleeding	6.9% (8/116)	0	Life-Threatening or Disabling Bleeding	N/A	N/A
Acute Kidney Injury (Stage 3)	2.6% (3/116)	0	Acute Kidney Injury (Stage 3)	0.4% (1/231)	0
Coronary Artery Obstruction Requiring Intervention	0.9% (1/116)	0	Coronary Artery Obstruction Requiring Intervention	N/A	N/A
Major Vascular Complication	8.6% (10/116)	0	Major Vascular Complication[3]	8.6% (21/244)	5.9% (7/119)
TG3 Access Site-Related	1.7% (2/116)	0	Sentinel Access Site-Related	0.4% (1/244)	N/A
TAVR or Other Access Site-Related	6% (7/116)	0	TAVR or Other Access Site-Related	N/A	N/A
Secondary Access Site-Related	0	0	Secondary Access Site-Related	N/A	N/A
Aortic Vascular Injury	1.7% (2/116)	0	Aortic Vascular Injury	N/A	N/A
Valve Related Dysfunction Requiring Intervention	0.0% (0/157)	0	Valve Related Dysfunction Requiring Intervention	N/A	N/A

[1] Phase II CSR, Table 18 and Keystone AINN Response, Table 18

[2] FDA Sentinel Executive Summary, Table 8

[3] FDA Sentinel Executive Summary, Table 12; all major vascular complications, including TAVR access as well as Sentinel (radial, brachial)

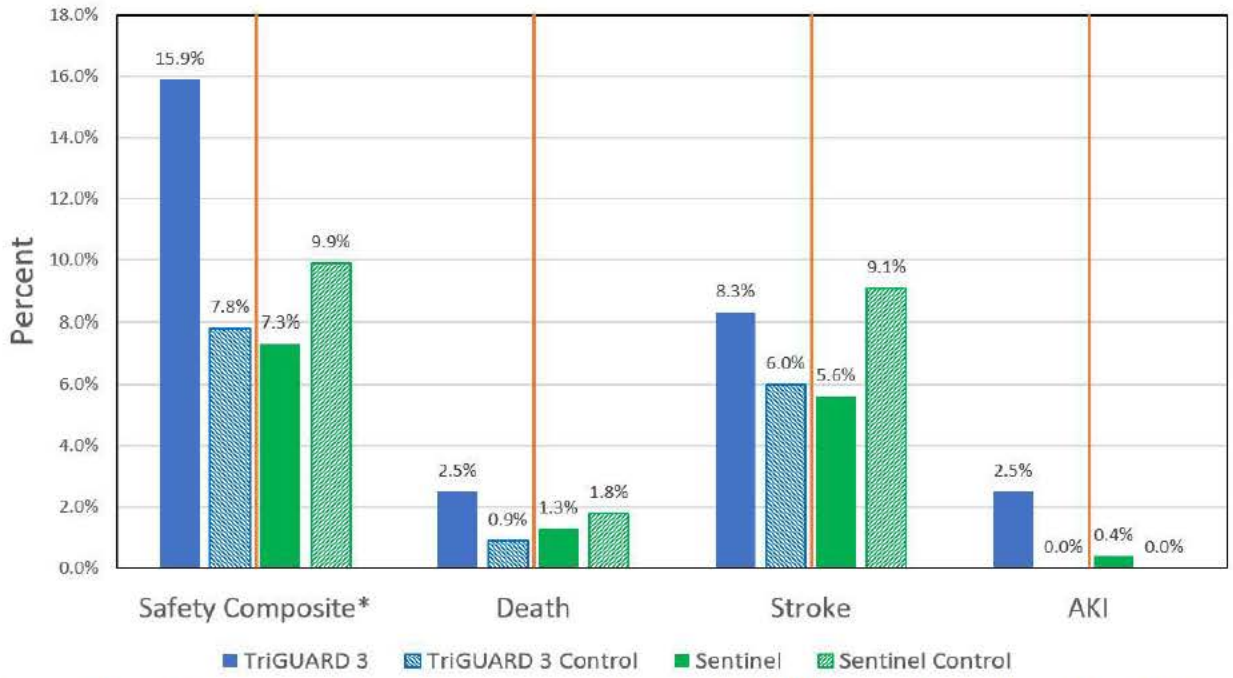

Figure 13: Safety composite and components for TriGUARD 3 vs. Control and Sentinel vs. Control.

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

Stroke rates were numerically higher for the TriGUARD 3 group (AT population) compared to its control group (11.2% vs 5.3%, respectively). In contrast, the Sentinel test group had a numerically lower stroke rate compared to its control group (5.6% vs 9.1%, respectively).

Vascular complications observed in the REFLECT Phase II study are discussed in Section 9.1.10.1.3. In the SENTINEL study, there was 1/244 (0.4%) subject with a brachial artery vascular complication event with probable or highly probable relation to the Sentinel system within 30 days of the index procedure. Note that the predicate Sentinel device is placed through a radial artery, so access site complications are more easily attributable to the embolic protection device.

<u>FDA Comment 18</u>: FDA notes that these observations are numerical comparisons, and neither study was powered to compare stroke rates between test and control groups. FDA acknowledges that comparing event rates between studies has limitations and does not account for potential differences between studies such as patient selection, endpoint definitions, and analysis populations.

However, FDA notes the numerically higher stroke rate in the TriGUARD 3 arm compared to its control group was not observed in the SENTINEL trial.

9.3.3 REFLECT Primary Effectiveness Endpoint Compared to Sentinel Device

The REFLECT Phase II and SENTINEL trials used different primary effectiveness endpoints, rendering a comparison of effectiveness results across the studies challenging. The primary effectiveness endpoints for the REFLECT Phase II and SENTINEL trials are shown in Table 24.

The SENTINEL Study utilized a purely imaging based endpoint for effectiveness analysis. In contrast, the REFLECT Phase II study utilized a composite endpoint for effectiveness that included both clinical and imaging components.

Table 24: REFLECT Phase II vs. SENTINEL Primary Effectiveness Endpoints

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

The primary effectiveness results for the REFLECT Phase II study are shown in Section 9.1.10.2, and the primary effectiveness results for the SENTINEL trial are shown in Table 25.

Table 25: SENTINEL Primary Effectiveness Endpoint Results

	Sentinel device Median, (IQR), n, min, max	Control Median, (IQR), n, min, max	Observed Treatment Difference (Test - Control)	p-value[1]
Criterion 1: Median DW-MRI Total New Lesion Volume at 2-7 days (protected territories), mm^3	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	0.24
	Sentinel device Median, (IQR), n, min, max	**Control Median, (IQR), n, min, max**	**Target**	**Observed % Reduction (Test-Control)/Control**
Criterion 2: 30% reduction in DW-MRI Median Total Lesion Volume at 2-7 days (protected territories), mm^3	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

For the SENTINEL study, the sponsor defined "protected territories" as a limitation based on the device design since the Sentinel inherently does not cover all 3 great vessels. However, results from SENTINEL are also available representing "all territories" not limited to those protected by the Sentinel and provide a closer comparison to data presented for the TriGUARD 3, which is intended to cover all territories.

Table 26: REFLECT Phase II vs. SENTINEL DW-MRI Lesion Volume Comparison

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

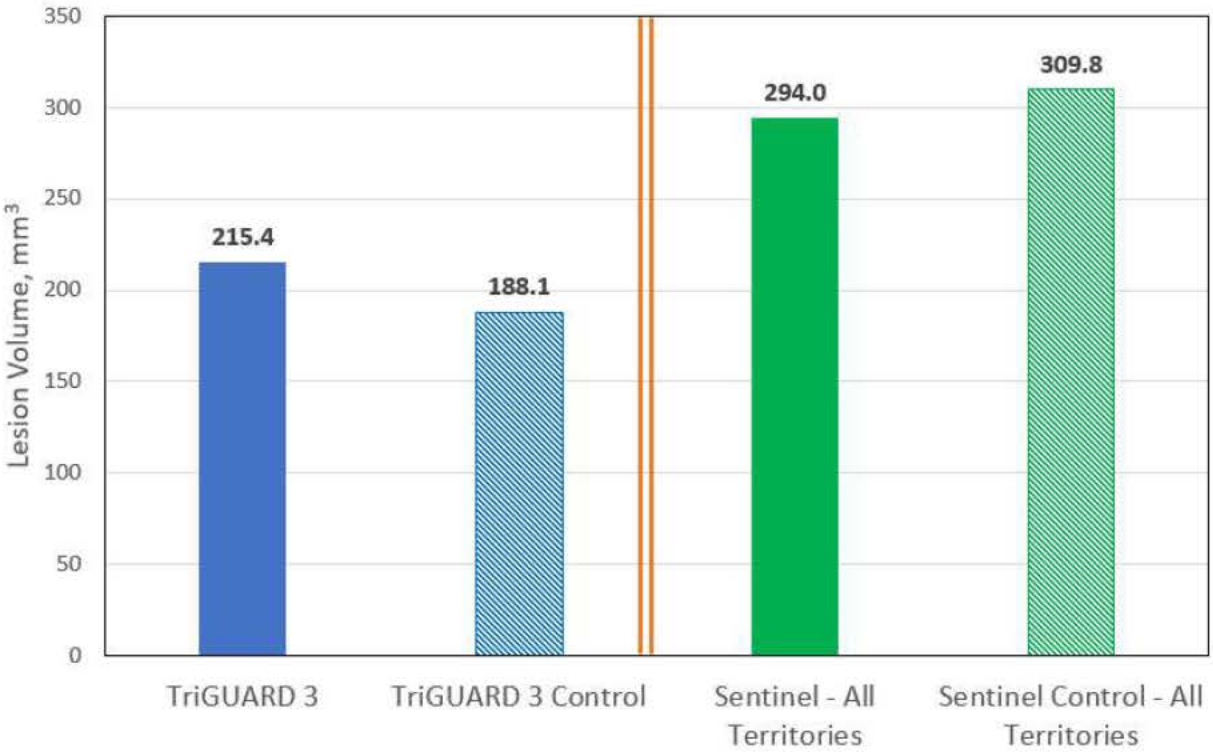

Figure 14: Median Cerebral Lesion Volume for TriGUARD 3 v. Control and Sentinel v. Control

FDA Comment 19: Given that device comparative information consists of data from two separate randomized trials, drawing conclusions from TriGUARD 3 vs. Sentinel effectiveness outcomes has limitations. When performing a numerical assessment of individual components of the primary effectiveness endpoint of the TriGUARD 3 compared to the Phase II control, all endpoint components in the eITT and ITT populations numerically favored the control (Table 13).

Neither the Phase II TriGUARD nor the Sentinel trial met its pre-specified effectiveness endpoint. However, the SENTINEL study defined two criteria for the primary effectiveness assessment and met Criterion 2 (a prespecified descriptive assessment). For both effectiveness criteria, numerical outcomes favored the Sentinel device group vs. the control group. Conversely, as noted in Table 13, numerical outcomes favored the pooled control group vs. the TriGUARD control group (6.7% vs. 9.8% for all-cause mortality or any stroke at 30 days and 7.6% vs. 14.1% for NIHSS worsening for the eITT population).

Furthermore, benefit was not observed for the TriGUARD 3 compared to the pooled control when considering either imaging endpoint (cerebral ischemic lesions detected by DW-MRI and total volume of cerebral ischemic lesions) for the eITT population. Only when the analysis is limited to the PT population do rates for all-cause mortality or any stroke become comparable between TriGUARD 3 and the pooled control (6.5% vs 6.7%). Even here, the NIHSS worsening continues to be numerically worse for TriGUARD 3 population in comparison to the control (13.8% vs 7.6%).

The sponsor presented the primary effectiveness analysis using the PT cohort. FDA does not agree that the PT population most appropriately represents the intended population. FDA believes that the eITT cohort should be considered in the primary study analysis.

9.3.4 TriGUARD 3 Positioning Compared to Sentinel

The TriGUARD 3 device is designed to be deployed in the aortic arch and deflect debris from entering any cerebral vessel. The predicate Sentinel device is designed with 2 filter baskets to capture debris and "protect" 3 of the 4 cerebral vessels and leaves the left vertebral artery "unprotected."

Secondary performance endpoints in the REFLECT Phase II study related to successful device positioning in terms of the TriGUARD 3 device achieving 3-vessel coverage were discussed in Section 9.1.10.3.4. There are no comparative data for the Sentinel device, since successful positioning during the course of the TAVR procedure was not measured in the SENTINEL trial; therefore, no direct comparison is possible.

During the SENTINEL trial, the rate of successful deployment and retrieval was 94.4% for the Sentinel device, and debris was captured in the retrieved filters in 99% of subjects receiving the device. There were 9/296 (3.1%) device malfunctions reported in the SENTINEL trial, none of which were associated with adverse events. However, angiographic data was not collected to determine device positioning after filter deployment in the SENTINEL trial.

Considering the totality of the data, FDA determined that the Sentinel device met special control 7(iii) for maintaining secure and stable positioning and that the device functioned as intended.

As shown in Table 15:

- Device interference with the TAVR device (defined as (1) inability to advance or manipulate the TAVR delivery system or valve prosthesis; (2) inability to deploy the TAVR valve prosthesis; or (3) inability to retrieve the valve prosthesis or delivery system) was observed in 9.6% of subjects who received the TriGUARD 3 device.
- Technical success (defined as successful device deployment, device positioning for complete coverage during TAVR, and successful device retrieval in the absence of device interference) was achieved in 71.0% of subjects who received the TriGUARD 3 device.
- Procedural success (defined as technical success in the absence of any investigational device-related or procedure-related in-hospital procedural safety events) was achieved in 69.7% of subjects who received the TriGUARD 3 device.

In the SENTINEL trial, procedural success (successful deployment of at least one filter) was achieved in 99.6% of subjects who received the Sentinel device.

9.4 FDA's Perspective

The Panel will be asked to discuss the REFLECT study safety and effectiveness results in terms of whether they support substantial equivalence of the TriGUARD 3 device to the Sentinel device. The panel will also be asked to comment on the clinical meaningfulness of various REFLECT study patient populations and outcomes. Specific comments regarding the following will be instructive:

- Poolability of Phase I and II control groups
- Inclusion of roll-ins in the primary safety analysis
- Analyses based on the PT group
- Impact of baseline characteristics in study interpretation and how observed baseline characteristic differences impact study outcomes
- Clinical relevance and importance of analyses that exclude events based on device relatedness as assessed by the CEC.
- The risk for vascular complications with the use of the TriGUARD 3 device compared to Control in the REFLECT Trial and as compared to the Sentinel device compared to its control in the SENTINEL Trial
- The clinical utility of the device regarding coverage of the cerebral circulation and ability to achieve stable positioning as compared to predicate Sentinel device.

In this section, FDA will offer their perspective on the key data and results that are under consideration in the assessment of substantial equivalence.

9.4.1 Poolability of Controls

While FDA agreed that pooling Phase I and Phase II controls would be acceptable under a least burdensome framework, this approach was contingent on poolability of the control groups. As discussed in Section 9.1.9.2.2, per the pre-specified SAP strategy, the Phase I and II control groups are non-poolable since the two groups were different regarding age and history of CHF. Given the above issues, if the Phase I and Phase II control groups are determined not to be poolable, the eITT analysis of the primary effectiveness endpoint with the Phase II control group only should be used as the primary analysis population. This analysis was not presented in the clinical study report since the sponsor determined the control groups to be poolable. Table 14 shows the components of the primary endpoint for both the pooled control group and the Phase II control group only.

9.4.2 Inclusion of Roll-In Subjects

A difference in primary safety outcomes was observed for the RI group compared to the randomized TriGUARD 3 group as discussed in Section 9.1.10.1.1. The observed outcome differences could not be attributed to differences in baseline characteristics of the patients in these groups. However, the sponsor suggested that the improved outcomes in RI subjects may be attributed to additional caution exercised in these initial subjects. For these reasons, there is uncertainty in the generalizability of the outcomes for RI subjects when applied to the intended population. For this reason, the clinical relevance of including RI subjects in the primary analysis is unclear.

9.4.3 The PT Population

Of the TriGUARD 3 populations, the PT population yielded the most favorable outcomes (Table 13). However, the PT population excludes TriGUARD 3 patients (and associated events) with incomplete aortic arch artery coverage (24/112 (21.4%) partial coverage; 20/112 (17.9%) no coverage; 6/112 (5.4%) uninterpretable angiograms).

FDA notes that the exclusion of subjects based on the technical performance of the device has the potential to bias results in favor of the TriGUARD 3 device by omitting events occurring in a subset of the target population.

Furthermore, based on the available data, patient predictors of TriGUARD 3 successful positioning have not been identified, and therefore refinement of the intended population to one that is more likely to experience positioning success is not possible.

9.4.4 Imbalances in Baseline Characteristics

Differences in baseline characteristics were noted between the TriGUARD 3 and pooled control group as discussed in Section 9.1.9.2.1. Differences in baseline characteristics are observed to serve in favor of and against both groups (Table 5). Specifically, there were patients in the TriGUARD 3 group who had a history of stroke and those in the Control group with IDDM whose baseline characteristics may have contributed to observed primary endpoint events. While FDA

acknowledges these observations, correlation between these differences and clinical outcomes are not readily obvious.

9.4.5 REFLECT Phase II: Primary Safety Endpoint Composite and Component Rates

Although the TriGUARD 3 met its primary safety endpoint, the individual components of the primary safety composite endpoint numerically favor the control vs. the TriGUARD 3. While these results raise questions overall, FDA particularly notes the numerically higher stroke rate (8.3% (13/157) TriGUARD 3 SP[AT] group vs. 5.3% (3/57) Phase II control) given the primary purpose of the TriGUARD 3 is to reduce the risk of brain injury by preventing embolic debris from entering the cerebral circulation during TAVR. The numerical imbalance in favor of the control group further increases when excluding RI subjects from the AT population (11.2% TriGUARD 3 AT group vs. 5.3% Phase II control group).

9.4.6 REFLECT Phase II: Primary Effectiveness Endpoint Composite and Component Rates

As discussed in Section 9.1.10.2, the primary effectiveness endpoint was not met. The composite effectiveness endpoint and its clinical and imaging components were intended to characterize the device's ability to prevent embolic debris from entering the cerebral circulation.

The sponsor provided several secondary endpoint analyses. The clinical importance of these endpoints is unclear when considering the device's intended use and the primary effectiveness endpoint results.

9.4.7 Clinical Interpretation of CEC Adjudication of Device Relatedness

The REFLECT and SENTINEL trials were randomized studies with control subjects receiving standard of care TAVR with no embolic protection. Randomization accounts for risks associated with the TAVR procedure. For these reasons, FDA believes that all events, not limited by device relatedness, should be considered in the primary safety analysis (as specified in the SAP and as presented in Section 9.1.10. of this document).

9.4.8 Vascular Events Related to Use of An Accessory Embolic Protection Device During TAVR

There is an increased bleeding risk with larger arteriotomies, and vascular complications are expected to increase in the TriGUARD 3 group compared to the control. However, within the context of a benefit-risk, the added risk of larger contralateral access was expected to be balanced by the benefit achieved from cerebral embolic protection.

Given the numerically higher stroke rates observed in the TriGUARD 3 vs. the control group, FDA notes that vascular complications impart a further negative impact on device benefit-risk.

9.4.9 Interpretation of Neurological and Imaging (DW-MRI) Effectiveness Endpoints

As discussed in Section 9.1.10.3.3, there were numerous secondary neurological and secondary imaging endpoints evaluated descriptively (see Table 14).

Considering primary and secondary endpoints, it is challenging to determine whether there is benefit of the TriGUARD 3 vs. no protection. In addition, a consensus regarding the most clinically meaningful imaging endpoints and effect size is lacking. These endpoints are not individually powered to test for significance, but a qualitative comparison of the numerical differences yields numerical advantages for both the TriGUARD 3 and control groups for various metrics. The clinical significance of the two imaging secondary endpoints that favored the TriGUARD 3 group (per-patient average single lesion volume and single cerebral ischemic lesion volume) vs. no protection is unclear.

9.4.10 Coverage / Positioning

In Table 15, FDA noted a low rate of subjects with 3-vessel coverage throughout the TAVR procedure (55.8%) and a higher than expected rate of subjects with no vessel coverage (17.2%) during the TAVR implant. Similarly, positioning difficulties and interference with the TAVR device may be correlated with rates for technical and procedural success. The adequacy of these positioning success rates in the context of special control 7(iii) are unclear.

Depending on deployment/positioning throughout the procedure, incomplete coverage of the cerebral circulation is possible, and the vessels with incomplete or lack of coverage do not predictably vary (e.g., any or all of the internal carotid arteries or vertebral arteries could be left exposed). The likelihood that a given patient will achieve complete coverage throughout the procedure also cannot be predicted.

10 Conclusions

The REFLECT Study was a prospective, multicenter, 2:1 randomized, controlled trial comparing the TriGUARD 3 device used during TAVR (test group) vs. standard unprotected TAVR (control group). REFLECT Phase I enrolled 204 of the planned 355 randomized subjects. REFLECT Phase II enrolled 179 of the planned 225 randomized subjects.

In Phase II, the TriGUARD 3 device met the pre-specified performance goal for the primary safety endpoint at 30 days. The primary effectiveness endpoint was not met. The components of the primary safety and primary effectiveness endpoints favored the control group over the TriGUARD 3 group.

FDA notes the numerically higher stroke rate observed in the TriGUARD 3 group compared to the control particularly because the primary aim of this device to prevent ischemic cerebral injury by reducing embolic material from entering the cerebral circulation. Further, it is also unclear if the added risks of AKI and vascular complications are offset by a cerebral circulation protection benefit.

To address the problem of low successful device positioning rates, additional data was provided from commercial use of the TriGUARD 3 device at a single center in Netherlands. However, there are limitations with the validity and generalizability of this data to overcome the issues with maintaining stable positioning of the device throughout the TAVR procedure observed in the REFLECT Phase II study.

Overall, the primary and supplementary data provided in the marketing submission are challenging to interpret in order to draw clear conclusions regarding the device's substantial equivalence (with respect to both safety and effectiveness) to the predicate device.

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 in terms of both safety and effectiveness. The Panel will be asked to assess the significance of the clinical results presented and comment on the benefit-to-risk profile of using the TriGUARD 3 during TAVR procedures.

11 References

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12 Appendix A – Clinical Experience with the TriGUARD 3 and TriGUARD HDH devices

Table 27: Known clinical experience with TriGUARD 3 and TriGUARD HDH devices

Study	Description	Patient Enrollment	Comments
REFLECT Phase I TriGUARD HDH used during TAVR vs. unprotected TAVR Enrollment: June 2016 – July 2017	Pivotal 2:1 randomization (TriGUARD HDH: unprotected TAVR) 26 Sites: 20 US, 6 EU	N = 445 planned enrollment; 355 randomized, 90 roll-in N actual enrollment = 258	Enrollment suspended because of safety concerns Blinding preserved to combine Phase I control patients with Phase II control patients for TG3 clearance. See Section 20 for a study results
REFLECT Phase II TriGUARD 3 used during TAVR vs. unprotected TAVR Enrollment from May 2018 – March 2019	Pivotal 2:1 randomization (TG3: unprotected TAVR) 18 US sites	N = 275 planned enrollment; 225 randomized, 50 roll-in N actual enrollment = 220	Primary Study Supporting TriGUARD 3 marketing submission Enrollment suspended at DMC and FDA recommendation for safety concerns See Section 9.1 for study results
RWE: Netherlands Heart Registry TriGUARD 3 Enrollment: July 2020 – December 2020	Single-arm physician initiated registry Single Center (Utrecht, NL) Includes the modified crimper to aid device positioning.	50 consecutive cases	Ongoing See Section 9.2.2 for study of results
DEFLECT I TG HDH only	Single-group, 6-center, OUS real-world registry	N=37	Completed The primary safety endpoint (death, stroke, life-threatening or

Study	Description	Patient Enrollment	Comments
			disabling bleeding, Stage2/3 AKI, major vascular complications) occurred in 18.1% of subjects (2 life-threatening bleeding events and 1 vascular complication).
DEFLECT II TG HDH only	OUS Pilot Study	N=14	Completed No MACCE events. Post-procedural DWI (N=11) compared to historical control group; no reduction in number (median 5.5 vs 5.0; p=0.857), however there was a significant reduction in mean lesion volume per patient (median 13.8 vs 15.1; p=0.49)
DEFLECT III TG HDH vs. unprotected TAVR NCT02070731	1:1 (TG HDH: unprotected TAVR) OUS Pivotal Study, 13-center	N= 85 subjects	Completed The primary in-hospital procedural safety endpoint (death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney injury, or major vascular complications) occurred in 21.7% of TG HDH vs. 30.8% of control subjects; P = 0.34.
First-in-Man Registry	Single Center (Utrecht, NL) TAVR with Edwards SAPIEN valve	N=15 DW-MRI at baseline and within 1 week of the TAVR in 10 patients, and retrospectively compared to a	Completed In all cases the device was successfully deployed across the aortic arch, covered the ostia of the three supra-aortic trunks as evaluated by fluoroscopy, did not

Study	Description	Patient Enrollment	Comments
		historical cohort of 20 patients who had previously undergone TAVR at the same institution.	interfere with the index procedure, and was successfully retrieved. In patients undergoing TAVR with the use of the device, patients had an average of 3.2 new ischemic lesions, compared with 7.2 in the historical comparison group. One patient suffered a TIA 2 days post-procedure. No other neurological events occurred, resulting in a 6.7% (1/15) rate of neurological complications. No vascular or bleeding complications occurred at the femoral access site, and no symptomatic peripheral (non-cerebral) embolism occurred.

13 Appendix B – Summary of Using Finkelstein-Schoenfeld Method to Conduct the Hypothesis Test for the Primary Effectiveness Endpoint

This Appendix describes the procedure for conducting the pre-specified hypothesis test for the primary effectiveness endpoint using the analytical method proposed by Finkelstein and Schoenfeld (1999).

The primary effectiveness endpoint was defined as a hierarchical 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]
- 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.

The primary effectiveness hypotheses were as follows:

H_0: The hierarchical composite of death/stroke, NIHSS worsening, any lesions detected by DW-MRI, and total lesion volumes is not different between TriGUARD 3 and control groups

vs.

H_1: The TriGUARD 3 group performs better compared to the control group regarding the hierarchical composite of death/stroke, NIHSS worsening, any lesions detected by DW-MRI, and total lesion volumes

To conduct hypothesis test using the Finkelstein-Schoenfeld (FS) method, each subject i ($i = 1, \dots, N$; N being the total number of subjects) in the study population is compared to every other subject j ($j \neq i$) in a pairwise fashion regarding the primary effectiveness endpoint. The resulting score for subject i from each comparison, u_{ij}, is 1 if subject i performed better than subject j regarding the hierarchical composite primary effectiveness endpoint; u_{ij} is -1 if subjects i performed worse than subject j; and u_{ij} is 0 if it cannot be determined which subject performed better. The details of the algorithm for obtaining u_{ij} are as follows:

1. First, the two subjects are compared regarding the first tier of the hierarchy, all-cause mortality and/or stroke at 30 days. If subject i did not experience the event while subject j had the event, or subject i experienced the event later than subject j , then $u_{ij} = 1$; if subject i had the event while subjects j did not experience the event, or subject i experienced the event before subject j, then $u_{ij} = -1$. If neither subject i nor subject j experienced the event, or subject i and subject j had the same event day, or the event status is not known for subject i and/or subject j, or it is not known which subject had the event first, then the comparison goes to the next tier.

2. At the second tier, the two subjects are compared regarding NIHSS worsening. If subject i did not experience NIHSS worsening while subject j did, or subject i experienced less severe NIHSS worsening than subject j, then $u_{ij} = 1$; if subject i experienced NIHSS worsening while subject j did not, or subject i experienced more severe NIHSS worsening than subject j, then $u_{ij} = -1$; if subject i and subject j experienced the same degree of NIHSS worsening, then $u_{ij} = 0$. If neither subject i nor subject j experienced NIHSS worsening, or NIHSS is unknown for subject i and/or subject j, then the comparison goes to the next tier.

3. At the third tier, the two subjects are compared regarding the occurrence of cerebral ischemic lesions. If subject i did not have the lesions while subject j had the lesions, $u_{ij} = 1$; if subject i had the lesions while subject j did not have the lesions, then $u_{ij} = -1$; if both subjects were lesion free or if lesion status is unknown for at least one subject, then $u_{ij} = 0$. If both subjects had cerebral ischemic lesions, then the comparison goes to the next tier.

4. At the fourth tier, the two subjects are compared regarding the total volume of cerebral lesions. If subject i had a lower total lesion volume than subject j, then $u_{ij} = 1$; if subject i had a higher total lesion volume than subjects j, then $u_{ij} = -1$; if it cannot be determined which subject had higher total lesion volume, then $u_{ij} = 0$.

Subject i's score, U_i, is the sum of u_{ij} over all $j \neq i$:

$$U_i = \sum_{j \neq i} u_{ij}$$

To conduct the hypothesis test for the hierarchical composite primary effectiveness endpoint, the total score of all TriGUARD 3 subjects, T, is computed:

$$T = \sum_{i=1}^{N} U_i D_i,$$

where D_i equals to 1 if subject i was in the TriGUARD 3 group and equals to 0 otherwise. The variance of T is

$$V = \frac{N_{TriGUARD\,3} N_{control}}{N(N-1)} \left(\sum_{i=1}^{N} U_i^2 \right),$$

where $N_{TriGUARD\,3}$ and $N_{control}$ are the number of subjects in the TriGUARD 3 group and the control group, respectively. To compute the p-value, the test statistic $Z = T/V^{\frac{1}{2}}$ is compared to the standard normal distribution. For more details of the FS method, please refer to Finkelstein and Schoenfeld (1999).

14 Appendix C - Hypothesis Driven Secondary Endpoint Results

Table 28: Hypothesis Driven Secondary Endpoint Results

	TriGUARD 3				Pooled Control
	eITT[1] *N=112*	SP(eITT)[2] RI+RCT *N=153*	PT[3] *N=62*	Roll-in[4] *N=41*	eITT[5] *N=119*
Stroke to 7 days	9.8% (11/112)	7.2% (11/153)	6.5% (4/62)	0.0% (0/41)	5.7% (7/119)
NIHSS worsening	14.1% (14/99)	12.6% (17/135)	13.8% (8/58)	8.3% (3/36)	7.6% (8/105)
All-cause mortality or any stroke at 7 days	9.8% (11/112)	7.2% (11/153)	6.5% (4/62)	0.0% (0/41)	5.9% (7/119)
CNS Infarction (NeuroARC defined) at 30 days	80.4% (90/112)	77.8% (119/153)	74.2% (46/62)	70.7% (29/41)	77.3% (92/119)
Total volume of cerebral ischemic lesions (mm^3)					
Mean ± SD (n)	587.8 ± 1028.42 (100)	552.7 ± 950.3 (134)	375.8 ± 617.7 (54)	449.5 ± 672.1 (34)	508.2 ± 1124.0 (106)
Range (Min, Max)	(0.0, 5681.3)	(0.0, 5681.3)	(0.0, 3519.00)	(0, 3688)	(0.00, 8133.60)
Median	215.4	233.4	145.71	281.3	188.1

[1]Phase II CSR, Table 22a
[2]Phase II CSR, Table 22b
[3]Phase II CSR, Table 22c
[4]Phase II CSR, Table 22d
[5]Phase II CSR, Table 22a-c

15 Appendix D – Secondary Endpoint Results

15.1 Secondary Safety Endpoints

Table 29: Secondary Safety Endpoints

Secondary Safety Endpoint	TG3 SP[AT]; RI+RCT		TG3 Roll-In		Phase II Control	
	In-hospital[1] *N=157*	30 days[2] *N=153*	In-hospital[5] *N=41*	30 days[6] *N=41*	In-hospital[3] *N=57*	30 days[4] *N=57*
MACCE (In-hospital procedural safety endpoint)	**14.0% (22/157)**	**15.9% (25/157)**	2.4% (1/41)	2.4% (1/41)	**5.3% (3/57)**	**7.0% (4/57)**
All-cause mortality	1.9% (3/157)	2.5% (4/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	1.8% (1/57)
All stroke (disabling and non-disabling)	6.4% (10/157)	8.3% (13/157)	0.0% (0/41)	0.0% (0/41)	5.3% (3/57)	5.3% (3/57)
Life threatening (or disabling) bleeding	5.7% (9/157)	5.7% (9/157)	2.4% (1/41)	2.4% (1/41)	0.0% (0/57)	0.0% (0/57)
Acute Kidney Injury - Stage 2 or 3 (including renal replacement therapy)	2.5% (4/157)	2.5% (4/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
Major vascular complication	7.0% (11/157)	7.0% (11/157)	0.0% (0/41)	2.4% (1/41)	0.0% (0/57)	0.0% (0/57)
TAVR device success[5]	**68.5% (85/124)**	**N/A**	**0.0% (0/41)**	**0.0% (0/41)**	**73.3% (33/45)**	**N/A**
Mortality			**0.0% (0/41)**	**0.0% (0/41)**		
All-cause mortality	1.9% (3/157)	2.5% (4/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	1.8% (1/57)
Cardiovascular death	1.9% (3/157)	2.5% (4/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	1.8% (1/57)
Neurologic event related death	0.0% (0/157)	0.0% (0/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
Non-cardiovascular death	0.0% (0/157)	0.0% (0/157)			0.0% (0/57)	0.0% (0/57)
Myocardial infarction	**0.0% (0/157)**	**0.0% (0/157)**	**0.0% (0/41)**	**0.0% (0/41)**	**0.0% (0/57)**	**1.8% (1/57)**

Neurological Events			**0.0% (0/41)**	**0.0% (0/41)**		
Stroke	6.4% (10/157)	8.3% (13/157)	0.0% (0/41)	0.0% (0/41)	5.3% (3/57)	5.3% (3/57)
Ischemic	5.7% (9/157)	7.6% (12/157)	0.0% (0/41)	0.0% (0/41)	5.3% (3/57)	5.3% (3/57)
Hemorrhagic	0.0% (0/157)	0.0% (0/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
Undetermined	0.6% (1/157)	0.6% (1/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
Disabling Stroke	0.6% (1/157)	2.5% (4/157)	2.4% (1/41)	2.4% (1/41)	1.8% (1/57)	1.8% (1/57)
Non-disabling Stroke	4.5% (7/157)	5.1% (8/157)	0.0% (0/41)	0.0% (0/41)	3.5% (2/57)	3.5% (2/57)
Transient ischemic attack (TIA)	0.6% (1/157)	1.3% (2/157)	46.3% (19/41)	70.7% (29/41)	0.0% (0/57)	1.8% (1/57)
Overt CNS Injury	6.4% (10/157)	8.3% (13/157)	2.4% (1/41)	2.4% (1/41)	5.3% (3/57)	5.3% (3/57)
Covert CNS Injury	47.1% (74/157)	68.8% (108/157)	0.0% (0/41)	70.7% (29/41)	38.6% (22/57)	63.2% (36/57)
Neurological dysfunction without CNS injury	1.3% (2/157)	1.9% (3/157)	0.0% (0/41)	0.0% (0/41)	1.8% (1/57)	5.3% (3/57)
CNS infarction	53.5% (84/157)	77.1% (121/157)			43.9% (25/57)	68.4% (39/57)
CNS hemorrhage	0.0% (0/157)	0.0% (0/157)	2.4% (1/41)	2.4% (1/41)	1.8% (1/57)	1.8% (1/57)
Bleeding Complications			**0.0% (0/41)**	**0.0% (0/41)**		
Life-threatening or disabling bleeding (VARC-2)	5.7% (9/157)	5.7% (9/157)	14.6% (6/41)	17.1% (7/41)	0.0% (0/57)	0.0% (0/57)
Major bleeding	7.6% (12/157)	7.6% (12/157)			0.0% (0/57)	1.8% (1/57)
Minor bleeding	5.1% (8/157)	6.4% (10/157)	0.0% (0/41)	0.0% (0/41)	7.0% (4/57)	8.8% (5/57)
Acute Kidney Injury			**0.0% (0/41)**	**0.0% (0/41)**		
Acute kidney injury - Stage 2	0.6% (1/157)	0.6% (1/157)			0.0% (0/57)	0.0% (0/57)
Acute kidney injury - Stage 3 (including renal	1.9% (3/157)	1.9% (3/157)	2.4% (1/41)	2.4% (1/41)	0.0% (0/57)	0.0% (0/57)

replacement therapy)						
Vascular Complications			**2.4% (1/41)**	**2.4% (1/41)**		
Major vascular complications	7.0% (11/157)	7.0% (11/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
TG3 access site related	1.9% (3/157)	1.9% (3/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
TAVR or other access site related	4.5% (7/157)	4.5% (7/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
Secondary access site-related	0.0% (0/157)	0.0% (0/157)	0.0% (0/41)	0.0% (0/41)	0.0% (0/57)	0.0% (0/57)
Aortic vascular injury	1.3% (2/157)	1.3% (2/157)	63.6% (21/33)	N/A	0.0% (0/57)	0.0% (0/57)
Major vascular complications related to TG3[6]	1.3% (2/157)	1.3% (2/157)			0.0% (0/57)	0.0% (0/57)

[1]Phase II CSR, Table 23a
[2]Phase II CSR, Table 24a
[3]Phase II CSR, Table 23a
[4]Phase II CSR, Table 23a-c
[5]TAVR Device success is defined as (1) Absence of procedural mortality AND (2) Correct positioning of a single prosthetic heart valve into the proper anatomical location AND (3) Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (VARC-defined) AND (4) mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, AND (5) no moderate or severe prosthetic valve regurgitation (VARC-defined).
[6]Includes only events adjudicated as "Related" to the TG3 device or procedure; therefore, does not necessarily include all major vascular complications adjudicated as "TriGUARD access site related" if these events were adjudicated as "probably related" or "possibly related" to TG3.

15.2 Secondary Effectiveness Endpoints

Table 30: Secondary Effectiveness Endpoints

	TG3			Pooled Control (Phase I + Phase II)
	eITT[1] *N=112*	**PT[2]** *N=62*	**Roll-in[3]** *N=41*	**eITT[4]** *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[7]				

	TG3			Pooled Control (Phase I + Phase II)
	eITT[1] *N=112*	PT[2] *N=62*	Roll-in[3] *N=41*	eITT[4] *N=119*
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) [4]				
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) [8]				
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)
Neurologic Efficacy				
NIHSS worsening [5]				
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[6]				
2-5 days post-procedure	10.0% (9/90)	7.8% (4/51)	3.4% (1/29)	6.4% (6/94)

	TG3			Pooled Control (Phase I + Phase II)
	eITT[1] *N=112*	PT[2] *N=62*	Roll-in[3] *N=41*	eITT[4] *N=119*
30 days (±7 days) post-procedure [2]	8.6% (6/70)	5.4% (2/37)	3.7% (1/27)	2.6% (2/78)

[1]Phase II CSR, Table 27a
[2]Phase II CSR, Table 27b
[3]Phase II CSR, Table 27c
[4]Phase II CSR, Table 27a-c
[5]Worsening of NIHSS score is defined as a higher NIHSS score at the time of assessment than at baseline.
[6]Defined as NIHSS worsening accompanied by the presence of cerebral ischemic lesions. Endpoints evaluated at 30 days post-procedure are based on NIHSS collected at 30 days and MRI results collected at post-procedure.
[7]Number of lesions is transformed with a square root for p-value calculations.
[8]Volume=0 is assigned to patients without cerebral ischemic lesions. Endpoint is transformed with a cubic-root for p-value calculations.

Table 31: Secondary Safety endpoints by TriGUARD 3 Relatedness[1] (events to 30 days)

	TriGUARD 3 SP[AT] RI+RCT (N=157)					
	Number of subjects [2]	Not Related	Unlikely to be Related	Possibly Related	Probably Related	Related
MACCE (In-hospital procedural safety endpoint)	25	10.2% (16/157)	0.0% (0/157)	6.4% (10/157)	0.0% (0/157)	1.3% (2/157)
All-cause mortality	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
All stroke (disabling and non-disabling)	13	3.2% (5/157)	0.0% (0/157)	5.7% (9/157)	0.0% (0/157)	0.0% (0/157)
Life threatening (or disabling) bleeding	9	5.1% (8/157)	0.0% (0/157)	0.6% (1/157	0.0% (0/157)	0.0% (0/157)
Acute Kidney Injury - Stage 2 or 3 (including renal replacement therapy)	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Major vascular complication	11	5.1% (8/157)	0.0% (0/157)	0.6% (1/157	0.0% (0/157)	1.3% (2/157)
All-cause mortality	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Cardiovascular death	4	2.5% (4/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)

	TriGUARD 3 SP[AT] RI+RCT (N=157)					
	Number of subjects [2]	Not Related	Unlikely to be Related	Possibly Related	Probably Related	Related
Neurologic event related death	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Non-cardiovascular death	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Myocardial infarction	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Neurological Events (VARC-2/NeuroARC defined)						
Stroke	13	3.2% (5/157)	0.0% (0/157)	5.7% (9/157)	0.0% (0/157)	0.0% (0/157)
Ischemic	12	2.5% (4/157)	0.0% (0/157)	5.7% (9/157)	0.0% (0/157)	0.0% (0/157)
Hemorrhagic	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Undetermined	1	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Disabling Stroke	4	0.6% (1/157)	0.0% (0/157)	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)
Non-disabling Stroke	8	1.3% (2/157)	0.0% (0/157)	3.8% (6/157)	0.0% (0/157)	0.0% (0/157)
Transient ischemic attack (TIA)	2	1.3% (2/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Overt CNS Injury	13	3.2% (5/157)	0.0% (0/157)	5.7% (9/157)	0.0% (0/157)	0.0% (0/157)
Covert CNS Injury	108	0.0% (0/157)	0.0% (0/157)	68.8% (108/157)	0.0% (0/157)	0.0% (0/157)
Neurological dysfunction without CNS injury	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
CNS infarction	121	3.2% (5/157)	0.0% (0/157)	74.5% (117/157)	0.0% (0/157)	0.0% (0/157)
CNS hemorrhage	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Bleeding Complications						

	TriGUARD 3 SP[AT] RI+RCT (N=157)					
	Number of subjects [2]	Not Related	Unlikely to be Related	Possibly Related	Probably Related	Related
Life-threatening or disabling bleeding (VARC-2)	9	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)
Major bleeding	12	3.2% (5/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	3.8% (6/157))
Minor bleeding	10	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.9% (3/157)
Acute Kidney Injury (AKIN Classification)						
Acute kidney injury - Stage 2	1	0.6% (1/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Acute kidney injury - Stage 3 (including renal replacement therapy)	3	1.9% (3/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Vascular Complications						
Major vascular complications	11	5.1% (8/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)
TriGUARD access site related	3	0.0% (0/157)	0.0% (0/157)	0.6% (1/157)	0.0% (0/157)	1.3% (2/157)
TAVR or other access site related	7	4.5% (7/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Secondary access site-related	0	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)
Aortic vascular injury	2	1.3% (2/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)	0.0% (0/157)

[1] Phase II CSR, Table 26b. If the relationship to TriGUARD 3 Device is different than the relationship to TriGUARD 3 Procedure, then the most related of the two is considered for evaluation.

[2] Number of subjects who experienced the respective safety endpoint at least once.

15.3 Secondary Performance Endpoints

Table 32: Secondary Performance Endpoints

	ITT/AT[11]	Roll-In [12]	SP[ITT][13] ITT+RI
Successful device deployment [2]	100.0% (116/116)	100.0% (41/41)	100.0% (157/157)
1 attempt needed to successfully deploy TG3 device	98.3% (114/116)	97.6% (40/41)	98.1% (154/157)
2 attempts needed to successfully deploy TG3 device	1.7% (2/116)	2.4% (1/41)	1.9% (3/157)
Aortic arch successfully accessed with the TG3 delivery catheter	100.0% (116/116)	100.0% (41/41)	100.0% (157/157)
Device positioning at: [3, 4]			
Pre-TAVR:			
Complete	62.1% (59/95)	58.8% (20/34)	61.2% (79/129)
Partial	15.8% (15/95)	26.5% (9/34)	18.6% (24/129)
None	22.1% (21/95)	14.7% (5/34)	20.2% (26/129)
During TAVR			
Complete	72.4% (76/105)	80.0% (32/40)	74.5% (108/145)
Partial	8.6% (9/105)	7.5% (3/40)	8.3% (12/145)
None	19.0% (20/105)	12.5% (5/40)	17.2% (25/145)
Post-TAVR [5]			
Complete	71.4% (80/112)	72.5% (29/40)	71.7% (109/152)
Partial	12.5% (14/112)	15.0% (6/40)	13.2% (20/152)
None	16.1% (18/112)	12.5% (5/40)	15.1% (23/152)
3-vessel coverage for 2 of 3 timepoints[6]			
Complete	80.9% (89/110)	87.5% (35/40)	82.7% (124/150)
Partial	22.7% (25/110)	25.0% (10/40)	23.3% (35/150)
None	19.1% (21/110)	12.5% (5/40)	17.3% (26/150)

	ITT/AT[11]	Roll-In [12]	SP[ITT][13] ITT+RI
Device interference [7]	8.6% (10/116)	12.2% (5/41)	9.6% (15/157)
Successful device retrieval [8]	100.0% (116/116)	100.0% (41/41)	100.0% (157/157)
Technical success [3, 9]	69.5% (73/105)	75.0% (30/40)	71.0% (103/145)
Procedural success [3, 10]	67.6% (71/105)	75.0% (30/40)	69.7% (101/145)

[1] Five (5) TG3 randomized subjects did not undergo the TAVR procedure and were not followed, and therefore are not included in the denominators.

[2] Successful device deployment: Ability to access the aortic arch with the TG3 delivery catheter and deploy the device into the aortic arch.

[3] Device positioning: Ability to position the TG3device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by angiography) until specified.

[4] Subjects with Coverage = N/A (due to indiscernible angiograms) are not included in the denominator.

[5] Post-TAVR: After any additional post-dilatation or valve implantations have been completed, and the TAVR delivery system has been removed.

[6] Patients where 3-vessel coverage was achieved in 2 of the 3 timepoints (Pre-, During, Post-TAVR).

[7] Device interference: Interaction of the TG3 device with the TAVR system leading to (1) inability to advance or manipulate the TAVR delivery system or valve prosthesis, OR (2) inability to deploy the TAVR valve prosthesis, OR (3) inability to retrieve the valve prosthesis or delivery system.

[8] Successful device retrieval: Ability to retrieve the TG3 device.

[9] Technical success: Successful device deployment, device positioning for complete coverage during TAVR, and successful device retrieval in the absence of device interference.

[10] Procedure success: Technical success in the absence of any investigational device-related or procedure-related in-hospital procedural safety events.

[11] Phase II CSR, Table 28a

[12] Phase II CSR, Table 28a

[13] Phase II CSR, Table 28a

16 Appendix E – Tipping Point Analyses for Primary Effectiveness Endpoint Components

16.1 Tipping Point Analyses Background

The target enrollment for the Phase II randomized cohort was capped at 225 subjects. Phase II enrollment was suspended pre-maturely based on DMC and FDA recommendations following unblinded safety data review. The actual enrollment in the Phase II randomized cohort included 121 TriGUARD 3 subjects and 58 control subjects, which was 46 subjects away from the target enrollment of 225 subjects. FDA conducted tipping point analyses to assess the potential impact of the early stopping of study enrollment on the evaluation of primary effectiveness endpoint components.

16.2 Tipping Point Method

Tipping point analysis is a missing data assessment strategy commonly used in medical device trials (Yan et al, 2009[1]; Campbell et al, 2011[2]). In a tipping point analysis, the study endpoint is evaluated based on all possible outcome scenarios of the missing data, and the tipping points are the scenarios on which the study conclusion, based on the observed data, would be flipped. No specific assumption regarding missing mechanism is needed in the tipping point analysis, and the interpretation of the tipping point analysis result relies heavily on clinical assessment.

In the tipping point analyses regarding each component of the primary effectiveness endpoint, we simulated all possible outcomes scenarios for the 46 subjects who would be enrolled into the study if the target enrollment of 225 subjects was reached (referred to as future subjects). For simplicity, we assumed that 29 out of these 46 future subjects would be randomized to the TriGUARD 3 group and the other 17 future subjects would be randomized to the control group, so that the target enrollment would consist of 150 TriGUARD 3 subjects and 75 control subjects under the 2:1 randomization scheme. In addition, in the tipping point analyses, all-cause mortality or any stroke at 30 days (also referred to as 30-day death or stroke in this Appendix), NIHSS worsening, and cerebral ischemic lesions were treated as binary outcomes, while total volume of cerebral ischemic lesions (TLV) was treated as a semi-continuous outcome. The tipping point analyses were conducted based on the eITT population with Pooled Controls, and the corresponding observed primary effectiveness endpoint component results are presented in Table 33.

[1] Yan, X., Lee, S., and Li, N. (2009), "Missing Data Handling Methods in Medical Device Clinical Trials," Journal of Biopharmaceutical Statistics, 19, 1085–1098. DOI:10.1080/10543400903243009.

[2] Campbell, G., Pennello, G., and Yue, L. (2011), "Missing Data in the Regulation of Medical Devices," Journal of Biopharmaceutical Statistics, 21, 180–195. DOI:10.1080/10543406.2011.550094.

Table 33: Primary Effectiveness Endpoint Components (eITT Population, Pooled Controls) (Primary Analysis)

Phase II Primary Effectiveness Endpoint Component[1] eITT Population	TriGUARD 3 *N=112*	Pooled Control *N=119*
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)
Median (Q1, Q3)	215.39 (68.13, 619.71)	188.09 (52.08, 453.12)

[1]Phase II CSR, Table 20a

Two sets of tipping point analyses have been conducted. In Set A, tipping point analyses were conducted for each component to evaluate under which scenarios the treatment effect estimate would **numerically favor** the TriGUARD 3 group if the future 46 subjects had evaluable primary effectiveness endpoint data. This assumes that the 46 future subjects were enrolled and had evaluable primary effectiveness endpoint data. For this set of analyses, the TriGUARD 3 group would be considered a "win" for a specific component if the rate or mean of this component based on the target enrollment numerically favors the TRIGUARD 3 group compared to the control group. In Set B, tipping point analyses were conducted for each component to evaluate under which scenarios there would be a **statistically significant** treatment effect favoring the TriGUARD 3 group at a one-sided alpha level of 0.15 based on the target enrollment, if the future 46 subjects had evaluable primary effectiveness endpoint data. For this set of analyses, the TriGUARD 3 group would be considered a "win" for a specific component if the one-sided p value of the corresponding two-group comparison was less than 0.15 favoring the TriGUARD 3 group. Fisher Exact test was used for each of the three binary components; while for the semi-continuous component, total volume of cerebral ischemic lesions, Z test was applied under the assumption that the population variance was same as observed sample variance in each study group. In both sets of analyses, the missing data among the enrolled subjects were not imputed, since the focus of the analyses was to evaluate the impact of the early stopping of study enrollment.

In each tipping point analysis, the discussion is focused on the following 4 special scenarios:

- **Scenario A**: Assuming the future subjects were to perform similarly as the observed subjects in each study group (missing completely at random), this scenario assesses whether the TriGUARD 3 group would win.

- **Scenario B**: Assuming the future TriGUARD 3 subjects performed similarly as the observed TriGUARD subjects, what would be the best observed performance for the future control subjects which would allow the TriGUARD 3 group to "win".

- **Scenario C**: Assuming the future control subjects performed similarly as the observed control subjects, what would be the worst performance for the future TriGUARD 3 subjects which would allow the TriGUARD 3 group to "win".

- **Scenario D**: What would be the best performance for the future control subjects or the worst performance for the future TriGUARD 3 subjects which would allow the TriGUARD 3 group to "win". This scenario would be presented when it is clinically relevant.

16.3 Tipping Point Results

16.3.1 Results of Tipping Point Analysis Set A

The results of the tipping point analysis Set A for the primary effectiveness endpoint components are presented in Figure 15. In each Panel, the horizontal axis represents the potential outcome of the 29 future TriGUARD 3 subjects, while the vertical axis represents the potential outcome of the 17 future controls subjects. Using the result for all-cause mortality or any stroke at 30 days (the upper-left Panel) as an example, the horizontal axis represents the number of subjects with 30-day death or stroke events among the future 29 TRIGUARD 3 subjects; likewise, the vertical axis represents the number of subjects with 30-day death or stroke events among the future 17 control subjects. For example, Point A located on (3, 1) represents one possible outcome scenario for the 46 future subjects: 3 (10.3%) out of the 29 future TriGUARD 3 subjects and 1 (5.9%) out of the future 17 control subjects were with 30-day death or stroke events; while the other 26 future TriGUARD 3 subjects and 16 future control subjects were event free. In each graph Panel, the green area represents all possible outcome scenarios of the future 46 subjects where a rate or mean favoring the TRIGUARD 3 group would be observed based on the target enrollment; while the white area represents all the possible outcome scenarios where the observed rate or mean would favor the control group based on the target enrollment. The red line, which is the boundary of the green region, is called the tipping point boundary. Generally speaking, the bigger the green area, the more possible outcome scenarios where a favorable result would be observed for the TriGUARD 3 group if the target enrollment is reached. Blue points A, B, C, and D represent Scenarios A, B, C, and D, respectively.

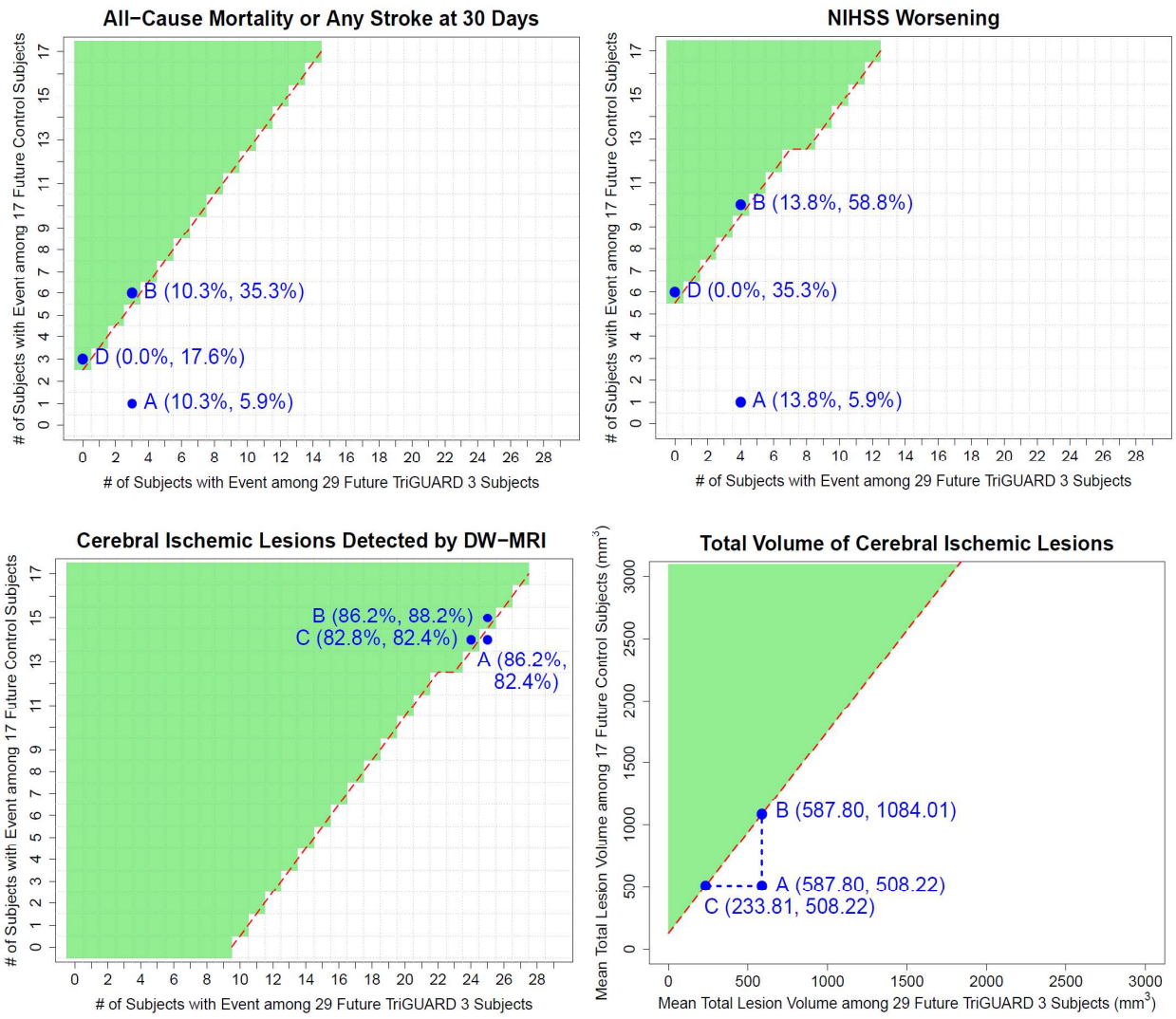


Figure 15. Tipping Point Analyses for the Primary Effectiveness Endpoint Components, Set A

*In each panel, the shaded area represents scenarios yielding lower observed event rate/mean in TriGUARD 3 group compared to that in the control group based on the target enrollment.

16.3.1.1 All-cause mortality or any stroke at 30 days

The tipping point analysis result for all-cause mortality or any stroke at 30 days is shown in the upper-left Panel of Figure 15. Given the observed 30-day death or stroke rate of 9.8% (11/112) for the TriGUARD 3 group and 6.7% (8/119) for the control group based on the actual enrollment, the results of the four scenarios are listed below:

- Scenario A: Assuming that the future subjects perform similarly as the enrolled subjects in both study groups, there would be 3 (10.3%) out of the future 29 TriGUARD 3 subjects and 1 (5.9%) out of the 17 future control subjects with 30-day death or stroke. Therefore, the observed 30-day death or stroke rate in the TriGUARD 3 group would be 9.9% (14/141)

based on the target enrollment, which is higher than that in the control group (6.6% (9/136)). Accordingly, Point A falls in the white area, indicating a "loss" for the TriGUARD 3 group.

- Scenario B: Assuming that the future TriGUARD 3 subjects perform similarly as the enrolled TriGUARD 3 subjects, with a 30-day death or stroke rate of 10.3% (3/29), to observe a treatment effect favoring the TriGUARD 3 group based on the target enrollment, at least 6 (35.3%) out of the future 17 control subjects would need to experience a 30-day death or stroke event, a much higher event rate than the observed rate of 6.7% in the enrolled control group. FDA believes the likelihood of this scenario occurring is very low.

- Scenario C: If the future control subjects perform similarly as the enrolled control subjects (30-day death or stroke rate: 1/17=5.9%), it would be impossible to observe a treatment effect favoring the TriGUARD 3 group based on the target enrollment. Therefore, Point C is not on the graph.

- Scenario D: To observe a treatment effect favoring the TriGUARD 3 group, even if all future TriGUARD 3 subjects are event-free, at least 3 (17.6%) subjects among the future 17 control subjects would need to experience a 30-day death or stroke event, which is much higher than the observed rate of 6.7% in the enrolled control group. FDA believes the likelihood of this scenario occurring is very low.

16.3.1.2 NIHSS Worsening

Tipping point analysis for NIHSS worsening was conducted in a similar fashion and is presented in the upper-right Panel of Figure 15. Based on the observed NIHSS worsening rate of 14.1% (14/99) for the TriGUARD 3 group and 7.6% (8/105) for the control group on the actual enrollment, the results for Scenarios A, B, C, and D are as follows:

- Scenario A: Assuming the future subjects perform similarly as the enrolled subjects in both study groups, there would be 4 (13.8%) out of the 29 future TriGUARD 3 subjects and 1 (5.9%) out of the 17 future control subjects with NIHSS worsening. The observed NIHSS worsening event rate based on the target enrollment would be higher in the TriGUARD 3 group (18/128=14.1%) compared to the control group (9/122=7.4%), with Point A located in the white area.

- Scenario B: Assuming that the future TriGUARD 3 subjects perform similarly as the enrolled TriGUARD 3 subjects, with a NIHSS worsening rate of 13.8% (4/29), to observe a treatment effect favoring the TriGUARD 3 group, at least 10 (58.8%) out of the future 17 control subjects would need to be observed with NIHSS worsening, with an much higher event rate than the observed rate of 7.6% among the enrolled control subjects. FDA believes the likelihood of this scenario occurring is very low.

- Scenario C: If the 17 future control subjects perform similarly as the enrolled control subjects (NIHSS worsening rate: 1/17=5.9%), it would be impossible to observe a treatment effect favoring the TriGUARD 3 group based on the target enrollment. Therefore, Point C is not on the graph.

- Scenario D: To observe a treatment effect favoring the TriGUARD 3 group, even if all future TriGUARD 3 subjects are event-free, at least 6 (35.3%) subjects among the future 17 control subjects would need to experience NIHSS worsening, which is much higher than the observed rate of 7.6% among the enrolled control subjects.

16.3.1.3 Cerebral Ischemic Lesion

The tipping point analysis result for cerebral ischemic lesion is presented in the lower-left Panel of Figure 15. Based on the actual enrollment, the observed cerebral ischemic lesion rate was 85.0% (85/100) for the TriGUARD 3 group and 84.9% (90/106) for the control group. For Scenario A, assuming the future subjects perform similarly as the enrolled subjects in each study group, there would be 25 (86.2%) future TriGUARD 3 subjects and 14 (82.4%) future control subjects with cerebral ischemic lesions. Then the observed event rate would be 85.3% (110/129) for the TriGUARD 3 group and 84.6% (104/123) for the control group based on the target enrollment. Under this scenario, the observed event rate would be higher in the TriGUARD 3 group based on the target enrollment. Accordingly, Point A falls in the white area, close to the tipping point boundary as well as Points B and C, indicating that the observed event rates in the two study groups would be close to each other based on the target enrollment.

16.3.1.4 Total volume of cerebral ischemic lesions (TLV)

The result of the analysis for total volume of cerebral ischemic lesions (TLV) is presented in the lower-right Panel of Figure 15.

- Scenario A: Assuming the observed mean TLV among the future subjects are the same as that among the enrolled subjects in each study group (mean TLV: 587.80 mm^3 in the TriGUARD 3 group vs. 508.22 mm^3 in the control group), the overall observed mean TLV based on the target enrollment would be higher in the TriGUARD 3 group compared to the control group (Point A is in the white area).

- Scenario B: Assume that the observed mean TLV among the future 29 TriGUARD 3 subjects is same as that observed mean among the enrolled TriGUARD 3 subjects (587.80 mm^3). To observe a lower mean TLV among the TriGUARD 3 group based on the target enrollment, the observed mean TLV among the future 17 control subjects would need to be higher than 1084.01 mm^3, approximately double of the observed mean among enrolled control subjects.

- Scenario C: Assume that the observed mean TLV among the future 17 control subjects is same as that observed among the enrolled control subjects (508.22 mm^3). To observe a treatment effect favoring the TriGUARD 3 group, the observed mean TLV among the future 29 TriGUARD 3 subjects needs to be lower than 233.81 mm^3. In other words, to observe a lower mean TLV in the TriGUARD 3 group based on the target enrollment, the

mean TLV among the future 29 TriGUARD 3 group subjects could not be higher than 233.81 mm^3, which is less than half of the observed mean TLV among the enrolled TriGUARD 3 group.

16.3.2 Results of Tipping Point Analysis Set B

The results of the tipping point analysis Set B for the primary effectiveness endpoint components are presented in Figure 16. In each graph Panel, the green area represents all the possible outcome scenarios of the future 46 subjects which correspond to a statistically significant lower rate/mean favoring the TRIGUARD 3 group based on the target enrollment; while the white area represents all the possible outcome scenarios on which the event rate or mean in the TriGUARD 3 group would not be significantly lower than that in the control group based on the target enrollment. Please be aware that statistical significance was evaluated at a one-sided 0.15 alpha level in Set B analyses. It can be found that compared to the results in Set A, the green area in each graph Panel of Figure 2 is smaller, since the criterion for "win" of the TriGUARD 3 group is to have a statistically significant treatment effect favoring the TriGUARD 3 group, which is more stringent than that in Set A which only requires an event rate or mean numerically favoring the TriGUARD 3 group. In addition, blue Points A, B, C, and D represent Scenarios A, B, C, and D, respectively.

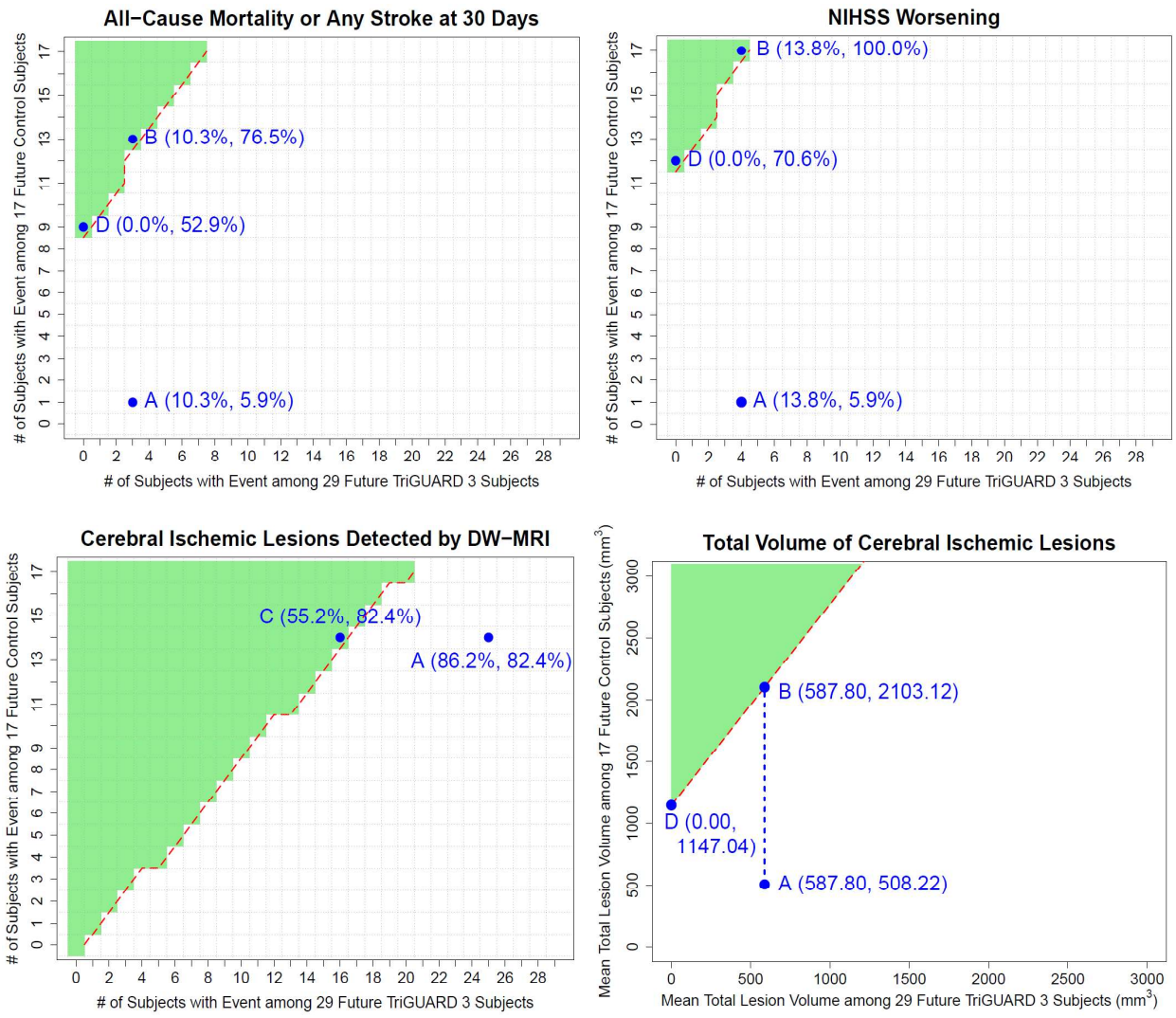


Figure 16. Tipping Point Analyses for the Primary Effectiveness Endpoint Components, Set B

*In each panel, shaded area represents scenarios yielding statistically significantly lower event rate/mean in TriGUARD 3 group compared to that in the control group at one-sided 0.15 alpha level based on the target enrollment.

16.3.2.1 All-cause mortality or any stroke at 30 days

The tipping point analysis result for all-cause mortality or any stroke at 30 days is shown in the upper-left Panel of Figure 16. The results of the four scenarios of interest are listed below:

- Scenario A: If the future subjects perform similarly as the enrolled subjects in both study groups (30-day death/stroke rate: 9.8% in TriGUARD 3 vs. 6.7% in Control), then Point A falls in the white area, indicating no statistically significantly lower event rate in the TriGUARD 3 group based on the target enrollment.

- Scenario B: To have a statistically significant treatment effect favoring the TriGUARD 3 group, at least 13 (76.5%) subjects among the future 17 control subjects need to be observed with all-cause mortality or any stroke at 30 days if future TriGUARD 3 subjects perform similarly as the enrolled TriGUARD 3 subjects (3/29=10.3%).

- Scenario C: It would be impossible to observe a statistically significant treatment effect favoring the TriGUARD 3 group if the future control subjects perform similarly as the enrolled control subjects (1/17=5.9%). Therefore, Point C is not depicted in the graph.

- Scenario D: To detect a statistically significant treatment effect favoring the TriGUARD 3 group, at least 9 (52.9%) subjects among the future 17 control subjects would need to be observed with 30-day death/stroke even if all future TriGUARD 3 subjects are event-free.

16.3.2.2 NIHSS Worsening

Tipping point analysis for NIHSS worsening is presented in the upper-right Panel of Figure 16:

- Scenario A: Assuming the future subjects perform similarly as the enrolled subjects in both study groups, there would be 4 (13.8%) out of the 29 future TriGUARD 3 subjects and 1 (5.9%) out of the 17 future control subjects with NIHSS worsening. Then based on the target enrollment, a significantly lower NIHSS worsening rate would not be detected in the TriGUARD 3 group and Point A falls in the white area (18/128=14.1% in the TriGUARD 3 group vs. 9/122=7.4% in the control group).

- Scenario B: Assuming the future TriGUARD 3 subjects perform similarly as the enrolled TriGUARD 3 subjects (NIHSS worsening rate: 4/29=13.8%), all 17 (100%) future control subjects would need to be observed with NIHSS worsening to detect a statistically significant treatment effect favoring the TriGUARD 3 group.

- Scenario C: If the 17 future control subjects perform similarly as the enrolled control subjects (NIHSS worsening rate: 1/17=5.9%), it would be impossible to have a statistically significant treatment effect favoring the TriGUARD 3 group. Therefore, Point C is not on the graph.

- Scenario D: To detect a statistically significant treatment effect favoring the TriGUARD 3 group, even if all the remaining 29 subjects in the TriGUARD 3 are event-free, at least 12 (70.6%) subjects among the future 17 control subjects would need to be observed with NIHSS worsening, a much higher event rate than the observed rate of 7.6% among the enrolled control subjects. FDA believes the likelihood of this scenario occurring is very low.

16.3.2.3 Cerebral Ischemic Lesions

The tipping point analysis result for cerebral ischemic lesion is presented in the lower-left Panel of Figure 16:

- Scenario A: Assuming the future subjects perform similarly as the enrolled subjects in each study group, there would be 25 (86.2%) future TriGUARD 3 subjects and 14 (82.4%) future control subjects with cerebral ischemic lesions. In this scenario, a statistically significant treatment effect favoring the TriGUARD 3 group would not be detected. Point A falls in the white area.

- Scenario B: If the future TriGUARD 3 subjects perform similarly as the enrolled TriGUARD 3 subjects (cerebral ischemic lesion rate: 25/29 = 86.2%), it would be impossible to detect a statistically significant treatment effect favoring the TriGUARD 3 group. Therefore, Point B is not on the graph.

- Scenario C: Assume that the future control subjects perform similarly as the enrolled control subjects, with a cerebral ischemic lesion rate of 82.4% (14/17). To detect a statistically significant treatment effect favoring the TriGUARD 3 group, at most 16 (55.2%) subjects among the future 29 TriGUARD 3 subjects could have cerebral ischemic lesion, a much lower event rate than the observed event rate of 85.0% among the enrolled TriGUARD 3 subjects. FDA believes the likelihood of this scenario occurring is very low.

16.3.2.4 Total volume of cerebral ischemic lesions(mm^3) Cerebral Ischemic Lesions

The result of the analysis for total volume of cerebral ischemic lesions (TLV) is presented in the lower-right Panel of Figure 16.

- Scenario A: Assuming the observed mean TLV among the future subjects is same as that among the enrolled subjects in each study group (TLV: 587.80 mm^3 in TriGUARD 3 vs. 508.22 mm^3 in Control), a statistically significant treatment effect favoring the TriGUARD 3 group would not be detected (Point A is in the white area).

- Scenario B: Assume that the observed mean TLV among the future 29 TriGUARD 3 subjects is same as that observed mean among the enrolled TriGUARD 3 subjects (587.80 mm^3). To have a statistically significant treatment effect favoring the TriGUARD 3 group, the observed mean TLV among the future 17 control subjects would need to be higher than 2103.12 mm^3, approximately four times that of the observed mean among enrolled control subjects.

- Scenario C: If the future control subjects perform similarly as the enrolled control subjects (mean TLV = 508.22 mm^3), it would be impossible to have a statistically significant treatment effect favoring the TriGUARD 3 group. Therefore, Point C is not on the graph.

- Scenario D: To detect a statistically significant treatment effect favoring the TriGUARD 3 group, even if all future TriGUARD 3 subjects have zero volume, the observed mean TLV among the future 17 control subjects would need to be higher than 1147.04 mm^3, which was more than double the observed mean TLV among the enrolled control subjects.

17 Appendix F - Minor Vascular Complications for TriGUARD 3 and Control

Table 34: Phase II CEC Adjudicated Minor Vascular Complications (from Phase II CSR, Appendix F-1: Adjudicated Adverse Event Narratives)

TriGUARD 3 group		Relatedness				
Subject ID	Event	TAVR device	TAVR procedure	TG3 device	TG3 procedure	Comments
(b)(6)	Stenosis of right iliac	Possibly	Related	Not related	Not related	
(b)(6)	Right groin bleed	Not related	Not related	Not related	Not related	
(b)(6)	Left groin hematoma	Possibly	Related	Not related	Not related	TAVR Access site related
(b)(6)	Right groin hematoma	Not related	Probably	Not related	Not related	
(b)(6)	Pseudoaneurysm and hematoma	Not related	Related	Not related	Related	Left groin, TriGUARD Access site related
(b)(6)	Left groin hematoma	Not related	Related	Related	Related	TriGUARD Access site related
	Right groin hematoma	Possibly	Related	Not related	Not related	TAVR Access site
(b)(6)	Arteriovenous fistula	Not related	Related	Not related	Related	TriGUARD Access site related
(b)(6)	CFA pseudoaneurysm	Not related	Related	Not related	Related	TriGUARD Access site related
(b)(6)	Right femoral artery blockage	Not related	Related	Not related	Not related	
(b)(6)	Vascular complication	Not related	Related	Not related	Not related	TAVR Access site
(b)(6)	Vascular complication	Possibly	Related	Not related	Not related	TAVR Access site related

(b)(6)	Stenosis of RCFA	Possibly	Related	Not related	Not related	TAVR Access site; Right femoral artery stenosis following closure
(b)(6)	Left common femoral artery pseudoaneurysm	Not related	Related	Not related	Related	
Phase II Control group		**Relatedness**				
Subject ID	**Event**	**TAVR device**	**TAVR procedure**	**N/A**	**N/A**	**Comments**
(b)(6)	Right femoral artery vascular dissection	Possibly	Related	--	--	
(b)(6)	Right femoral artery dissection	Possibly	Related	--	--	TAVR Access site related
(b)(6)	Right groin hematoma	Possibly	Related	--	--	TAVR Access site related
	Left femoral artery pseudoaneurysm	Not related	Related	--	--	Non-TAVR Access site related
(b)(6)	Surgical cutdown closure	Not related	Not related	--	--	
(b)(6)	Pseudoaneurysm right groin	Not related	Related	--	--	

18 Appendix G – REFLECT Phase II CEC-Adjudicated Minor Vascular Complications

The events adjudicated as minor vascular complications in the TriGUARD 3 group and control group are presented in Table 35. Of the minor vascular complication events in the TriGUARD 3 group, there were 5 adjudicated as related to the TriGUARD 3 device and/or procedure.

Table 35: Minor Vascular Complications with CEC Adjudication for Device Relatedness

TriGUARD 3 group		Relatedness				
Subject ID	Event	TAVR device	TAVR procedure	TriGUARD 3 device	TriGUARD 3 procedure	Comments
(b)(6)	Stenosis of right iliac	Possibly	Related	Not related	Not related	
(b)(6)	Right groin bleed	Not related	Not related	Not related	Not related	
(b)(6)	Left groin hematoma	Possibly	Related	Not related	Not related	TAVR Access site related
(b)(6)	Right groin hematoma	Not related	Probably	Not related	Not related	
(b)(6)	**Pseudoaneurysm and hematoma**	**Not related**	**Related**	**Not related**	**Related**	**Left groin, TriGUARD Access site related**
(b)(6)	**Left groin hematoma**	**Not related**	**Related**	**Related**	**Related**	**TriGUARD Access site related**
	Right groin hematoma	**Possibly**	**Related**	**Not related**	**Not related**	**TAVR Access site**
(b)(6)	**Arteriovenous fistula**	**Not related**	**Related**	**Not related**	**Related**	**TriGUARD Access site related**
(b)(6)	**CFA pseudoaneurysm**	**Not related**	**Related**	**Not related**	**Related**	**TriGUARD Access site related**
(b)(6)	Right femoral artery blockage	Not related	Related	Not related	Not related	
(b)(6)	Vascular complication	Not related	Related	Not related	Not related	TAVR Access site
(b)(6)	Vascular complication	Possibly	Related	Not related	Not related	TAVR Access site related
(b)(6)	Stenosis of RCFA	Possibly	Related	Not related	Not related	TAVR Access site; Right femoral artery stenosis following closure
(b)(6)	**Left common femoral artery**	**Not related**	**Related**	**Not related**	**Related**	

	pseudoaneurysm					
Control group		**Relatedness**				
Subject ID	**Event**	**TAVR device**	**TAVR procedure**	**N/A**	**N/A**	**Comments**
(b)(6)	Right femoral artery vascular dissection	Possibly	Related			
(b)(6)	Right femoral artery dissection	Possibly	Related			TAVR Access site related
(b)(6)	Right groin hematoma	Possibly	Related			TAVR Access site related
	Left femoral artery pseudoaneurysm	Not related	Related			Non-TAVR Access site related
(b)(6)	Surgical cutdown closure	Not related	Not related			
(b)(6)	Pseudoaneurysm right groin	Not related	Related			

19 Appendix H – REFLECT Phase II Statistical Analysis Plan

Statistical Analysis Plan

History of Changes

Rev	CO	By	Date	Description of Change
01	N/A	LN	10.06.2019	Reflects changes that were made to the REFLECT phase 2 CIP-09 Rev. 13 protocol, replaced SAP-09-1
02	2019-014	C.Pietras	08 Oct 2019	Edited the flowcharts, removed the poolability based on the endpoints, left only the one based on the baselines. Adjustments made to baseline NIHSS for the imaging endpoints and to pre-existing DW-MRI variable for the primary efficacy endpoint.

S.H
Controlled Document
Date: 29/10/2019

Effective date:

Prepered By:				
Function	Title	Name	Date	Signature
Consultant	Biostatistician	(b)(6)	Oct 27, 2019	(b)(6)
Reviewed By:				
Function	Title	Name	Date	Signature
Consultant	Lead Physician	(b)(6)	Oct 28, 2019	(b)(6)
Approved By:				
Function	Title	Name	Date	Signature
RA/QA	VP RA/QA	(b)(6)	Oct 26, 2019	(b)(6)
Clinical	CMO	(b)(6)	Oct 24, 2019	(b)(6)

Distribution List

Number of Copy	Document Name	Department
1	REFLECT_Phase II SAP	QA
2	REFLECT_Phase II SAP	eTMF

Statistical Analysis Plan

A RANDOMIZED EVALUATION OF THE TRIGUARD HDH CEREBRAL EMBOLIC PROTECTION DEVICE AND THE TRIGUARD 3 CEREBRAL EMBOLIC PROTECTION DEVICE TO REDUCE THE IMPACT OF CEREBRAL EMBOLIC LESIONS AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION:

(REFLECT)

Phase II

Protocol Number: (b) (4)

October 8, 2019

Version 2.0

Statistical Analysis Plan Review

The intention of this Statistical Analysis Plan (SAP) is to detail the planned analysis and reporting for the REFLECT Trial.

The undersigned hereby jointly declare that they have reviewed this statistical analysis plan and agree to its content. Furthermore, they confirm that the statistical analysis plan contains the information relevant for the evaluation of the study data.

Author' Signatures (b)(6) May 31, 2019

(b)(6) Date
Biostatistician
(b) (4)

Approvers' Signatures (b)(6) May 31, 2019

(b)(6) Date
Lead Physician
(b) (4)

Sponsor Representative's Signature (b)(6) Oct 24, 2019

(b)(6) Date
VP and Chief Medical Officer
Keystone Heart, Ltd.

Table of Contents

Figures, Tables and Listings

1. INTRODUCTION

This SAP serves as the guideline for analyzing the REFLECT Phase II trial including definitions of analysis populations, sample size considerations, details on propensity score stratification, analysis of the primary endpoint, analysis of the secondary endpoints, analysis of subgroups, sensitivity analysis, and missing data considerations. Phase I is addressed in a separate SAP.

The current version of the SAP reflects the most recent protocol (v.13), and we additionally note this SAP is subject to change throughout the course of the REFLECT trial.

2. STUDY OBJECTIVES

To assess the safety and efficacy of the TriGUARD *3* cerebral embolic protection device in patients undergoing transcatheter aortic valve implantation/replacement (TAVI), in comparison with a control group of patients undergoing unprotected TAVI.

3. STUDY DESIGN

In Phase II, up to 295 randomized subjects and 40-50 roll-in subjects will be enrolled at up to 25 sites in the United States (inclusive of sites enrolling subjects in Phase I). No single site will be permitted to enroll more than 20% of all randomized subjects in Phase II.

Subjects with indications for TAVI and who meet study eligibility criteria will be randomized 2:1 (stratified by study site) to one of two treatment arms:

- Intervention – TAVI with the TriGUARD 3 CEPD
- Control – standard unprotected TAVI

Randomization will be stratified by implanted valve type (Medtronic vs. Edwards).

No single valve type will be implanted in more than approximately 70% of randomized patients (phase II).

All subjects will be followed clinically in-hospital and at 30 days, undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and undergo neurologic (NIHSS) testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 days. A follow-up phone-call to assess the occurrence of death or stroke will be done at 90 days.

4. ENDPOINTS

A Clinical Events Committee (CEC) will review and adjudicate all site-reported cardiovascular adverse events and all site-reported adverse events potentially meeting endpoint criteria during the study, following established explicit rules in the CEC charter which outlines the data required and the algorithm followed in order to classify a clinical event.

4.1 Primary Endpoints

1. Primary Safety Endpoint
   Combined safety, defined as a composite of death, stroke, life-threatening or disabling bleeding, acute kidney injury (stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure evaluated at 30 days.

2. Primary Efficacy Endpoint
   A hierarchical composite endpoint of (i) all-cause mortality and/or any stroke evaluated at 30 days, (ii) NIHSS worsening from baseline to 2-5 days post-procedure, (iii) freedom from any cerebral ischemic lesions detected by diffusion weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure, and (iv) total volume of cerebral ischemic lesions detected by DW-MRI 2 to 5 days post-procedure.

4.2 Secondary endpoints

All secondary endpoints will be evaluated at protocol defined in-hospital and 30 days post-procedure unless otherwise stated.

1. **Safety Endpoints**

In-hospital procedural safety, defined as the composite of the following MACCE:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening (or disabling) bleeding
- Acute kidney injury – Stage 2 or 3 (or requiring renal replacement therapy)
- Major vascular complications

2. **TAVI device success** (VARC) evaluated in-hospital defined as:

- Absence of procedural mortality AND
- Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
- Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (VARC-defined) and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation (VARC-defined) (site-reported)

3. **General safety** defined as the composite of the following:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Acute kidney injury – Stage 3 (including renal replacement therapy)

4. **Mortality** [evaluated in-hospital, at 30 and at 90 days]

- All-cause mortality
  - Cardiovascular mortality

        - Neurologic event related mortality
    - Non-cardiovascular mortality

5. **Myocardial infarction** (MI)
    - Peri-procedural MI (≤ 72 hours after the index procedure)
    - Spontaneous MI(>72 hours after the index procedure)
6. **Neurological events** (component and composite) [evaluated in-hospital, at 30 and at 90 days unless otherwise indicated]
    - Stroke (VARC-2 defined)
        - Ischemic Stroke
        - Hemorrhagic stroke
        - Undetermined
    - Disabling stroke (VARC-2 defined)
    - Non-disabling stroke (VARC-2 defined)
    - Transient ischemic attack (TIA) (VARC-2 defined) [evaluated in-hospital and at 30 days]
    - Overt CNS injury (NeuroARC defined Type 1)
    - Covert CNS injury (NeuroARC defined Type 2) [evaluated in-hospital and at 30 days]
    - Neurological dysfunction without CNS injury (NeuroARC defined Type 3) [evaluated in-hospital and at 30 days]
    - CNS infarction (NeuroARC defined composite neurological endpoint) [evaluated in-hospital and at 30 days]
    - CNS hemorrhage (NeuroARC defined composite neurological endpoint) [evaluated in-hospital and at 30 days]
7. **Bleeding complications**
    - Life-threatening bleeding (VARC-2)
    - Major bleeding (VARC)
    - Minor Bleeding (VARC)
8. **Acute Kidney Injury** (AKIN classification)

- Stage 2
- Stage 3

9. **Vascular complications**

- Major vascular complications
- Major vascular complications related to TriGUARD 3

4.3 Secondary Efficacy Endpoints

1. **Hypothesis-driven Secondary Endpoints** (Phase II)

For the following secondary endpoints, a test for superiority of each intervention group to the control group will be performed. To address the issue of multiple tests among these secondary endpoints, sequential testing is planned. Secondary endpoints will be formally tested if and only if the primary study hypotheses are confirmed. The secondary endpoints will be tested individually, in the order in which they are listed as follows:

- **All stroke** [evaluated at 7 days in the eITT population]
- **NIHSS worsening**, defined as any NIHSS score increase from baseline [evaluated at 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]. A sensitivity analysis will further compare ≥2 points NIHSS worsening [evaluated at 2-5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]
- **Composite of all-cause mortality and all stroke** [evaluated at 7 days in the eITT population]
- **CNS Infarction** (NeuroARC defined) [evaluated at 30 days in the eITT analysis population]
- **Total volume of cerebral ischemic lesions** detected by DW-MRI, [evaluated 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

The above endpoints will be tested by this pre-specified sequence, until the first non-significant difference is found between the two treatment groups. After that, other treatment comparisons will be examined in an exploratory manner.

2. **Imaging Efficacy Endpoints**

All imaging efficacy endpoints are detected with DW-MRI 2-5 days post-procedure

- Presence of cerebral ischemic lesions
- Number of cerebral ischemic lesions

- Per-patient average single ischemic lesion volume
- Single cerebral ischemic lesion volume (lesion-level analysis)
- Total volume of cerebral ischemic lesions

3. **Neurologic efficacy endpoints**

   - **NIHSS worsening**, defined as an increase in NIHSS score compared to baseline [baseline NIHSS compared to NIHSS evaluated 2-5 days post-procedure and at 30 days]
   - **New neurologic impairment**, defined as NIHSS worsening from baseline accompanied by cerebral ischemic lesions [evaluated 2-5 days post-procedure and at 30 days]

4.4 Secondary performance endpoints

1. **Successful device deployment**, defined as ability to access the aortic arch with the TriGUARD *3* delivery catheter and deploy the device from the delivery catheter into the aortic arch

2. **Device positioning**, defined as ability to position the TriGUARD 3 device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by fluoroscopy) until the following time points:

   - Final deployment of the first prosthetic valve
   - Final procedure (after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed)

   Extent of cerebral artery coverage will be reported as:

   - Complete (coverage of all 3 cerebral artery branches)
   - Partial (coverage of 1-2 cerebral artery branches)
   - None

3. **Device interference**, defined as interaction of the TriGUARD 3 device with the TAVI system leading to:

   - Inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR
   - Inability to deploy the TAVI valve prosthesis, OR
   - Inability to retrieve the valve prosthesis or delivery system

4. **Successful device retrieval**, defined as ability to retrieve the TriGUARD 3.

5. **Technical success**, defined as successful device deployment, device positioning, and successful device retrieval in the absence of device interference. All parameters should be assessed at first attempt.

6. **Procedure success**, defined as technical success in the absence of any investigational device-related or investigational procedure-related in-hospital procedural safety events

4.5 Other Measures

The following additional measures will also be reported:

1. **Device deployment time** − Time elapsed between insertion of the TriGUARD *3* device into the groin access point and successful device deployment [evaluated post-procedure]

2. **Total procedural time** − Time elapsed between first arterial access and removal of the last catheter from the arterial access sheath [evaluated post-procedure]

3. **Total fluoroscopy time** [evaluated post-procedure]

4. **Total contrast utilization** [evaluated post-procedure]

4.6 Subgroup analyses

Primary and secondary endpoints will be analyzed within

- Patients with baseline paroxysmal or persistent atrial fibrillation

- Patients stratified by valve type (Edwards versus Medtronic)

5. ANALYSIS SETS

1. Efficacy Intention to treat (eITT) analysis population
   - Subjects who are enrolled in the trial and randomized to a treatment group, regardless of treatment actually received AND
   - Who do not have conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI

2. Intention to treat analysis population (ITT)
   The Intention To Treat (ITT) analysis population is defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received.

3. As treated analysis population (AT)
   The As treated analysis population is defined by the treatment actually received, rather than the treatment assigned.

4. Per treatment population (PT)
   The Per Treatment (PT) analysis population is defined as subjects in the Intervention group in whom device positioning is maintained until final procedure with complete cerebral coverage, and all Control group subjects.

5. Roll-in patients (RI)

The Roll-In (RI) patient population is defined as all subjects who undergo TAVI with the TriGUARD 3 prior to enrollment of the first evaluable subject at each investigational site. A subject is considered enrolled in the Roll-In phase of the study when:

- The patient has been judged to meet all inclusion and no exclusion criteria, and has signed a Patient Informed Consent form
- The TriGUARD 3 device has been introduced into the patient's bloodstream

6. Safety Population (SP)
   In Phase II, the Safety population will consist of the population of randomized subjects (AT or ITT as identified in the applicable analysis) and roll-in subjects.

6. STATISTICAL ANALYSES AND METHODOLOGY

The below table indicates which analysis sets are analyzed for which endpoints. An X is placed in a box if that endpoint will be analyzed for this analysis set.

	1' Efficacy	2' Efficacy*	2' Performance	1' Safety	2' Safety	Hyp-Driven 2'	Other
RI	X	X	X	X	X	X	X
eITT	**X**	**X**				**X**	
ITT	X	X	**X**	X	X		**X**
AT			X	X	X		X
PT	X	X				X	X
SP (AT)				**X**	**X**	X	X
SP (ITT)			X	X			X
RI+Rand. (eITT)	X	X				X	

*Imaging and Neurologic

1' Efficacy = Primary Efficacy
2' Efficacy = Secondary efficacy
2' Performance = Secondary performance
1' Safety = Primary safety
2' Safety = Secondary safety
Hyp-Driven 2' = Secondary hypothesis driven
Other = Other Measures

Bold and underlined Xs denote the primary population

6.1 Primary Efficacy Analysis

Primary efficacy endpoint will be analyzed on eITT population.

1. Power calculation for Phase II

Assumptions for phase II power calculation (TriGUARD 3)

- 30-day Death or Stroke rate = 6%
- NIHSS worsening from baseline to 2-5 days post-procedure = 6%
- Freedom from cerebral ischemic lesions = 27%
- Total volume of post-procedure cerebral ischemic lesions
    - 19% between >0-50 mm^3
    - 7.5% between >50-150 mm^3
    - 46% larger than >150 mm^3

Assumptions for power calculation (Control)

- 30-day Death or Stroke rate = 11%
- NIHSS worsening from baseline to 2-5 days post-procedure = 9%
- Freedom from cerebral ischemic lesions = 11%
- Total volume of post-procedure cerebral ischemic lesions
    - 7% between >0-50 mm^3
    - 33% between >50-150 mm^3
    - 48% larger than >150 mm^3

Additional assumptions

- Number of TriGUARD patients = 150 patients
- Number of Control patients = 75 patients
- Type I error = 5%
- 15% missing MRI follow up (tiers 3 & 4) and 5% missing for all other tiers

The above assumptions will provide this trial with at least 80% power to demonstrate superiority of the TriGUARD 3 device + TAVI over the control TAVI patients.

2. How to compute wins and losses

Each TriGUARD 3 patient will be compared to each patient in control and intervention group, and the number of TriGUARD 3 wins minus the number of control wins will be compared, defining the main test statistic $U = \sum_{i=1}^{N} \sum_{j=i}^{N} u_{ij}$. When making comparisons with reference to

patient *i*, ties will add 0 points, a winning comparison will add +1 point, and a losing comparison will add -1 point.

Tier 1: Death and Stroke at 30 days

A patient *X* wins against a patient *Y* if patient *X* does not die or have a stroke and patient *Y* does die or have a stroke, or if both patients *X* and *Y* suffer a death/stroke and patient *Y* experiences the death/stroke before (smaller number of days to event) patient *X*. Patient X ties with patient Y if both patients *X* and *Y* do not have a death/stroke, or both have a death/stroke on the same post procedure day. Otherwise, patient *X* loses.

In the event both patients have an event each patient is assigned "0" and the comparison stops. In the event both patients did not have an event, the comparison proceeds to the next Tier.

Tier 2: NIHSS worsening at 2-5 days post procedure

A patient *X* wins against a patient *Y* if patient *X* does not have a NIHSS worsening (increase from baseline) and patient *Y* does have NIHSS worsening. Patient *X* ties with *Y* if both patients have or don't have worsening NIHSS scores 2-5 days post-procedure. Otherwise, patient *X* loses. NIHSS worsening is only assessed for the period deemed to be acceptably close to the protocol-specified 2-5 day window (defined as 1-7 days), assigning assessments that are unacceptably far out of window (before 1 day or after 7 days) as missing for this analysis.

In the event of a tie, when both of the patients have a worsening, both are assigned score "0" and the comparison stops. If none of the two patients had a worsening, the comparison proceeds to the next Tier.

Tier 3: Freedom from cerebral ischemic lesions

A patient *X* wins against a patient *Y* if DW-MRI finds no cerebral ischemic lesions present in patient *X* and does find lesions in patient *Y*. If both patients X and Y do not have cerebral lesions, it is equilibrium (both patients receive 0 points). If both patients have cerebral lesions, it is a tie and the comparison moves to the next Tier. Otherwise, patient *X* loses. DW-MRI is only defined for assessments deemed to be acceptably close to the protocol-specified 2-5 day window (defined as 1-7 days), assigning assessments that are unacceptably far out of window (before 1 day or after 7 days) as missing for this analysis.

Tier 4: Total volume of cerebral ischemic lesions

TLV_X is the total lesion volume of patient X, in mm^3:

Patient X wins and patient Y loses if $TLV_X > TLV_Y$, and patient X loses and patient Y wins if $TLV_X > TLV_Y$

If in any comparison, either patient X or patient Y has missing data, or either measurement was out of window then we consider this comparison a tie. The TLV is assessed for measurements deemed to be acceptably close to the protocol-specified 2-5 day window (defined as 1-7 days post-index procedure).

3. Hypothesis

Formally, we test

$$H_{Null}: U \leq 0$$

$$H_{Alternative}: U > 0$$

Where $U = \sum_{i=1}^{N} \sum_{j=i}^{N} u_{ij}$, where u_{ij} equals 0 when tied, +1 when winning against patient *j*, and -1 when losing to patient *j*. We compute U's variance as

$$Var(U) = \frac{N_{TriGUARD3}\, N_{Control}}{N} \sum_{i=1}^{N} U_i^2$$

Where N equals the number of patients, and $U_i$equals the number of wins for patient *i*.

We compare

$$\chi^2 = \frac{U^2}{var(U)}$$

to a Chi-squared distribution with 1 degree of freedom and consider a statistically significant difference one with a pvalue < 0.025. If this endpoint is met in the eITT population, we will rerun this analysis in the ITT population.

4. Sensitivity analysis

- NIHSS

We will rerun the primary efficacy endpoint analysis, counting an absolute difference between two patients' post procedure minus baseline NIHSS a tie if <2 point difference.

- DW-MRI

We will impute 10 separate datasets for DW-MRI total lesion volume using a linear regression model with covariates: device versus control, age at time of enrollment, body mass index, race, smoking status, creatinine level, hyperlipidemia, hypertension, aortic arch disease burden, porcelain aorta, aortic valve area at baseline, procedure time, country, valve type, balloon post dilatation, arch type, and level of calcification.

For each dataset, the primary efficacy endpoint's χ^2 statistic will be computed and combined using Fisher's procedure. Fisher's procedure compares

$$-2 \sum_{\text{imputed dataset (i)}=1}^{10} \text{pvalue}(i)$$

against a χ^2 with 2*10 degrees of freedom at the 0.025 significance level, claiming significance if

$$-2 \sum_{\text{imputed dataset (i)}=1}^{10} \text{pvalue}(i) \geq \chi^2_{20,0.025}$$

Primary efficacy endpoint adjusting for pre-existing lesion volumes.

Difference among device and control across will be assessed, accounting for pre-existing lesion volume, by assigning each patient a score equal to $u_i = \sum_{j=1}^{N} u_{ij}$ and regressing this dependent variable on treatment and pre-existing lesion volume, minimizing the loss function

$$\sum_{i=1}^{N} |u_i - (\beta_0 + \beta_1 \text{TriGUARD} + \beta_2 \text{Preexisting lesion volume})|$$

and the formal hypothesis test

$$H_{\text{null}}: \beta_1 \leq 0$$

$$H_{\text{null}}: \beta_1 > 0$$

held at a p-value 0.025 will determine significance.

The results of this analysis will be reported as an adjusted p-value for the difference between the study groups (Table 18).

5. Combined Phase I/ Phase II controls population, data validity, and poolability

Control patients from Phase I and Phase II may be pooled together, increasing power to detect differences in the primary efficacy endpoint. As described in the protocol (Section 12.4.3), Poolability of the Phase I and Phase II control subjects will be assessed at the time of the primary analysis and the results will determine the control population used for the primary analysis of the primary efficacy endpoint. If Phase I and Phase II control patients are deemed poolable, the primary analysis of the primary efficacy endpoint and all secondary efficacy endpoints will include Phase I control subjects. If Phase I and Phase II control patients are deemed not poolable, the primary analyses for the primary and secondary efficacy endpoints will be performed in the Phase II population only.

Phase I and Phase II control patients are poolable if we find no statistically significant differences between the two groups (at significance level p-value < 0.15) in baseline characteristics (Table 19).

6.2 Primary Safety Analysis

Primary Safety analysis will be performed on SP(AT) population including Roll-Ins.

1. Power calculation:

Assumptions for power calculation

- 30-day combined safety endpoint rate in intervention group = 25%
- Performance goal (PG) = 34.4%
- Number of TriGUARD 3 patients = 190 patients (including at least 40 roll-ins)
- Type I error = 5%
- 5% loss to clinical follow-up or dropout at 30 days

From the above assumptions and using a one-sample z-test for proportions, both phase I and phase II will have at least 85% power to determine whether the intervention group meets the PG.

2. Hypothesis

Formally, we test

$$H_{Null}: \pi \geq 0.344$$

$$H_{Alternative}: \pi < 0.344$$

where π is the true safety event rate for the TriGuard group.

We compute the upper limit as

$$U.L. = \pi + 1.645\sqrt{\frac{\pi(1-\pi)}{n}}$$

Where n is sample size in intervention group. We compare upper bound of the one-sided 95% confidence interval of the primary safety endpoint event rate in the intervention arm to the performance goal ($\pi_0 = 0.344$). If upper limit is less than 0.344, we consider the PG met and will report the pvalue.

3. Poolability and consistency analysis

In addition, in the final analysis, assessments of study-center and of region effect on the primary safety endpoint will be carried out on **the interventional group** within the SP(AT) population using logistic regressions. A 0.15 level of significance will be used to assess the significance of each of the study center and region effects on the safety endpoint. A non-significant result for each of study centers and regions will support the pooling of patients across study centers and across regions for the primary safety analysis. A significant result will require further inspection of the by-center and by-region results to assess if poolability is appropriate. Note that centers with less than 5 subjects will be pooled with other centers by closest geographic region; this pooling will be carried out prior to the unblinding.

We will assess poolability across clinical site by measuring how death/stroke rates change as a function of site. We can model this process with a logistic regression, modeling the distribution of death/stroke rate conditional on site. We will conclude sites cannot be pooled if we find this model significantly explains the data better than the null (intercept) model.

Sites

We treat the covariate site as a random variable. We will assume $\beta_{\text{Site}} \sim N(0, \sigma^2)$, that the site variable follows a Normal distribution with 0 mean and variance sigma squared. Our hypothesis test follows a similar structure,

$$\text{H}_{\text{Null}}: \sigma^2 = 0$$

$$\text{H}_{\text{alternative}}: \sigma^2 \neq 0$$

or in words, is we cannot show sigma squared is statistically different than zero, then this model including a variable for site does not fit the data any better than a model not including a site term, and we would consider the clinical sites poolable. This tests also hold type I error to 0.15.

4. Tipping point analysis

The impact of missing data to bias results can be assessed with a tipping point analysis, where we fill-in missing data, replacing missing with event or non-events, and can assess whether replacing missing data with events could cause a difference in safety's statistical significance. Looking at a tipping point a second way, we generate a function mapping the number of missing TriGuard and missing control events imputed as experiencing an event, to the pvalue from our test of safety or

$$(\text{E}_{\text{TriGuard}}, \text{E}_{\text{Controls}}) \rightarrow \text{pvalue}$$

Our goal is to build this function.

In detail, given $\text{M}_{\text{TriGuard3}}$ missing events in the device population and $\text{M}_{\text{control}}$ missing events in the control population, start by imputing all $\text{M}_{\text{control}}$ missing events as non-events, then from E=1 to $\text{M}_{\text{TriGuard3}}$, impute E events in the TriGuard population, re-compute the safety test, and record the pvalue. Our tipping point analysis will display this function as a grid $\text{M}_{\text{TriGuard}} \times \text{M}_{\text{Controls}}$ grid with the corresponding pvalue inside grid point ($\text{E}_{\text{TriGuard}}$, $\text{E}_{\text{Control}}$), the p-value from imputing $\text{E}_{\text{TriGuard}}$events in the TriGuard population and $\text{E}_{\text{Control}}$ events in the control population.

6.3 Secondary endpoints

1. Hypothesis-driven

Hypothesis-driven endpoints will be formally tested for superiority, but only if the trial meets both the primary efficacy and primary safety endpoints. We guard against type I error inflation by testing these endpoint in sequence. Continuous variables will be assumed normally distributed, with hypothesis test

$$H_{\text{null}}: \mu_{\text{TriGUARD}} - \mu_{\text{Control}} = 0$$

$$H_{\text{alternative}}: \mu_{\text{TriGUARD}} - \mu_{\text{Control}} < 0$$

and test statistic

$$t = \frac{\langle c_{\mathrm{TriGUARD}} \rangle - \langle c_{\mathrm{Control}} \rangle}{\left[{\Delta^2(c_{\mathrm{TriGUARD}})}/{\mathrm{N}_{\mathrm{TriGUARD}}} + {\Delta^2(c_{\mathrm{Control}})}/{\mathrm{N}_{\mathrm{Control}}} \right]^{1/2}}$$

We will compare *t* to a Student's t distribution, concluding superiority if the corresponding pvalue is less than 0.025

Categorical variables will be assumed Binomially distributed, with hypothesis test

$$H_{\mathrm{null}}: \pi_{\mathrm{TriGUARD}} - \pi_{\mathrm{Control}} \geq 0$$

$$H_{\mathrm{alternative}}: \pi_{\mathrm{TriGUARD}} - \pi_{\mathrm{Control}} < 0$$

and χ^2 test statistic, concluding superiority if the corresponding pvalue is less than 0.025.

The sequentially-tested endpoints are:

1. All stroke up to 7 days
2. NIHSS worsening at 7 days
3. Composite of all-cause mortality and all stroke up to 7 days
4. CNS infarction at 30 days
5. Total volume of cerebral ischemic lesions [2-5 days]

If non-significant results are found, the remaining endpoints will be analyzed as exploratory endpoints.

2. Imaging

Continuous measures of lesion volume will be reported with mean (standard deviation), median (IQR), minimum, maximum, and the number of evaluable patients, and categorical variables will be reported with percentages and frequencies. No formal hypothesis tests are prespecified, but continuous lesion volume variables will be tested with Student's t-test and categorical variables with the χ^2 test. The following imaging endpoints will be studied

- Number of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Per-patient average single cerebral ischemic lesion volume detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Single cerebral ischemic lesion volume (lesion-level analysis) detected by DW-MRI, evaluated at 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure

3. Neurologic

Categorical variables will be reported with percentages and frequencies. No formal hypothesis tests are prespecified, but continuous lesion volume variables will be tested with Student's t-test and categorical variables with the χ^2 test.

- NIHSS worsening, defined as an NIHSS score increase from baseline [baseline score compared with score evaluated at 2-5 days post-procedure and at 30 days]
- New neurologic impairment, defined as an NIHSS score increase from baseline accompanied by the presence of cerebral ischemic lesions [evaluated at 2-5 days post-procedure and at 30 days]

Adjusting for pre-existing lesion volume

Imaging and Neurologic endpoints will be reanalyzed, adjusting for pre-existing lesion volume by logistic regression (for Binary variables), poisson regression (for count variables) or Negative binomial regression if the dependent variable is overdispersed, and Linear/Poisson/Negative-Binomial regression for continuous variables (raising lesion volume to the 1/3 power (Table 22).

4. Secondary Performance Endpoints

Categorical variables will be reported by treatment groups with percentages and frequencies.

- Successful device deployment, defined as ability to access the aortic arch with the TriGUARD 3 delivery catheter and deploy the device from the delivery catheter into the aortic arch
- Successful device positioning, defined as ability to position the TriGUARD 3 device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by fluoroscopy) until the following time points:
    - Final deployment of the first prosthetic valve
    - Final procedure (after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed)

Extent of cerebral artery coverage will be reported as:

- Complete (coverage of all 3 cerebral artery branches)
- Partial (coverage of 1-2 cerebral artery branches)
- None

Note: Maintenance of device positioning to each time point and extent of cerebral artery coverage will be evaluated by the Angiographic Core Laboratory.

- Device interference, defined as interaction of the TriGUARD 3 device with the TAVI system leading to:
    - Inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR
    - Inability to deploy the TAVI valve prosthesis, OR
    - Inability to retrieve the valve prosthesis or delivery system
- Successful device retrieval, defined as ability to retrieve the TriGUARD 3 CEPD.
- Technical success, defined as successful device deployment, device positioning, and successful device retrieval in the absence of device interference

- Procedural success, defined as technical success in the absence of any investigational device-related or investigational procedure-related in-hospital safety events

5. Secondary Safety Endpoints

All secondary safety endpoints, including the components of the primary safety endpoint. will be evaluated in-hospital and at 30 days and reported by treatment group in the AT population of evaluable subjects using appropriate descriptive statistics (sample size, mean, standard deviation, median, minimum, maximum for continuous characteristics; counts and percentages of patients for dichotomous characteristics).

The endpoints will be analyzed on AT population, followed by the ITT subset. Relationship to the investigational device/investigational procedure (as determined by an independent CEC) will also be reported for Intervention and Roll-In groups.

6.4 Other Measures

Continuous measures will be reported with mean (standard deviation), median (IQR), minimum, maximum, and the number of evaluable patients. Continuous variables will be tested with Wilcoxon test.

- Device deployment time − Time elapsed between insertion of the TriGUARD 3 device into the groin access point and successful device deployment [evaluated post-procedure]
- Total procedural time − Time elapsed between first arterial access and removal of the last catheter from the arterial access sheath [evaluated post-procedure]
- Total fluoroscopy time [evaluated post-procedure]
- Total contrast utilization [evaluated post-procedure]

7. POOLING AND CONSISTENCY ANALYSIS WITHIN PHASE II

We will assess poolability (within eITT patients) across clinical sites, and between gender, valve type (Edwards vs. Medtronic), STS risk score, either pre or peri-procedural antiplatelet treatment, and DAPT vs Monotherapy vs Warfarin plus antiplatelet therapy to 30 days vs other. A bulleted list of covariates is included below. All interaction tests will be considered significant is the pvalue is below 0.15.

- Subject gender (male versus female)
- Valve prosthesis type (Edwards vs. Medtronic)
- Operative risk (by Society of Thoracic Surgeons [STS] Risk Score)
- Type and duration of antiplatelet therapy:
    - Maintenance therapy:
        - Dual antiplatelet therapy (DAPT) to 90 days vs.

- Monotherapy (aspirin or clopidogrel) to 90 days vs.
- Warfarin with antiplatelet therapy to 90 days vs.
- Other

Primary efficacy endpoint

Difference among device and control across sites will be assessed by assigning each patient a score equal to $u_i = \sum_{j=1}^{N} u_{ij}$ and regressing this dependent variable on treatment using a mixed models approach where each site will be assigned a random effect for treatment, with poisson or negative-binomial distribution of the dependent variable. The formal hypothesis will test whether the random slope term in the regression varies across the sites. We will conclude on poolability across the sites based on the significance level of the random slope.

Sites with less than 5 patients will be pooled into one combined site by closest geographic location.

Death/stroke will be modeled with logistic regression

$$\text{Death/Stroke} \sim \text{Bin}(\text{N}, \pi)$$

where $\pi = \text{logit}^{-1}\left(\beta_0 + \beta_{\text{TriGuard}}\text{TriGuard} + \beta_{\text{V}}\text{V} + \beta_{\text{TriGuard} \times \text{V}}(\text{TriGuard} \times \text{V})\right)$

and V is one of the covariates above. NIHSS and DW-MRI lesion volume (raising lesion volume to the 1/3 power) will be modeled with Linear / Poisson or Negative Binomial regression depending on the final distribution of the outcome.

$$Y \sim N(\beta_0 + \beta_{\text{TriGUARD}} + \beta_V + \beta_{\text{TriGUARD} \times \text{V}}, \sigma^2)$$

where Y is NIHSS for one set of analyses, and DW-MRI for the second set of analyses. For the death/stroke logistic regression, NIHSS and lesion volumes Poisson / Negative Binomial regression, our hypotheses can be stated as

$$H_{\text{null}}: \beta_{\text{TriGUARD} \times \text{V}} = 0$$

$$H_{\text{alternative}}: \beta_{\text{TriGUARD} \times \text{V}} \neq 0$$

8. GENERAL METHODOLOGY AND CONVENTIONS

8.1 Summary analysis

Descriptive statistics for continuous variables include the number of observations available, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum. We will compare continuous variables with a t-test, or Wilcoxon rank-sum tests if data fail to meet the assumption for normality per the Shapiro-Wilks test.

Descriptive statistics for categorical variables include frequency, number of observations available, and percentage. We will compare categorical variables with a Chi-square test, or Fisher's exact test for discrete value with 20% or more of expected frequencies are less than 5.

Descriptive statistics for time to event variables include the number of events and Kaplan-Meier estimated event rates. Comparisons will be performed by the log-rank test. We will also report the Hazard ratio and 95% confidence intervals.

8.2 Methods to Manage Missing data

We will not take any extra steps to impute missing data beyond what was specified in the primary analyses.

8.3 Controlling for Multiplicity

No adjustment for multiplicity is needed beyond the sequential testing in the hypothesis driven endpoints.

8.4 Adjustment for Covariates

No adjustment for covariates is needed, other than the previously specified analyses of primary and secondary efficacy endpoints adjusted for pre-existing lesion volume.

8.5 Adaptive Design and Interim Analysis Methodology

When the trial has enrolled at least 50% of all patients in Phase II of the study and these patients have reached their 30 day follow-up visit, the same method used to power the study will be re-run with assumptions based on the collected data. Our adaptive design will rely on work by Mehta and Pocock's promising zone---enrolling 112 patients (n_1) out of a planned total 225(n_2), allowing a maximum possible enrollment of 337 patients (n_{max}). Then the ratio of interim patients divided by planned final patients is (n_1/n_2=0.5), allowable patients divided by final planned patients is (n_{max}/n_2 = 1.5), and our promising zone, given an 80% conditional power, starts at ~40% and ends at 80%. This can be verified in Table 1 of Mehta and Pocock. Below we include a step-by-step, prespecified, procedure for the interim analysis.

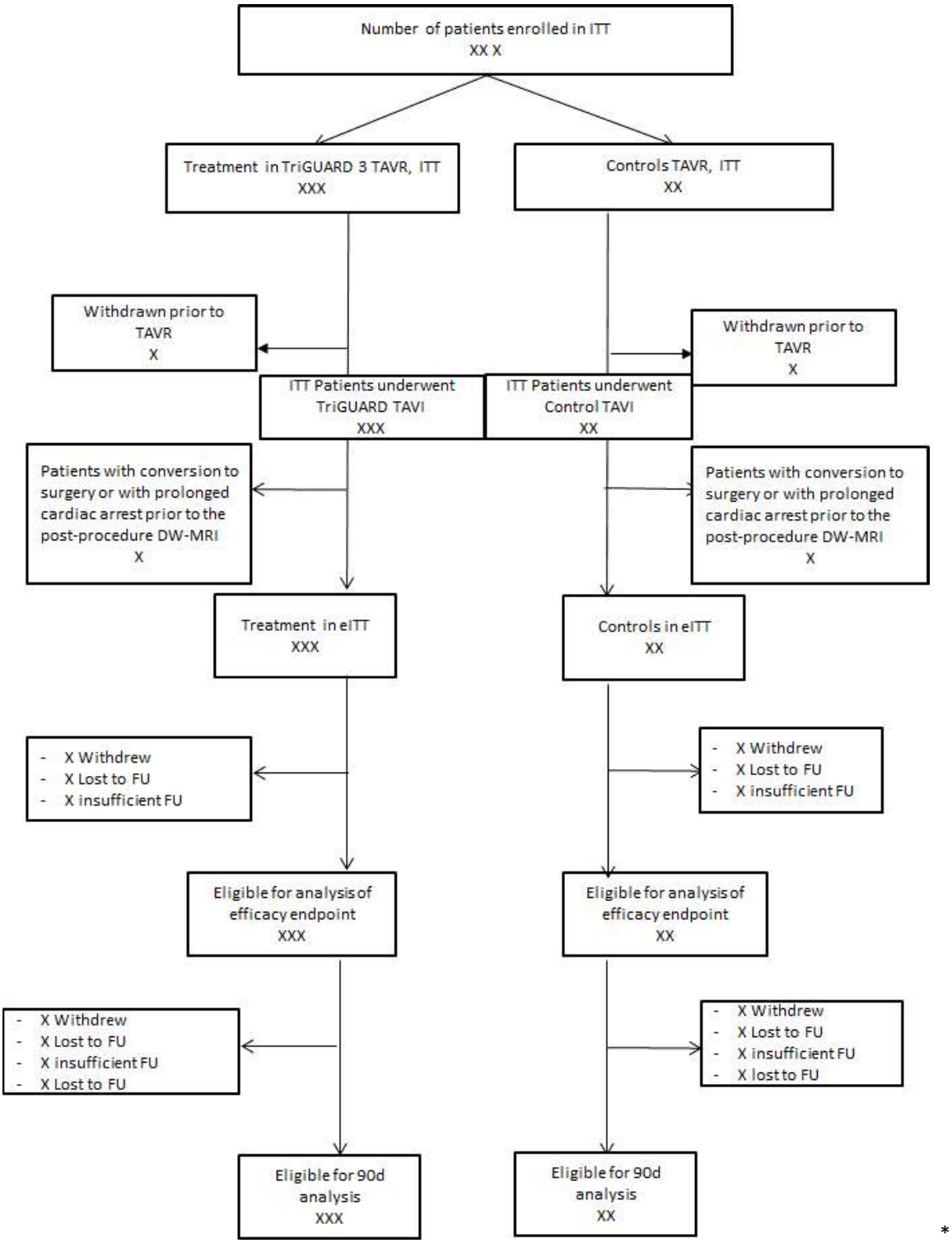
1. Interim data on at least 112 Phase II patients, eligible for their 30 day follow-up, will be provided to the unblinded statistician
2. All assumptions (listed below) used for the original power analysis will be replaced with estimates from the interim data:
    a. 30 day composite Death/Stroke rate
    b. NIHSS worsening from baseline to 2-5 days post-procedure
    c. Freedom from cerebral ischemic lesions
    d. Total volume of post-procedure cerebral ischemic lesions
        i. Percent between >0-50 mm^3
        ii. Percent between >50-150 mm^3
        iii. Percent larger than >150 mm^3
    e. Loss to follow-up (including dropout from the primary analysis population)

3. Using the same program that originally powered the study and updated interim estimates, the conditional power will be computed for the planned 225 Phase II subjects.
4. If the conditional power falls below 40% or above 80%, then the trial will not enroll any additional patients beyond the planned 225 Phase II subjects.
5. If the conditional power is between 40% and 80%, we will compute:
    a. The number of additional phase II patients required for 80% power
6. The unblinded statistician will provide the following information to the Sponsor (table below):

Description	N
Number of Additional Phase II pts needed for 80% power	xx

If during a comparison, one or both patients are missing data, we will consider this a tie.

Figure 1a: Trial flowchart for ITT population



*

Category "withdrawn" includes the following reason for early termination: "non-compliance with study procedures", "refusal to continue/withdraws consent" and "investigator order due to subject's health or safety," based on field EXT.EXTREASON.

Figure 1b: Trial flowchart for SP(AT) population

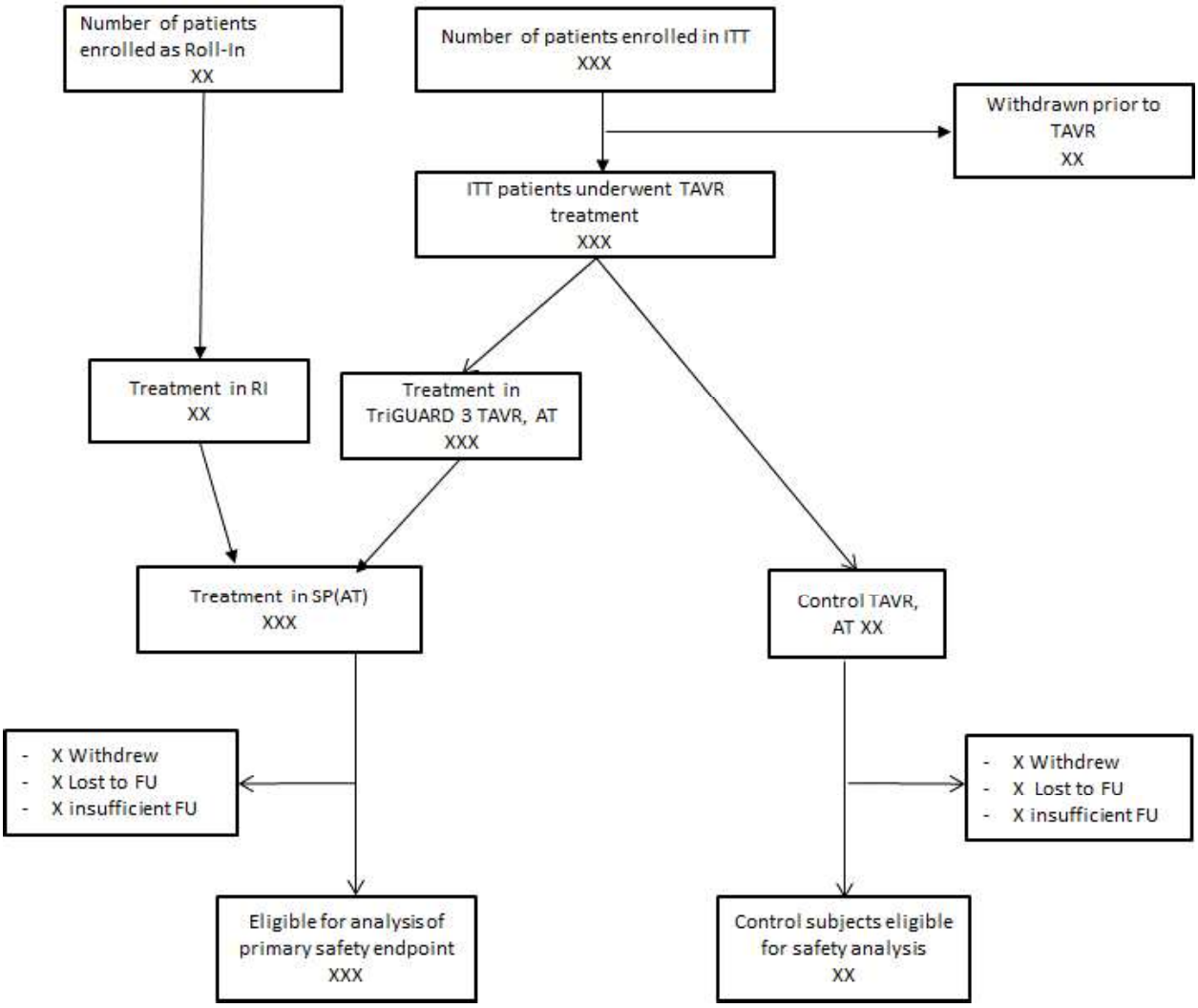


Table 1a: Analysis of the Primary Safety Endpoint

Primary Safety Endpoints	TriGuard 3 system (N=XXX)	95% CI**	Upper limit of one-sided 95% CI	Performance Goal (PG)	p-value,*** comparison to PG
*SP(AT) population***					
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**(xx.x; xx.x)**	**x.xx%**	**34.4%**	x.xxx
Death	x.x% (x/xxx)	(xx.x; xx.x)	CEC.DEATH or YCEC.YDEATH="Cardiovascular" or "Non-cardiovascular"		
Stroke	x.x% (x/xxx)	(xx.x; xx.x)	CEC.STROKE="Yes" or YCEC.YSTROKE="Yes"		
Life-threatening or disabling bleeding	x.x% (x/xxx)	(xx.x; xx.x)	YCEC.YBLEED="Yes" and CEC.BLEEDTYPE="Life-Threatening or disabling Bleeding"		
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	(xx.x; xx.x)	CEC.AKI="Yes" or YCEC.YAKI="Yes" **& CEC.AKISTAGE in (2 3)**		
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	(xx.x; xx.x)	**CEC.CAO="Yes" or YCEC.YCAO="Yes"**		
Major vascular complication	x.x% (x/xxx)	(xx.x; xx.x)	CEC.MAJVASC="Yes" or YCEC.YMAJVASC="Yes"		
TriGUARD access site	x.x% (x/xxx)	(xx.x; xx.x)	TriGuard HDH or TriGUARD 3 ACCESS SITE-RELATED		
TAVI or other access site	x.x% (x/xxx)	(xx.x; xx.x)	TAVI access site-related OR SECONDARY ACCESS SITE-RELATED (non-TriGuard or TriGUARD site-related)		
Not access site-related	x.x% (x/xxx)	(xx.x; xx.x)	Aortic vascular injury (other than access site-related)		
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	(xx.x; xx.x)	CEC.VRD="Yes" or YCEC.YVRD="Yes"		
*As treated (AT) population***					
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**(xx.x; xx.x)**	**x.xx%**	**34.4%**	x.xxx
Death	x.x% (x/xxx)	(xx.x; xx.x)			
Stroke	x.x% (x/xxx)	(xx.x; xx.x)			
Life-threatening or disabling bleeding	x.x% (x/xxx)	(xx.x; xx.x)			
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	(xx.x; xx.x)			
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	(xx.x; xx.x)			
Major vascular complication	x.x% (x/xxx)	(xx.x; xx.x)			
TriGUARD access site	x.x% (x/xxx)	(xx.x; xx.x)			
TAVI or other access site	x.x% (x/xxx)	(xx.x; xx.x)			
Not access site-related	x.x% (x/xxx)	(xx.x; xx.x)			
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	(xx.x; xx.x)			
*ITT population***					
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**(xx.x; xx.x)**			
Death	x.x% (x/xxx)	(xx.x; xx.x)			
Stroke	x.x% (x/xxx)	(xx.x; xx.x)			
Life-threatening or disabling bleeding	x.x% (x/xxx)	(xx.x; xx.x)			
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	(xx.x; xx.x)			
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	(xx.x; xx.x)			
Major vascular complication	x.x% (x/xxx)	(xx.x; xx.x)			
TriGUARD access site	x.x% (x/xxx)	(xx.x; xx.x)			
TAVI or other access site	x.x% (x/xxx)	(xx.x; xx.x)			
Not access site-related	x.x% (x/xxx)	(xx.x; xx.x)			
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	(xx.x; xx.x)			
SP(ITT) population					
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**(xx.x; xx.x)**			
Death	x.x% (x/xxx)	(xx.x; xx.x)			
Stroke	x.x% (x/xxx)	(xx.x; xx.x)			
Life-threatening or disabling bleeding	x.x% (x/xxx)	(xx.x; xx.x)			
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	(xx.x; xx.x)			
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	(xx.x; xx.x)			
Major vascular complication	x.x% (x/xxx)	(xx.x; xx.x)			
TriGUARD access site	x.x% (x/xxx)	(xx.x; xx.x)			
TAVI or other access site	x.x% (x/xxx)	(xx.x; xx.x)			
Not access site-related	x.x% (x/xxx)	(xx.x; xx.x)			
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	(xx.x; xx.x)			
RI population					
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**(xx.x; xx.x)**			
Death	x.x% (x/xxx)	(xx.x; xx.x)			
Stroke	x.x% (x/xxx)	(xx.x; xx.x)			
Life-threatening or disabling bleeding	x.x% (x/xxx)	(xx.x; xx.x)			
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	(xx.x; xx.x)			
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	(xx.x; xx.x)			
Major vascular complication	x.x% (x/xxx)	(xx.x; xx.x)			
TriGUARD access site	x.x% (x/xxx)	(xx.x; xx.x)			
TAVI or other access site	x.x% (x/xxx)	(xx.x; xx.x)			
Not access site-related	x.x% (x/xxx)	(xx.x; xx.x)			
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	(xx.x; xx.x)			

*Events defined for the period of 30 days post-procedure follow up are reported for patients with at least 23 days of follow-up or with a composite primary safety endpoint to 30 days post-procedure.

**Confidence interval is based on the binomial approximation to the normal distribution.

***Z-test

Table 1b: Analysis of the Primary Efficacy Endpoint

Primary Efficacy Endpoints	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Efficacy Intention-to-treat (eITT) population			
Primary Efficacy Hierarchical Endpoint			
Mean±SD (n)	xx xx±xx.xx (n)	xx.xx±xx xx (n)	x xxx*
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
All-cause mortality or any stroke at 30 days	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
NIHSS worsening post-procedure/pre-discharge worsening **	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Freedom from cerebral ischemic lesions	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 days post-procedure, mm^3***			
Mean±SD (n)	xx xx±xx.xx (n)	xx.xx±xx xx (n)	Wilcoxon test
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
Intention to treat (ITT) population			
Primary Efficacy Hierarchical Endpoint			
Mean±SD (n)	xx xx±xx.xx (n)	xx.xx±xx xx (n)	x xxx*
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
All-cause mortality or any stroke at 30 days	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
NIHSS worsening post-procedure/pre-discharge worsening **	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Freedom from cerebral ischemic lesions	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 days post-procedure, mm^3***			
Mean±SD (n)	xx.xx±xx.xx (n)	xx xx±xx.xx (n)	Wilcoxon test
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
SP (eITT) population			
Primary Efficacy Hierarchical Endpoint			
Mean±SD (n)	xx xx±xx.xx (n)	xx.xx±xx xx (n)	x xxx*
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
All-cause mortality or any stroke at 30 days	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
NIHSS worsening post-procedure/pre-discharge worsening **	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Freedom from cerebral ischemic lesions	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 days post-procedure, mm^3***			
Mean±SD (n)	xx.xx±xx.xx (n)	xx xx±xx.xx (n)	Wilcoxon test
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
Per Treatment (PT) population			
Primary Efficacy Hierarchical Endpoint			
Mean±SD (n)	xx.xx±xx.xx (n)	xx xx±xx.xx (n)	x xxx*
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
All-cause mortality or any stroke at 30 days	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
NIHSS worsening post-procedure/pre-discharge worsening **	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Freedom from cerebral ischemic lesions	x.x% (x/xxx)	x.x% (x/xxx)	Fisher Exact test
Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 days post-procedure, mm^3***			
Mean±SD (n)	xx.xx±xx.xx (n)	xx xx±xx.xx (n)	Wilcoxon test
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
Roll-In (RI) population			
Primary Efficacy Hierarchical Endpoint			
Mean±SD (n)	xx.xx±xx.xx (n)	xx xx±xx.xx (n)	x xxx*
Median	xx.xx	xx.xx	
Q1; Q3	xx xx; xx xx	xx.xx; xx xx	
Min; Max	(xx xx; xx xx)	(xx xx; xx xx)	
All-cause mortality or any stroke at 30 days	x.x% (x/xxx)		
NIHSS worsening post-procedure/pre-discharge worsening **	x.x% (x/xxx)		
Freedom from cerebral ischemic lesions	x.x% (x/xxx)		
Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 days post-procedure, mm^3***			
Mean±SD (n)	xx.xx±xx.xx (n)		
Median	xx.xx		
Q1; Q3	xx xx; xx xx		
Min; Max	(xx xx; xx xx)		

*p-value is a result of a hierarchical algorithm described in SAP, pages XX-XX

**Worsening of NIHSS score is calculated as difference in NIH.NIHSCOR at pre-discharge - baseline being above "0" (higher values are assigned to worse conditions). The timing is verified by NIH.NIHDATE.

***The timing is verified as 2days<(MR.MRDOMR-MR.MRDOTAVR)< 5 days.

Table 2a: Study Enrollment – Phase II

Site	Location	Number of Roll-In Patients	Number of Patients in the ITT population	Number of Patients in the TriGuard 3 system Group	Number of Patients in the Control Group	Date of First Patient Enrolled in the Study	Date of Last Patient Enrolled in the Study
						SC.SCICFDATE	SC.SCICFDATE
Total							

Table 2b: Study Enrollment – Phase I

Table 3: Compliance in the study

Analysis Set	Patients Enrolled	Study Groups	Number of Patients with Index Forms*	Number of Patients with Procedure Forms	Number of Patients with in-hospital form**	Number of Patients with 30-Day Visit Forms***	Number of Patients with 90-day Visit Forms****	Mean Follow-up time, days*****
Efficacy Intention to Treat (eITT)	xxx	Intervention	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Control	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
As Treated (AT)	xxx	Intervention	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Control	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
Intention to Treat Analysis (ITT)	xxx	Intervention	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Control	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
Roll-In (RI)	xxx	Intervention	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)
		Total	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	Mean+/-SD, (Min; Max)

* Patient is considered to have index forms if all of the following forms required at baseline have been filled out: informed consent, medical history and physical examination.

**In-hospital form is defined by non-missing field PH.PHDDOE on "Physical Exam – Post-procedure/pre-discharge" form.

***Number of patients with forms is reported for patients patients whose forms should have been collected and entered, e.g. excluding patients with insufficient follow-up (prior to 37 days or 104 days for visits 30d and 90d, respectively) or patients who died/withdrew consent by the time of the visit (prior to 37 and 104 days).

****Contact Forms at 30 and 90 include physical examination form, clinical assessment of anginal status, concomitant medications forms and cognitive assessmenrs by NIH Stroke Scale.

*****Mean Follow-up is calculated as the last date recorded for the patient in the database minus the procedure date.

******Intervention and Control status is defined based on the relevant population set definition.

Table 4a: Medical History – ITT population

Pa ient Characteristics	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Demography			
Age (yrs)		*PR.PRDATE-SC.SCDOB*	
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	t-test
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Male gender	xx.x% (xx/xxx)	*SC.SCGENDER*	Fisher Exact test
Hispanic or Latino Ethnicity	xx.x% (xx/xxx)	*SC.SCETH*	Fisher Exact test
Medical History			
Smoking/Tobacco Usage		*MHX.MHXSMO*	
Current wi hin last year	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Chi-square, Raw Mean Score
Ex-Smoker	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Never	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Diabetes Mellitus (DM)	xx.x% (xx/xxx)	MHX.MHXD	Fisher Exact test
Insulin Dependent (IDDM)	xx.x% (xx/xxx)	MHX.MHXIDDM	Fisher Exact test
Diet-controlled	xx.x% (xx/xxx)	MHX.MHXDIET	Fisher Exact test
Oral hypoglycemic controlled	xx.x% (xx/xxx)	MHX.MHXORALHYP	Fisher Exact test
History of Hypertension	xx.x% (xx/xxx)	*MHX.MHXHTN*	Fisher Exact test
History of Hyperlipidemia	xx.x% (xx/xxx)	*MHX.MHXDYS*	Fisher Exact test
History of History of Peripheral Vascular Disease (PVD)	xx.x% (xx/xxx)	*MHX.MHXPVD*	Fisher Exact test
History of aortic artery disease (aneurysm)	xx.x% (xx/xxx)	*MHX.MHXAA*	Fisher Exact test
History of prior treatment/repair	xx.x% (xx/xxx)	*MHX.MHXHXTRT*	Fisher Exact test
Caro id artery disease	xx.x% (xx/xxx)	*MHX.MHXCAD*	Fisher Exact test
Prior cerebral vascular attack (CVA)	xx.x% (xx/xxx)	*MHX.MHXCVA*	Fisher Exact test
Prior trans ischemic attack (TIA)	xx.x% (xx/xxx)	*MHX.MHXTIA*	Fisher Exact test
History of anemia requiring transfusion	xx.x% (xx/xxx)	*MHX.MHXANEM*	Fisher Exact test
History of renal disease	xx.x% (xx/xxx)	*MHX.MHXRENALDIS*	Fisher Exact test
Frac ion (LVEF) performed or documented previously	xx.x% (xx/xxx)	*MHX.MHXLVEFPERF*	Fisher Exact test
History of conges ive heart failure (CHF)	xx.x% (xx/xxx)	*MHX.MXHCHF*	Fisher Exact test
History of atrial fibrilla ion/atrial flutter	xx.x% (xx/xxx)	*MHX.MHXAF*	Fisher Exact test
History or presence of intracardiac mass, thrombus or vegetation	xx.x% (xx/xxx)	*MHX.MHXICMTV*	Fisher Exact test
History of prior coronary artery bypass graft(s) (CABG)	xx.x% (xx/xxx)	*MHX.MHXCABG*	Fisher Exact test
History of prior percutaneous coronary interven ion (PCI)	xx.x% (xx/xxx)	*MHX.MHXPPCI*	Fisher Exact test
Chronic Lung disease/ COPD	xx.x% (xx/xxx)	*MHX.MHXCOPD*	Fisher Exact test
In home Oxygen Use	xx.x% (xx/xxx)	*MHX.MHXOXYGENUSE*	Fisher Exact test
Severe Pulmonary HTN	xx.x% (xx/xxx)	*MHX.MHXSVRHTN*	Fisher Exact test

Table 4b: Medical History – PT population
Table 4c: Medical History – RI population
Table 4d: Medical History – SP(AT) population

Table 5a: Physical Assessment at baseline – ITT population

Patient Characteristics at baseline	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Heart Rate, beats per minute	*PH.PHBHR*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	t-test
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Systolic Blood Pressure, mmHg	*PH.PHBSYSBP*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	t-test
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Diastolic Blood Pressure, mmHg	*PH.PHBDIABP*		t-test
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Mean Arterial Pressure, mmHg	*PH.PHBDIABP+1/3 *(PH.PHBSYSBP-PH.PHBDIABP)*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	t-test
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Height, cm	*PH.PHBHEIGHT*		t-test
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Weight, kg	*PH.PHBWEIGHT*		t-test
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Body Mass Index	*PH.PHBWEIGHT/(PH.PHBHEIGHT/100)^2*		t-test
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Clinical Frailty Scale	*PH.PHFRAILTY*		
Very fit (1)	xx.xx (xx/xxx)		Wicoxon
Well (2)	xx.xx (xx/xxx)		
Managing well (3)	xx.xx (xx/xxx)		
Vulnerable (4)	xx.xx (xx/xxx)		
Mildly frail (5)	xx.xx (xx/xxx)		
Moderately frail (6)	xx.xx (xx/xxx)		
Severely frail (7)	xx.xx (xx/xxx)		
Very severely frail (8)	xx.xx (xx/xxx)		
Terminally ill (9)	xx.xx (xx/xxx)		
Subcategories of the Clinical Frailty Scale	*PH.PHFRAILTY*		Wicoxon
No frailty (1-3)	xx.xx (xx/xxx)		
Mild frailty (4-5)	xx.xx (xx/xxx)		
Severe frailty (6-9)	xx.xx (xx/xxx)		

Table 5b: Physical Assessment at baseline – PT population
Table 5c: Physical Assessment at baseline – RI population
Table 5d: Physical Assessment at baseline – SP(AT) population

Table 6a: Cardiac Status and Risk Assessment at baseline – ITT population

Pa ient Characte is ics at baseline	T · =	I Group (⁻	- lue
Cardiac status			
An inal status		*PH.PHBANG*	
Asymptoma ic/Free of symptoms	x . /xxx)		C i-
Stable An ina	x . /xxx)		
Unstable An ina	x . /xxx)		
By Cana ian Car iovascular So iety gra ing scale		*.PHBSTANG*	
CCS I	x . /xxx)		C i-
CCS II	x . /xxx)		
CCS III	x . /xxx)		
CCS IV	x . /xxx)		
NYHA class at baseline		*.PHBNYHADIS*	
Class I	x . /xxx)		i-
Class II	x . /xxx)		
Class III	x . /xxx)		
Class IV	x . /xxx)		
Risk Scores			
STS Score		*.PHBSTSSCOR*	ilcoxon test
Mean±SD (N)	x		
ian	x		
in, Max)	[x	.	
II		*PH.PHBESII*	ilcoxon test
Mean±SD (N)	x		
ian	x		
in, Max)	[x		

Table 6b: Cardiac Status and Risk Assessment at baseline – PT population
Table 6c: Cardiac Status and Risk Assessment at baseline – RI population
Table 6d: Cardiac Status and Risk Assessment at baseline – SP(AT) population

Table 7a: Baseline Anatomic characteristics – ITT population

Patients' Characteristics	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Baseline Anatomic characteristics			
Aortic valve leaflet calcification	worst of HT. HTRCC/HTLCC/HTNCC		Chi-square, Raw Mean Score
None	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Mild	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Moderate	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Severe	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Ascending aorta degree of calcification	HT.HTDEGCAL		Chi-square, Raw Mean Score
None	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Mild	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Moderate	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Severe	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Aortic arch degree of calcification	HT.HTBCCAL		Chi-square, Raw Mean Score
None	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Mild	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Moderate	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Severe	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Aortic Valve Mean Gradient (mmHg)			
Mean±SD (N)	xx.x±xx.x (xxx)	EC.ECAVMNGRD	Wilcoxon
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Peak Aortic valve velocity (m/s)		EC.ECPAVVEL	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Indexed effective orifice area (cm2/m2)		EC.ECINDXEOA	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Aortic Valve Regurgitation- Overall		EC.ECAVREGOVR	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		

Table 7b: Baseline Anatomic characteristics – PT population
Table 7c: Baseline Anatomic characteristics – RI population
Table 7d: Baseline Anatomic characteristics – SP(AT) population

Table 8a. Laboratory tests at baseline – ITT population

Laboratory tests at baseline	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Cardiac Enzymes (14 days prior to procedure)			
CK	*CE.CECKRES (allign units using: CE.CECKUNIT)*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
CK-MB	*CE.CECKMB (allign units using: CE.CECKMBUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Troponin I	*if CE.CETRTYPE="Troponin I": CE.CETROPRES (units CE.CETROPUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Troponin T	*if CE.CETRTYPE="Troponin T": CE.CETROPRES (units CE.CETROPUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Hematology			
Hematocrit (HCT)	*HM.HMHCT (allign units using: HM.HMHCTUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Hemoglobin (HGB)	*HM.HMHGL (allign units using: HM.HMHGLUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Platelet (Plt) Count	*HM.HMPL (allign units using: HM.HMPLUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
White blood cell count (WBC)	*HM.HMWBC (allign units using: HM.HMWBCUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Chemistry Panel			
Serum creatinine	*CH.CHBSC (allign units using: CH.CHBSCUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
eGFR	*186 x Creatinine^(-1.754) x age^(-0.203) x 0.742 (if female) x 1.210 (if African-American)*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
ALT (SGPT)	*CH.CHBALT (allign units using: CH.CHBALTUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
AST (SGOT)	*CH.CHBAST (allign units using: CH.CHBASTUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	

Verify the timing of laboratiry test using CE.CECKDT, CECKMBTM & CETROPTM for cardiac enzymes and HM.HMDATE for hematology.

Table 8b. Laboratory tests at baseline – PT population
Table 8c. Laboratory tests at baseline – RI population
Table 8d. Laboratory tests at baseline – SP(AT) population

Table 9a: Medications – ITT population

Medications	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Within 30 days post-procedure			
Antiplatelet therapy			
Aspirin	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Clopidogrel	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Prasugrel	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Ticagrelor	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Dual antiplatelet therapy - Aspirin and (Clopidogrel or Prasugrel or Ticagrelor or Ticlopidine)	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Monotherapy - Aspirin or Clopidogrel	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Anticoagulation therapy			
Warfarin	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Warfarin or NOAC	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Others	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Meds types	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Meds types	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Meds types	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Warfarin with antiplatelet therapy	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
31-90 days post-procedure			
Antiplatelet therapy			
Aspirin	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Clopidogrel	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Prasugrel	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Ticagrelor	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Dual antiplatelet therapy - Aspirin and (Clopidogrel or Prasugrel or Ticagrelor or Ticlopidine)	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Monotherapy - Aspirin or Clopidogrel	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Anticoagulation therapy			
Warfarin	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Warfarin and / or NOAC	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Others	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Meds types	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Meds types	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Meds types	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact
Warfarin with antiplatelet therapy	xx.x% (xx/xxx)	CM.CMTERM	Fisher Exact

Table 9b: Medications – PT population
Table 9c: Medications – RI population
Table 9d: Medications – SP(AT) population

Table 10a: TriGuard Insertion Procedure – ITT population

TriGuard device details	TriGuard 3 system group (N=XXX)	
Number of TriGuard devices used		Count using PR.PRSERNUM, PR.PRTGSECDEV, PR.PRD2LOTNUM
1	xx.x% (xx/xxx)	
2	xx.x% (xx/xxx)	
Number of attempts needed to successfully deploy TriGUARD device (device-level)		Count using PR.PRD1CORATT1, PR PRD1ATT2, PR PRD2CORATT1, PRD2ATT2 RATT1, PR PRD2ATT2
1	xx.x% (xx/xxx)	
2	xx.x% (xx/xxx)	
Aortic arch successfully accessed with the TriGUARD 3 delivery catheter		PR.PRARCSUC
TriGuard access site closure method		PR.PRTGCLSMTH
Surgical	xx.x% (xx/xxx)	
Vascular closure device	xx.x% (xx/xxx)	
Manual compression	xx.x% (xx/xxx)	
FemoStop	xx.x% (xx/xxx)	

Table 10b: TriGuard Insertion Procedure – PT population
Table 10c: TriGuard Insertion Procedure – RI population
Table 10d: TriGuard Insertion Procedure – SP(AT) population

Table 11a: Procedure Details – ITT population

Procedure Characteristics	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
		PR.PRTIMELSR-PR.PRTIME	
Total procedure time, minutes			
Mean±SD (N)	xx.x±xx.x (xxx)		Wilcoxon
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
TAVI access site closure method		*PR.PRTVCLSMTH*	Chi-square
Surgical	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Vascular closure device	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Manual compression	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
FemoStop	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Total fluoroscopy time, minutes		*PR.PRFLTIME/60*	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Peak ACT level during procedure, seconds		*PR.PRPEACT*	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Nadir ACT level during the procedure		*PR.PRNAACT*	
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Total contrast medium given, ml		*PR.PRCONTMED*	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Estimated Blood Loss (EBL), ml		*PR.PREBL*	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Adverse Events occur during the procedure	xx.x% (xx/xxx)	*PR.PRAE*	
The patient had hemodynamic instability during TAVI procedure that required any of the actions:	xx.x% (xx/xxx)	*PR.PRHEMOINST*	Fisher Exact
Bolus or infusion of IV pressor agents	xx.x% (xx/xxx)	*PR.PRBOLUS*	Fisher Exact
Mechanical circulatory support	xx.x% (xx/xxx)	*PR.PRMECHCIRC*	Fisher Exact
Cardiac massage or cardiopulmonary resuscitation (</= 3 minutes / >3 minutes)	xx.x% (xx/xxx)	*PR.PRCARMASL3*	Fisher Exact
Cardiac massage or cardiopulmonary resuscitation >3 minutes	xx.x% (xx/xxx)	*PR.PRPRCARMASG3*	Fisher Exact
Other devices used/implanted during the procedure (other than TriGuard device and those devices that are a standard part of the TAVI procedure)	xx.x% (xx/xxx)	*PR.PRPROOTHDEV*	Fisher Exact
Left atrial appendage closure device	xx.x% (xx/xxx)		Fisher Exact
Permanent Pacemaker	xx.x% (xx/xxx)	*PR.PRPACE*	Fisher Exact
Intra-aortic balloon pump	xx.x% (xx/xxx)	*PR.PRIABALPMP*	Fisher Exact
Tandem heart or other mechanical assist device	xx.x% (xx/xxx)	*PR.PRTANDEM*	Fisher Exact
Percutaneous coronary Intervention	xx.x% (xx/xxx)	*PR.PRPCI*	Fisher Exact
Treatment of vascular complication (peripheral or aortic) procedure (open heart, cardiac structure injury or other)	xx.x% (xx/xxx)	*PR.PRTRTVASC*	Fisher Exact
Conversion to open surgery	xx.x% (xx/xxx)	*PR.PRCONVER*	Fisher Exact

Table 11b: Procedure Details – PT population
Table 11c: Procedure Details – RI population
Table 11d: Procedure Details – SP(AT) population

Table 12a: TAVI Details – ITT population

TAVI Device Details	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Insertion Site	PR.PRACCESS		Chi-square
Right ilio-femoral	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Left ilio-femoral	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Other	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Access method		PR.PRACCMETH	Fisher Exact
Percutaneous	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Surgical	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Sheath french size	xx.x% (xx/xxx)	PR.PRFRSIZE	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Sheath length (cm)	xx.x% (xx/xxx)	PR.PRFRLEN	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Aortic Balloon Valvuloplasty (BAV) performed	xx.x% (xx/xxx)	PR.PRBAV	Fisher Exact
Total number of balloons used	xx.x% (xx/xxx)	PR.PRBAVBAL	Row Mean Score
1	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
2	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
3+	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Largest Balloon diameter (mm)	xx.x% (xx/xxx)	PR.PRBALDIA	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Number of inflations	xx.x% (xx/xxx)	PR.PRBALINF	
1	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
2	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
3+	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Number of TAVI devices attempted for implantation		Count attempts using PR PR MPLANT, PR PRPRO SUC, PR PRSECATT	Row Mean Score
1	xx.x% (xx/xxx)		
2	xx.x% (xx/xxx)		
3	xx.x% (xx/xxx)		
Number of TAVI devices implanted		Count attempts using PR PRPROSUC, PR.PRSECATT, PR PRVIVIMETH, PR.PRPRO2SUC	Row Mean Score
1	xx.x% (xx/xxx)		
2 (if valve-in implant method used)	xx.x% (xx/xxx)		
TAVI valve type	PR.PRIMPLANT		Fisher Exact
Medtronic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Edwards	xx.x% (xx/xxx)	xx.x% (xx/xxx)	
Other	xx.x% (xx/xxx)	xx.x% (xx/xxx)	

Table 12b: TAVI Details – PT population
Table 12c: TAVI Details – RI population
Table 12d: TAVI Details – SP(AT) population

Table 13a: ECHO assessment – ITT population

Patients' Characteristics	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Aortic Valve Mean Gradient (mmHg)			
Mean±SD (N)	xx.x±xx.x (xxx)	EC.ECAVMNGRD	Wilcoxon
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Peak Aortic valve velocity (m/s)		EC.ECPAVVEL	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Indexed effective orifice area (cm2/m2)		EC.ECINDXEOA	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Aortic Valve Regurgitation- Overall		EC.ECAVREGOVR	Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)		
Median	xx.x		
Range (Min, Max)	[xx.x; xx.x]		

Table 13b: ECHO assessment – PT population
Table 13c: ECHO assessment – RI population
Table 13d: ECHO assessment – SP(AT) population

Table 14a: Laboratory tests post-procedure – ITT population

Laboratory tests at post-procedure/ pre-discharge	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Cardiac Enzymes (12-72 hours after procedure)*			
CK	*CE.CECKRES (allign units using: CE.CECKUNIT)*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
CK-MB	*CE.CECKMB (allign units using: CE.CECKMBUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Troponin I	*if CE.CETRTYPE="Troponin I": CE.CETROPRES (units CE.CETROPUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Troponin T	*if CE.CETRTYPE="Troponin T": CE.CETROPRES (units CE.CETROPUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Hematology			
Hematocrit (HCT)	*HM.HMHCT (allign units using: HM.HMHCTUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Hemoglobin (HGB)	*HM.HMHGL (allign units using: HM.HMHGLUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Platelet (Plt) Count	*HM.HMPL (allign units using: HM.HMPLUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
White blood cell count (WBC)	*HM.HMWBC (allign units using: HM.HMWBCUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Chemistry Panel			
Serum creatinine	*CH.CHPSC (allign units using: CH.CHPSCUNIT)*		Wilcoxon
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
eGFR	*186 x Creatinine^(-1.754) x age^(-0 203) x 0.742 (if female) x 1.210 (if African-American)*		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	

*Verify the timing of laboratory test, allowing the earliest test taken at 12-3h post-procedure and the latest - at 72+6 hours post-procedure.If more than 1 value reported, the report will show the maximal value out of all.

Table 14b: Laboratory tests post-procedure – PT population
Table 14c: Laboratory tests post-procedure – RI population
Table 14d: Laboratory tests post-procedure – SP(AT) population

Table 15a: National Institutes of Health Stroke Scale (NIHSS) assessment at baseline – ITT population

Patients' Characteristics*	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
	Use NIH.NIHDATE to verify that the test was administered pre-procedure		
(1a) Level of consciousness (0-3 scale)			
Median	xx.x	NIH.NIHLOC	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(1b) LOC questions (0-2 scale)			
Median	xx.x	NIHLOCQ	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(1c) LOC commands (0-2 scale)			
Median	xx.x	NIH.NIHLOCC	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(2) Best Gaze (0-2 scale)			
Median	xx.x	NIH.NIHBG	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(3) Visual (0-3 scale)			
Median	xx.x	NIH.NIHVIS	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(4) Facial Palsy (0-3 scale)			
Median	xx.x	NIH.NIHFP	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(5a) Motor arm – Left (0-4 scale)			
Median	xx.x	NIH.NIHMAL	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(5b) Motor arm – Right (0-4 scale)			
Median	xx.x	NIH.NIHMAR	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(6a) Motor leg – Left (0-4 scale)			
Median	xx.x	NIH.NIHMLL	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(6b) Motor leg – Right (0-4 scale)			
Median	xx.x	NIH.NIHMLR	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(7) Limb ataxia (0-2 scale)			
Median	xx.x	NIH.NIHLA	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(8) Sensory (0-2 scale)			
Median	xx.x	NIH.NIHSEN	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(9) Best Language (0-2 scale)			
Median	xx.x	N H N HBLANG	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(10) Dysarthria (0-2 scale)			
Median	xx.x	NIH.NIHDYS	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(11) Extinction and inattention (0-2 scale)			
Median	xx.x	NIH.NIHEI	Wilcoxon
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
(12) Total NIHSS Score			
Mean±SD (N)	xx.x±xx.x (xxx)	NIH.NIHSCOR	Wilcoxon
Median	xx.x		
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		

*The scale lower values are assigned to a fully normal state.

Table 15b: National Institutes of Health Stroke Scale (NIHSS) assessment at baseline – PT population
Table 15c: National Institutes of Health Stroke Scale (NIHSS) assessment at baseline – RI population
Table 15d: National Institutes of Health Stroke Scale (NIHSS) assessment at baseline – SP(AT) population

Table 16a: NIHSS assessment at follow-up – ITT population

Change in the score values, as value at follow-up minus baseline	Post-Procedure			At 30 days		
	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
	Use NIH.NIHDATE to verify that the test was administered post-procedure			*Use NIH.NIHDATE to verify that the test was administered 30 days post-procedure +/-7 days*		
(1a) Level of consciousness (0-3 scale)						
Median	xx.x	NIH.NIHLOC	Wilcoxon	xx.x	NIH NIHLOC	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(1b) LOC questions (0-2 scale)						
Median	xx.x	NIHLOCQ	Wilcoxon	xx.x	NIHLOCQ	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(1c) LOC commands (0-2 scale)						
Median	xx.x	NIH.NIHLOCC	Wilcoxon	xx.x	NIH NIHLOCC	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(2) Best Gaze (0-2 scale)						
Median	xx.x	NIH.NIHBG	Wilcoxon	xx.x	NIH NIHBG	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(3) Visual (0-3 scale)						
Median	xx.x	NIH.NIHVIS	Wilcoxon	xx.x	NIH NIHVIS	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(4) Facial Palsy (0-3 scale)						
Median	xx.x	NIH.NIHFP	Wilcoxon	xx.x	NIH NIHFP	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(5a) Motor arm – Left (0-4 scale)						
Median	xx.x	NIH.NIHMAL	Wilcoxon	xx.x	NIH NIHMAL	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(5b) Motor arm – Right (0-4 scale)						
Median	xx.x	NIH.NIHMAR	Wilcoxon	xx.x	NIH NIHMAR	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(6a) Motor leg – Left (0-4 scale)						
Median	xx.x	NIH.NIHMLL	Wilcoxon	xx.x	NIH NIHMLL	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(6b) Motor leg – Right (0-4 scale)						
Median	xx.x	NIH.NIHMLR	Wilcoxon	xx.x	NIH NIHMLR	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(7) Limb ataxia (0-2 scale)						
Median	xx.x	NIH.NIHLA	Wilcoxon	xx.x	NIH NIHLA	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(8) Sensory (0-2 scale)						
Median	xx.x	NIH.NIHSEN	Wilcoxon	xx.x	NIH NIHSEN	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(9) Best Language (0-2 scale)						
Median	xx.x	NIH.NIHBLANG	Wilcoxon	xx.x	NIH NIHBLANG	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(10) Dysarthria (0-2 scale)						
Median	xx.x	NIH.NIHDYS	Wilcoxon	xx.x	NIH NIHDYS	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(11) Extinction and inattention (0-2 scale)						
Median	xx.x	NIH.NIHEI	Wilcoxon	xx.x	NIH NIHEI	Wilcoxon
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]			[xx.x; xx.x]		
(12) Total NIHSS Score						
Mean±SD (N)	xx.x±xx.x (xxx)	NIH.NIHSCOR	Wilcoxon	xx.x±xx.x (xxx)	NIH NIHSCOR	Wilcoxon
Median	xx.x			xx.x		
Q1; Q3	xx.x; xx.x			xx.x; xx.x		
Range (Min, Max)	[xx.x xx.x]			[xx.x xx.x]		

*Throughout the scale lower values are assigned to a fully normal state.

Table 16b: NIHSS assessment at follow-up – PT population
Table 16c: NIHSS assessment at follow-up – RI population
Table 16d: NIHSS assessment at follow-up – SP(AT) population

Table 17a: Assessment by mRS at baseline and follow-up – ITT population

Total mRS score values	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
	Use MRS.MRSDATE to verify the timing of the test		
Total mRS Score at baseline			
Mean±SD (N)	xx.x±xx.x (xxx)	MRS.MRSTTLSCR	Wilcoxon
Median	xx.x		
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
Change in score			
Post-Procedure minus baseline			
Mean±SD (N)	xx.x±xx.x (xxx)	MRS.MRSTTLSCR	Wilcoxon
Median	xx.x		
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		
At 30 days post-procedure minus baseline			
Mean±SD (N)	xx.x±xx.x (xxx)	MRS.MRSTTLSCR	Wilcoxon
Median	xx.x		
Q1; Q3	xx.x; xx.x		
Range (Min, Max)	[xx.x; xx.x]		

*Measured on 0-6 scale, where "0" is assigned to the state without symptoms and "6" - of a dead patient.

Table 17b: Assessment by mRS at baseline and follow-up – PT population
Table 17c: Assessment by mRS at baseline and follow-up – RI population
Table 17d: Assessment by mRS at baseline and follow-up – SP(AT) population

Table 18: Primary Efficacy and Safety Endpoints, Sensitivity Analysis

Primary Endpoints	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value*	Control Group in eITT (N XX in REFLECT I & N XX in REFLECT II)	p-value*
Efficacy Hierarchical Endpoint - eITT population					
NIHSS considered a tie if <2 point difference			x.xxx		
Mean±SD (n)	xx.xx±xx.xx (n)	xx.xx±xx.xx (n)			
Median	xx.xx	xx.xx			
Q1; Q3	xx xx; xx.xx	xx.xx; xx.xx			
Min; Max	(xx xx; xx.xx)	(xx.xx; xx.xx)			
DW-MRI - imputed**			x.xxx		x.xxx
Mean±SD (n)	xx.xx±xx.xx (n)	xx.xx±xx.xx (n)		xx xx±xx.xx (n)	
Median	xx.xx	xx.xx		xx xx	
Q1; Q3	xx xx; xx.xx	xx.xx; xx.xx		xx.xx; xx.xx	
Min; Max	(xx xx; xx.xx)	(xx.xx; xx.xx)		(xx.xx; xx.xx)	
Efficacy endpoint adjusted to pre-existing cerebral lesion volumes***			x.xxx		
Safety Endpoint - AT population					
Number of events of combined safety endpoint in drop-out patients needed to turn the conclusions towards the	**x/X missing observations**				

*p-value is a result of a hierarchical algorithm described in SAP, pages 12-15.

**Based on imputation of 10 separate datasets for DW-MRI total lesion volume using a linear regression model with covariates device versus control, age at time of enrollment, body mass index, ethnicity, smoking status, creatinine level, hyperlipidemia, hypertension, aortic arch disease burden, porcelain aorta, aortic valve area at baseline, procedure time, valve type, balloon post dilatation, arch type, and level of calcification.

***The adjustment will be performed using a quantile regression with the resultant score being the dependent variable and group and the pre-existing cerebral lesion volumes will be independent. Specifically, the PROC QUANTREG procedure will be used to model the median of the score with QUANTILE 0.5 option.

Table 19: Baseline Characteristics, Analysis of Poolability of the controls population in the two study Phases – eITT population

Pa i l' · i	l, Control popula i =XXX)	Phase ll, Control popula i =XXX)	- lue
Age (yrs)			
Mean±SD (n)	x . _x	. _x	
ian	x		x.xxx
i			
iabetes Mellitus (DM)	. /xxx)	. /xxx)	
ior CVA or TIA	. /xxx)	. /xxx)	
istory of conges ive heart f ilure (CHF)	. /xxx)	. /xxx)	
ies of the Cli ical Fr ilty			
No Fr ilty (	. /xxx)	. /xxx)	
ild Fr ilty (	. /xxx)	. /xxx)	x.xxx
Severe Fr ilty (	. /xxx)	. /xxx)	
STS Score			
Mean±SD (n)	x . _x	. _x	
ian	x		x.xxx
i		.	
IHSS Score			
Mean±SD (n)	x . _x	. _x	
ian	x		x.xxx
i		.	

Table 20a: Primary Safety Endpoint, Analysis of Poolability of the intervention population between the study sites – AT population

Center Names*	Primary safety composite endpoint to 30 days in Intervention population	p-value
US sites		
….	xx.xx% (xx/xx)	
….	xx.xx% (xx/xx)	
….	xx.xx% (xx/xx)	
….	….	
….	….	
Total for OUS patients	xx.xx% (xx/xx)	
OUS sites	xx.xx% (xx/xx)	
….		
….		
Total for OUS patients	xx.xx% (xx/xx)	
Total for ITT Patients	xx.xx% (xx/xx)	x.xxx**

*The "center" term, use in the analy is above includes all ites pro ided they treat 5 or more subjects. In the event that the number of subjects at any site is below 5, the sites are pooled by geographical proximity. Pooling of sites will be carried out prior to the unblinding.

**The p-value is originated from logistic regression with the incidence of the primary safety endpoint as the predicted variable and study center as the independent classification variable.

Table 20b: Primary Safety Endpoint, Analysis of Poolability of the intervention population between the study sites – SP(AT) population

Table 21a: Analysis of hypothesis-driven secondary endpoints – eITT population

Endpoints	TriGuard 3 system group (N=XXX in ITT, N=XXX in eITT)	Control Group (N=XXX in ITT, N=XXX in eITT)	p-value
In ITT population			
Stroke to 7 days	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
NIHSS worsening (increase from baseline to post-proc	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
All-cause death or stoke to 7 days	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
CNS Infarction (NeuroARC defined) at 30 days	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Total volume of cerebral ischemic lesions detected by DW-MRI at 2 to 5 days post-procedure, mm^3			Fisher
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	

*Worsening of NIHSS score is calculated as difference in N H.N HSCORE at pre-discharge - baseline being above "0" (higher values are assigned to worse conditions). The timing is verified by N H.N HDATE.

Table 21b: Analysis of hypothesis-driven secondary endpoints – SP(eITT) population
Table 21c: Analysis of hypothesis-driven secondary endpoints – PT population
Table 21d: Analysis of hypothesis-driven secondary endpoints – RI population
Table 21e: Analysis of hypothesis-driven secondary endpoints – eITT population, patients with AF at baseline
Table 21f: Analysis of hypothesis-driven secondary endpoints – eITT population, patients with Medtronic valve
Table 21g: Analysis of hypothesis-driven secondary endpoints – eITT ,population, patients with Edwards valve

Table 22a: Analysis of secondary imaging efficacy endpoints – ITT population

Endpoints	TriGuard 3 system group (N=XXX patients, N=XXX lesions)	Control Group (N=XXX patients, N=XXX lesions)	p-value	Adjusted p-value
Neurological and Cognitive Efficacy				
NIHSS worsening*				
Post-procedure/discharge	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher Exact	x.xxx**
30 days post-procedure	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher Exact	x.xxx**
New neurologic impairment at post-procedure/discharge	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher Exact	x.xxx**
Imaging Efficacy				
Presence of cerebral ischemic lesions	MR.MRNUMAIL>0 at 2 and 5 days			
at 2-5 days post-procedure	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher Exact	x.xxx**
Number of cerebral ischemic lesions				
at 2- 5 days post-procedure	*MR.MRNUMAIL at 2 days*			
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon	x.xxx***
Median	xx.x	xx.x		
Q1; Q3	[xx.x; xx.x]	[xx.x; xx.x]		
Per-patient average single cerebral ischemic lesion volume, mm^3	*based on AL.ALCALCVOL (patient level)*			
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon	x.xxx***
Median	xx.x	xx.x		
Q1; Q3	[xx.x; xx.x]	[xx.x; xx.x]		
Single cerebral ischemic lesion volume, mm^3	*AL.ALCALCVOL/the total number of ALCALCVOL fields (lesion level)*			
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon	x.xxx***
Median	xx.x	xx.x		
Q1; Q3	[xx.x; xx.x]	[xx.x; xx.x]		
Total volume of cerebral ischemic lesions, mm^3	*MR.MRAVGLESVOL (patient level for all lesions together)*			
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon	x.xxx***
Median	xx.x	xx.x		
Q1; Q3	[xx.x; xx.x]	[xx.x; xx.x]		

*Worsening of NIHSS score is calculated as difference in NIH.NIHSCORE at pre-discharge - baseline being above "0" (higher values are assigned to worse conditions). The timing is verified by NIH.NIHDATE.

**Based on logistic regression adjusting for pre-existing lesion volume.

**Based on Negative-Binomial or Poisson regression, depending on distribution, adjusting for pre-existing lesion volume.

Table 22b: Analysis of secondary imaging efficacy endpoints – eITT population
Table 22c: Analysis of secondary imaging efficacy endpoints – SP(eITT) population
Table 22d: Analysis of secondary imaging efficacy endpoints – PT population
Table 22e: Analysis of secondary imaging efficacy endpoints – RI population
Table 22f: Analysis of secondary imaging efficacy endpoints – ITT population, patients with AF at baseline
Table 22g: Analysis of secondary imaging efficacy endpoints – ITT population, patients with Medtronic valve
Table 22h: Analysis of secondary imaging efficacy endpoints – ITT population, patients with Edwards valve

Table 23a: Analysis of secondary performance and "other" endpoints – ITT population

Endpoints	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Secondary performance endpoints			
Successful device deployment*	xx.x% (xx/xxx)	----	
Device positioning maintained till:**			
Final deployment of the first prosthetic valve	xx.x% (xx/xxx)	----	
Final procedure***	xx.x% (xx/xxx)	----	
TriGuard device successfully positioned across all 3 vessels supplying cerebral	ACL.ACLPRETAV MOD		
Complete	xx.x% (xx/xxx)	----	
Partial	xx.x% (xx/xxx)	----	
None	xx.x% (xx/xxx)	----	
Device interference****	xx.x% (xx/xxx)	----	
Successful device retrieval*****	xx.x% (xx/xxx)	----	
Technical success******	xx.x% (xx/xxx)	----	
Procedure success*******	xx.x% (xx/xxx)	----	
Other secondary endpoints			
Device deployment time, minutes	successful device deployment minus insertion of the TriGuard HDH device into the delivery sheath (max(PR.PRTDDRAWN,PR PRD2TGDRAWN)-PR PRTGADV)		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)			
Total procedure time, minutes	removal of the last catheter from the arterial access sheath minus first arterial access (PR.PRTIMELSR-PR PRT ME)		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Total fluroscopy time, minutes	PR.PRFLTIME		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
Total contrast utilization, ml	PR.PRCONTMED		
Mean±SD (N)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	Wilcoxon
Median	xx.x	xx.x	
Range (Min, Max)	[xx.x; xx.x]	[xx.x; xx.x]	
TriGuard device successfully positioned across all 3 vessels supplying cerebral	PR.PRSUCCPOS	xx.xx (xx/xxx)	Fisher

*Successful device deployment, defined as ability to access the aortic arch with the TriGuard HDH delivery catheter and deploy the device from the delivery catheter into the aortic arch.

**Device positioning, defined as ability to position the TriGuard HDH device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by angiography) until the time points as listed in the table.

***Final procedure (after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed)

****Device interference, defined as interaction of the TriGuard HDH device with the TAVI system leading to: (1) inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR (2) inability to deploy the TAVI valve prosthesis, OR (3) Inability to retrieve the valve prosthesis or delivery system

*****Successful device retrieval, defined as ability to retrieve the TriGuard HDH device and remove the intact TriGuard HDH delivery system

******Technical Success is defined as successful device deployment (ACL.ACLDEPDEFLF L="Yes") AND device positioning (ACL.ACLPRETAV MOD="Complete" (2) AND ACL.ACLF NALPROCMOD) AND successful device retrieval="Complete" (2)) AND (ACL.ACLTGRET="Yes").

*******Procedure success, defined as technical success in the absence of any investigational device-related or investigational procedure-related in-hospital procedural safety events.

Table 23b: Analysis of secondary performance and "other" endpoints – AT population
Table 23c: Analysis of secondary performance and "other" endpoints – PT population
Table 23d: Analysis of secondary performance and "other" endpoints – SP(ITT) population
Table 23e: Analysis of secondary performance and "other" endpoints – RI population

Table 23f: Analysis of secondary performance and "other" endpoints – ITT population, patients with AF at baseline
Table 23g: Analysis of secondary performance and "other" endpoints – ITT population, patients with Medtronic valve
Table 23h: Analysis of secondary performance and "other" endpoints – ITT population, patients with Edwards valve

Table 24a: Analysis of secondary safety endpoints – ITT population

Neurological Endpoints in-hospital	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Ischemic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Hemorrhagic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Undertermined	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Disabling Stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Non-disabling stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Overt CNS Injury (Type 1)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
General Safety event	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
All-cause mortality	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
All stroke (diasbling and non-disabling)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Acute kidney injury – Stage 3 (including renal replacement therapy)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher

Endpoints to 30 days post-procedure	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
MACCE	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
All-cause mortality	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
All stroke (disabling and non-disabling)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Life threatening (or disabling) bleeding	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Acute kidney injury – Stage 2 or 3 (including renal replacement therapy)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Major vascular complications	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
All-cause death	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Cardiovascular death	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Neurologic event related death	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Non-cardiovascular death	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Myocardial infarction	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Peri-procedural MI (≤72 hours after the index procedure)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Spontaneous MI (>72 hours after the index procedure)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
General Safety event (composite of all-cause mortality, all stroke and AKI stage 3)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Acute kidney injury – Stage 3 (including renal replacement	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Neurological Events			
Stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Ischemic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Hemorrhagic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Undertermined	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Disabling Stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Non-disabling stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Transient ischemic attack (TIA) (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Overt CNS Injury (Type 1)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Covert CNS Injury (Type 2)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Neurological dysfunction without CNS injury (Type 3)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
CNS infarction	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
CNS hemorrhage	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Bleeding Complications			
Life-threatening or disabling bleeding (VARC-2)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Major bleeding	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Minor bleeding	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Acute Kidney Injury (AKIN Classification)			
Stage 2	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Stage 3	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Vascular Complications			
Major vascular complications	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
TriGUARD access site	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
TAVI or other access site	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Not access site-related	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Major vascular complications related to TriGUARD 3	xx.x% (xx/xxx)		
TAVI device success (VARC)*	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher

*TAVI Device success is defined as (1) Absence of procedural mortality AND (2) Correct positioning of a single prosthetic heart valve into the proper anatomical location AND (3) Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (VARC-defined) AND (4) mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s , AND (5) no moderate or severe prosthetic valve regurgitation (VARC-defined).

Neurological Endpoints to 90 days	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Ischemic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Hemorrhagic	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Undertermined	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Disabling Stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Non-disabling stroke (VARC-2 defined)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher
Overt CNS Injury (Type 1)	xx.x% (xx/xxx)	xx.x% (xx/xxx)	Fisher

Table 24b: Analysis of secondary safety endpoints – SP(AT) population
Table 24c: Analysis of secondary safety endpoints –RI population
Table 24d: Analysis of secondary safety endpoints – ITT population, patients with AF at baseline
Table 24e: Analysis of secondary safety endpoints – ITT population, patients with Medtronic valve
Table 24f: Analysis of secondary safety endpoints – ITT population, patients with Edwards valve

Table 25: MACCE to 30 days, time to event analysis – AT population

	Time post-procedure (days)				
Intervention	0	7	14	21	30
# Entered					
# Lost to Follow-up					
# Incomplete					
# Events					
Survival Estimate					
SE					
	Time post-procedure (days)				
Control group	0	7	14	21	30
# Entered					
# Lost to Follow-up					
# Incomplete					
# Events					
Survival Estimate					
SE					
Log-Rank test					x.xxx

Survival Curves

Table 26: TAVI early safety (Primary Safety Endpoint) to 30 days, time to event analysis – ITT population

	Time post-procedure (days)				
Intervention	0	7	14	21	30
# Entered					
# Lost to Follow-up					
# Incomplete					
# Events					
Survival Estimate					
SE					
	Time post-procedure (days)				
Control group	0	7	14	21	30
# Entered					
# Lost to Follow-up					
# Incomplete					
# Events					
Survival Estimate					
SE					
Log-Rank test					x.xxx

Survival Curves

Table 27a: Adverse events – ITT population

	TriGuard 3 system group (N=XXX)		Control Group (N=XXX)	
System Organ Class/Preferred Term	Number of Events	Number of Subjects	Number of Events	Number of Subjects
Any Adverse Events	xx	xx (xx.x%)	xx	xx (xx.x%)
System Organ Class/Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)

The data on events are based on Adverse Events (AE) form.

Table 27b: Adverse events – SP(AT) population

Table 28a: Serious adverse events – ITT population

	TriGuard 3 system group (N=XXX)		Control Group (N=XXX)	
System Organ Class/Preferred Term	Number of Events	Number of Subjects	Number of Events	Number of Subjects
Any Adverse Events	xx	xx (xx.x%)	xx	xx (xx.x%)
System Organ Class/Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)

The events in the table above are based on Adverse Events (AE) form and defined as serious by site.

Table 28b: Serious adverse events – PT population

Table 28c: Serious adverse events – RI population

Table 28d: Serious adverse events – SP(AT) population

Table 29a: Serious adverse device effects (SADE) – ITT population

System Organ Class/Preferred Term	Number of Events	Number of Subjects	Number of Events	Number of Subjects
Any Adverse Events	xx	xx (xx.x%)	xx	xx (xx.x%)
System Organ Class/Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)

The events in the table above are based on Adverse Events (AE) form and CEC-adjudication as SAEs that possibly/probably/definitely related to the TriGuard HDH device or TriGuard HDH procedure.

Table 29b: Serious adverse device effects (SADE) –PT population
Table 29c: Serious adverse device effects (SADE) –RI population
Table 29b: Serious adverse device effects (SADE) –SP(AT) population

Table 30: Unanticipated adverse device events (UADE) – ITT population

	TriGuard 3 system group (N=XXX)		Control Group (N=XXX)	
System Organ Class/Preferred Term	Number of Events	Number of Subjects	Number of Events	Number of Subjects
Any Adverse Events	xx	xx (xx.x%)	xx	xx (xx.x%)
System Organ Class/Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)
Preferred Term	xx	xx (xx.x%)	xx	xx (xx.x%)

The listing of Unticipated Adverse Device Events will be provided by the sponsor.

Table 31a: Protocol deviations – ITT population

Protocol Deviation	Patients with at least one deviation in categor	
	Intervention (N=XXX)	Control (N=XXX)
Informed consent was not properly obtained	PD.PDCAT	
Inclusion/Exclusion criteria were not met	xx (xx.x%)	xx (xx.x%)
Follow-up visit was missed	xx (xx.x%)	xx (xx.x%)
Follow-up visit was completed outside protocol window	xx (xx.x%)	xx (xx.x%)
Device was used outside protocol treatment plan	xx (xx.x%)	xx (xx.x%)
Protocol-required assessment was not completed	PD.PDREQASST	
Clinical Frailty Scale	xx (xx.x%)	xx (xx.x%)
Physical Exam	xx (xx.x%)	xx (xx.x%)
Hematology/Chemistry Panel	xx (xx.x%)	xx (xx.x%)
Cardiac Enzymes	xx (xx.x%)	xx (xx.x%)
MRI	xx (xx.x%)	xx (xx.x%)
mRS	xx (xx.x%)	xx (xx.x%)
NIHSS	xx (xx.x%)	xx (xx.x%)
12-lead ECG	xx (xx.x%)	xx (xx.x%)
CT Imaging	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)
Procedure or Assessment not performed per protocol guidelines	xx (xx.x%)	xx (xx.x%)
Other	PD.PDCATOTH	
Reasons for missed MRI	PD.PDDEVREASMRI	
Permanent pacemaker implant	xx (xx.x%)	xx (xx.x%)
Subject death	xx (xx.x%)	xx (xx.x%)
Subject refusal	xx (xx.x%)	xx (xx.x%)
Unstable clinical status	xx (xx.x%)	xx (xx.x%)
Other*	xx (xx.x%)	xx (xx.x%)

Protocol deviations are site-reported.

*Inclu ing category "TAVR procedure no i i iate .

Table 31b: Protocol deviations – PT population
Table 31c: Protocol deviations – RI population

Table 32: Poolability analysis of sites – descriptive analysis – eITT population

Center Names*	Male gender	Edwards Valve prosthesis	Medtronic Valve prosthesis	"Other" Valve prosthesis	Society of Thoracic Surgeons Operative risk Risk Score	Dual antiplatelet therapy (DAPT) to 90 days	Monotherapy (aspirin or clopidogrel) to 90 days	Warfarin with antiplatelet therapy to 90 days
US sites								
....	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.x±xx.x (xx) xx.x [xx.x; xx.x]	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)
....	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.x±xx.x (xx) xx.x [xx.x; xx.x]	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)
....	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.x±xx.x (xx) xx.x [xx.x; xx.x]	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)
....	....	....	....	....	....	....	....	....
....	....	....	....	....	....	....	....	....
Total for all patients	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.x±xx.x (xx) xx.x [xx.x; xx.x]	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.xx% (xx/xx)
Signiifcance of site varaince**	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

*The "center" term, used in the analysis above, includes all sites provided they treat 5 or more subjects. In the event that the number of subjects at any site is below 5, the sites are pooled by geographical proximity. Pooling of sites will be carried out prior to the unblinding.

**The P-value is originated from logistic omegative binomial regression with the descriptive parameter as the predicted variable and study center as the independent classification variable.

Table 33: Poolability analysis of primary efficacy endpoint across sites – eITT population

Center Names*	All-cause mortality or any stroke at 30 days	NIHSS worsening at post-procedure/pre-discharge	Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 days post-procedure, mm^3	Composite score	p-value
US sites					
….	xx.xx% (xx/xx)	xx.xx% (xx/xx)	xx.x±xx.x (xxx)	xx.x±xx.x (xxx)	x.xxx (from b2
….					
….					
….					
….					
….					
Total for US patients					

*The "center" term, used in the analysis above includes all sites provided they treat 5 or more subjects. In the event that the number of subjects is below 5, the sites are pooled by geographical proximity. Pooling of sites will be carried out prior to the unblinding.

The P-value is originated from poisson or negative-binomial regression with thecomposite score as the predicted variable and study group as the independent variable and the siteindicatoras covariates in the model. Regression of type: Score=b0+b1 x treatment + **b2 x sitenum

Table 34: Poolability analysis of primary efficacy endpoint across sites – eITT population

	Male gender	Edwards Valve prosthesis (vs. Medtronic +Others)	Medtronic Valve prosthesis (vs.Edwards+Others)	Society of Thoracic Surgeons Operative risk Risk Score	Dual antiplatelet therapy (DAPT) to 90 days	Monotherapy (aspirin or clopidogrel) to 90 days	Warfarin with antiplatelet therapy to 90 days
All-cause mortality or any stroke at 30 days	from the b3	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
NIHSS worsening at post-procedure/pre-discharge	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Total volume of cerebral ischemic lesions detected by DW-MRI 2-5 dayspost-procedure, mm^3	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Composite hierarchical endpoint	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

The table represents significance level of the site indicator, as an additional covariate in the model regressing composites of the primary efficacy endpoints on treatment, interaction of treatment group with sub-groups (shown in colums). The modeling is based on logistic an dnegative binomial distributions. Regression of type: Score=b0+b1 x treatment + b2 x treatment x covariate in the column + b3 x sitenum

Table 35: Subgroup analyses – Primarty Safety Outcomes – SP(AT) population

Primary Safety Endpoints	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value
Patients with AF at baseline			
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**x.x% (x/xxx)**	x.xxx
Death	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Stroke	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Life-threatening or disabling bleeding	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Major vascular complication	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
TriGUARD access site	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
TAVI or other access site	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Not access site-related	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Patients with Medtronic Valve			
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**x.x% (x/xxx)**	x.xxx
Death	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Stroke	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Life-threatening or disabling bleeding	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Major vascular complication	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
TriGUARD access site	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
TAVI or other access site	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Not access site-related	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Patients with Edwards Valve			
Combined Safety Endpoint to 30 days*	**x.x% (x/xxx)**	**x.x% (x/xxx)**	x.xxx
Death	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Stroke	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Life-threatening or disabling bleeding	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Acute Kidney Injury (stage 2/3)	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Coronary artery obstruction requiring intervention	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Major vascular complication	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
TriGUARD access site	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
TAVI or other access site	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Not access site-related	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx
Valve-related dysfunction requiring repeat procedure	x.x% (x/xxx)	x.x% (x/xxx)	x.xxx

*Events defined for the period of 30 days post-procedure follow up are reported for patients with at least 23 days of follow-up or with a composite primary safety endpoint to 30 days post-procedure.

Table 36: Subgroup analyses – Primary Efficacy Outcome - eITT

Primary Efficacy Endpoint	TriGuard 3 system group (N=XXX)	Control Group (N=XXX)	p-value*
Patients with AF at baseline			
Mean±SD (n)	xx.xx±xx.xx (n)	xx.xx±xx.xx (n)	x.xxx
Median	xx.xx	xx.xx	
Q1; Q3	xx.xx; xx.xx	xx.xx; xx.xx	
Min; Max	(xx.xx; xx.xx)	(xx.xx; xx.xx)	
Patients with Medtronic valve			
Mean±SD (n)	xx.xx±xx.xx (n)	xx.xx±xx.xx (n)	x.xxx
Median	xx.xx	xx.xx	
Q1; Q3	xx.xx; xx.xx	xx.xx; xx.xx	
Min; Max	(xx.xx; xx.xx)	(xx.xx; xx.xx)	
Patients with Edwards valve			
Mean±SD (n)	xx.xx±xx.xx (n)	xx.xx±xx.xx (n)	x.xxx
Median	xx.xx	xx.xx	
Q1; Q3	xx.xx; xx.xx	xx.xx; xx.xx	
Min; Max	(xx.xx; xx.xx)	(xx.xx; xx.xx)	

* Calculated as an hierachical endpoint.

Listing 1: SAE Listing - ITT population

Population Sets programming specifications

```
TriGUARD introduced
if (PRTGADV ^= ""  and ^missing(PRTGADV))
    or
   (PRD2TGADVANC ^= "" and ^missing(PRD2TGADVANC))
then TriGUARD_Introduced = 1;
else TriGUARD_Introduced = 0;

Meaning: We consider TriGUARD Introduced if any of PRTGADV or PRD2TGADVANC
variables are not empty


ITT
if ic_signed = 1 and PRASGMT in (1,2) then ITT_Group = PRASGMT;
/* 2 - Treatment, 1 - Control */
/* ====================================== */
Meaning: All subjects randomized to Treatment & Control groups, having their
Informed Consent (IC) signed, according to their randomization group.
/* ====================================== */


/* ============== RI ===================== */
if ic_signed = 1 and PRASGMT = 3 and TriGUARD_Introduced = 1 then ROLLIN = 1;
/* ====================================== */
Meaning: All subjects randomized to Roll-In group, having their Informed
Consent (IC) signed and TriGUARD Introduced (See definition above).
/* ====================================== */


/* ============== AT ===================== */
if ITT_Group in (1,2) then do;
   if TriGUARD_Introduced = 1 then AT_Group = 2; /* Treatment */
   if TriGUARD_Introduced = 0 and ^missing(PRTIME)  then AT_Group = 1; /*
Control */;
end;
/* ====================================== */
Meaning: All subjects randomized to Roll-In group, having their Informed
Consent (IC) signed and TriGUARD Introduced (See definition above).
/* ====================================== */



/* ============== eITT ===================== */
if (ITT_Group in (1,2) and PRPRCARMASG3 ^= "X" and PRCONVER ^= "X") or
PRASGMT = 1
then eITT_Group = PRASGMT;
/* 2 - Treatment, 1 - Control */
/* ====================================== */
Meaning: All subjects in ITT Group, excluding patients in Treatment Group
having procedural conversion to surgery or prolong CPR, according to their
randomization group.
/* ====================================== */

/* ============== ReITT ===================== */
if (ROLLIN = 1 and PRPRCARMASG3 ^= "X" and PRCONVER ^= "X")  then ReITT = 1;
```

```
/* ======================================== */
Meaning: Roll-In patients excluding patients having procedural conversion to
surgery or prolong CPR.
/* ======================================== */

/* ============== PT ==================== */
if PRASGMT in (1,2) then PT_Group = PRASGMT;
/* 2 - Treatment, 1 - Control */

if PRASGMT = 2 then do; /* Treatment */
   if YACLPRETAVI in ('0','1','2')
      or YACLDURTAVI in ('0','1','2')
      or YACLPOSTTAVI in ('0','1','2') then PT_Group = .;

   if (YACLPRETAVI = 'NA' or YACLDURTAVI = 'NA' or YACLPOSTTAVI = 'NA') and
      (PRINABMAINPOS = 1 or PRINABMAINPOS2 = 1) then PT_Group = .;

   if ^in_YACL then PT_Group = .;
end;
/* ======================================== */
Meaning: All subjects in ITT Group, excluding patients in Treatment Group
   a. having values other than 3 (complete) in one of YACLPRETAVI,
      YACLDURTAVI or YACLPOSTTAVI variables, or
   b. having one of above mentioned variables Not Available and PRINABMAINPOS
      or PRINABMAINPOS2 = 1 (YES) at the same time, or
   c. patients not found in YACL dataset (no info on ACL).
/* ======================================== */

/* ============== SP AT ==================== */
if AT_Group in (1,2) or ROLLIN = 1 then SP_AT_Group = AT_Group;
if ROLLIN = 1 then SP_AT_Group = 2;
/* ======================================== */
Meaning: All Patients in AT Group plus Roll-In patients added to Intervention
Group.
/* ======================================== */

/* ============== SP_ITT ==================== */
if ITT Group in (1,2) or ROLLIN = 1 then SP_ITT_Group = ITT_Group;
if ROLLIN = 1 then SP_ITT_Group = 2;
/* ======================================== */
Meaning: All Patients in ITT Group plus Roll-In patients added to
Intervention Group.
/* ======================================== */

/* ============== SP_eITT ==================== */
if eITT_Group in (1,2) or ReITT = 1 then SP_eITT_Group = eITT_Group;
if ReITT = 1 then SP_eITT_Group = 2;
/* ======================================== */
Meaning: All Patients in eITT Group plus eITT defined Roll-In patients added
to Intervention Group.
/* ======================================== */
```

Signature (b)(6)

Email

(b) (4)

(b) (4)

(b) (4)