Questions for the Circulatory System Devices Advisory Panel

August 3, 2021

Premarket Notification [510(k)] for
Keystone Heart, Ltd TriGUARD 3 Cerebral Embolic Protection Device
based on data from the REFLECT Phase II Study

1. Safety

The primary safety endpoint for the Phase II REFLECT study was a composite of all-death, all-stroke, life-threatening or disabling bleeding, Stage 2/3 acute kidney injury, coronary artery obstruction requiring intervention, major vascular complications, and valve related dysfunction requiring repeat procedure at 30 days. The As Treated Safety Population (SP[AT]) was the primary analysis cohort, which includes all randomized and roll-in subjects analyzed according to the treatment received.

The TriGUARD 3 device met the 30-day performance goal for the prespecified primary safety endpoint (Table 1).

Table 1: 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%		
Roll-ins	1/41 (2.4%)			

1. SP[AT] = As Treated Safety Population = all randomized and roll-in subjects analyzed according to treatment received; 157 = AT (116) + Roll-in (41). The SP[AT] population is the prespecified primary analysis population.
2. AT = As Treated population = all randomized subjects analyzed according to treatment received (randomized subjects only, excludes Roll-ins).

Roll-in subjects were observed to have a lower rate of safety events compared to the randomized TriGUARD 3 patients (2.4% vs. 20.7%, respectively). In a post-hoc analysis shown in Table 2, FDA compared the Phase II randomized TriGUARD 3 device group (i.e., TriGUARD 3 Roll-in subjects excluded) to the Phase II Control group. In this analysis, the primary safety endpoint rate in the randomized TriGUARD 3 group were nearly three-fold higher than the Phase II Control group, and individual components of the composite favored the Control group.

Table 2: Descriptive comparison of patients randomized to TriGUARD 3 (AT population)[1] or REFLECT Phase II Control

	TriGUARD 3	Phase II Control
	N=116	*N=57*
Combined Safety Endpoint within 30 Days	20.7% (24/116)	7.0% (4/57)
All-Cause Death	3.4% (4/116)	1.8% (1/57)
Stroke (Disabling and Non-Disabling)	11.2% (13/116)	5.3% (3/57)
Life-Threatening or Disabling Bleeding	6.9% (8/116)	0
Acute Kidney Injury (Stage 2/3)	3.4% (4/116)	0
Coronary Artery Obstruction Requiring Intervention	0.9% (1/116)	0
Major Vascular Complication	8.6% (10/116)	0
TriGUARD Access Site-Related	1.7% (2/116)	0
TAVR or Other Access Site-Related	6.0% (7/116)	0
Aortic Vascular Injury	1.7% (2/116)	0

1. AT = As Treated, all randomized subjects analyzed according to treatment received

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. FDA believes that there are limitations when directly comparing device vs. device results across two separate studies.

Although the SENTINEL study also used a 30-day combined primary safety endpoint and compared the event rate to a prespecified performance goal, components of the primary safety endpoint differed between the two studies. In addition, in contrast to the TriGUARD 3 REFLECT Phase II trial, all-cause death (1.3% Sentinel vs. 1.8% control) and stroke rates (5.6% Sentinel vs. 9.1% control) numerically favored the Sentinel device versus its control. In contrast, both the stroke and death rates were approximately 2-fold higher in the TriGUARD 3 group vs. Control. Safety event rates for the two trials are shown in Table 3.

Table 3: TriGUARD 3 REFLECT Phase II Study and SENTINEL Study Safety Results

REFLECT Phase II Study		
Safety Endpoints AT Population	**TriGUARD 3**	**Control**
All-Cause Death	3.4% (4/116)	1.8% (1/57)
Stroke (Disabling and Non-Disabling)	11.2% (13/116)	5.3% (3/57)
Acute Kidney Injury (Stage 3)	2.6% (3/116)	0
Major Vascular Complication	8.6% (10/116)	0
TriGUARD 3 Access Site-Related	1.7% (2/116)	0

SENTINEL Study		
Safety Endpoints ITT Population	**Sentinel**	**Control**
All-Cause Death	1.3% (3/234)	1.8% (2/111)
Stroke (Disabling and Non-Disabling)	5.6% (13/231)	9.1% (10/110)
Acute Kidney Injury (Stage 3)	0.4% (1/231)	0
Major Vascular Complication	8.6% (21/244)	5.9% (7/119)
Sentinel[1] Access Site-Related	0.4% (1/244)	N/A

1. Radial artery and brachial artery major vascular complications within 30 days of index procedure

Q1a. Please discuss your clinical interpretation of the safety results for TriGUARD 3 compared to Sentinel vs. their respective Control groups.

Q1b. Please discuss the clinical significance of including or excluding Roll-in subjects in the REFLECT Phase II primary safety analysis.

Q1c. The pre-specified safety endpoint in both the REFLECT and SENTINEL studies included all events through 30-days post-procedure, independent of CEC-assessed device-relatedness. Please discuss the relevance of safety assessments limited to CEC-assessed device-relatedness to the TriGUARD 3 device when considering adverse events in the REFLECT Phase II study.

2. Effectiveness

In the Phase II REFLECT trial, the prespecified primary effectiveness endpoint was a hierarchical composite of:

- All-cause mortality and/or stroke at 30 days;
- NIH Stroke Score (NIHSS) worsening 2-5 days post-procedure;
- Cerebral ischemic lesions detected by diffusion weighted magnetic resonance imaging (DW-MRI) evaluated 2-5 days post-procedure; and
- Total volume of cerebral ischemic lesions detected by DW-MRI evaluated 2-5 days post-procedure

The primary effectiveness endpoint was not met ($p = 0.857$), and the win ratio and win-percentage analyses favored the Control group.

The sponsor performed secondary endpoint analyses of DW-MRI imaging and neurological endpoints (Table 4). In the Efficacy Intention-to-Treat (eITT) population (defined as all

randomized subjects according to treatment assigned who did not have conversion to surgery or prolonged cardiac arrest prior to the post-procedure DW-MRI), mean per-patient average single cerebral ischemic lesion volume and maximum single cerebral ischemic lesion volume numerically favored the TriGUARD 3 group vs. Control. Conversely, the number of cerebral ischemic lesions and the total volume of cerebral ischemic lesions numerically favored the Control group vs. TriGUARD 3. Rates for NIHSS worsening and new neurologic impairment numerically also favored the Control group vs. TriGUARD 3.

The sponsor provided additional analyses in the Per Treatment (PT) population, defined as subjects with complete 3-vessel coverage in at least 2 of the 3 procedural timepoints (pre-, during, and post-TAVR, Table 4). The PT population comprised 59.3% (89/150) of the total Phase II REFLECT enrollment: 58.2% (64/110) of the randomized cohort and 62.5% (25/40) of Roll-in patients. When the PT population is compared to the pooled control group, most but not all, imaging endpoint components favor the TriGUARD 3 device, but clinical neurological endpoint event rates continued to favor the Control group.

Table 4: REFLECT Phase II Neurological and Imaging Effectiveness Secondary Endpoints

	TriGUARD 3		Pooled Control
	eITT[1] *N=112*	**PT[2]** *N=62*	**eITT[1]** *N=119*
Imaging Efficacy (at 1-7 days post-procedure)			
Presence of cerebral ischemic lesions	85.0% (85/100)	79.6% (43/54)	84.9% (90/106)
Number of cerebral ischemic lesions			
Mean ± SD (n)	6.0 ± 8.3 (100)	3.9 ± 4.8 (54)	4.6 ± 5.9 (106)
Median (Q1, Q3)	3.0 (1.5, 7.0)	2.5 (1.0, 5.0)	2.0 (1.0, 7.0)
Range (Min, Max)	(0, 51)	(0, 23)	(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)	83.3 ± 112.9 (106)
Median (Q1, Q3)	59.9 (35.7, 90.5)	52.7 (25.0, 83.9)	57.5 (34.0, 90.6)
Range (Min, Max)	(0.0, 341.4)	(0.0, 273.2)	(0.0, 936.9)
Maximal Single cerebral ischemic lesion volume (mm^3) [3]			
Mean ± SD (n)	74.9 ± 161.1 (785)	73.3 ± 135.1 (277)	81.4 ± 328.3 (662)
Median (Q1, Q3)	31.3 (18.8, 71.4)	35.7 (18.8, 76.5)	35.8 (0.0, 71.4)
Range (Min, Max)	(0.0, 2037.5)	(0.0, 1304.3)	(0.0, 6894.9)
Total volume of cerebral ischemic lesions (mm^3) [3]			
Mean ± SD (n)	587.8 ± 1028.4 (100)	375.8 ± 617.7 (54)	508.2 ± 1124.0 (106)

	TriGUARD 3		Pooled Control
	eITT[1] *N=112*	**PT[2]** *N=62*	**eITT[1]** *N=119*
Median (Q1, Q3)	215.4 (68.1, 619.7)	145.7 (43.8, 444.4)	188.1 (52.1, 453.1)
Range (Min, Max)	(0.0, 5681.3)	(0.0, 3519.0)	(0.0, 8133.6)
Neurologic Efficacy			
NIHSS worsening [4]			
2-5 days post-procedure/pre-discharge	14.1% (14/99)	13.8% (8/58)	7.6% (8/105)
30 days (±7 days) post-procedure	7.8% (6/77)	4.9% (2/41)	3.6% (3/84)
New neurologic impairment [5]			
2-5 days post-procedure	10.0% (9/90)	7.8% (4/51)	6.4% (6/94)
30 days (±7 days) post-procedure	8.6% (6/70)	5.4% (2/37)	2.6% (2/78)

1. eITT = All randomized subjects according to treatment assigned who did not have conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI.
2. PT = Per Treatment Population = randomized TriGUARD 3 subjects with complete TriGUARD 3 coverage for at least two of the three procedural time points (pre-, during, and post-TAVR) and all randomized control group subjects. In the analysis. The PT population excluded subjects who had conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI.
3. Volume=0 is assigned to patients without cerebral ischemic lesions.
4. Worsening of NIHSS score is defined as a higher NIHSS score at the time of assessment than at baseline.
5. 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.

There is uncertainty regarding whether the pooled REFLECT Phase I and Phase II control group is the more appropriate primary comparator in assessing TriGUARD 3 device effectiveness vs. the Phase II Control group alone, since the poolability criteria prespecified in the statistical analysis plan were not met.

Neither the TriGUARD Phase II REFLECT nor the SENTINEL study met its prespecified primary effectiveness endpoint. Of note, the two trials defined the primary effectiveness endpoints differently, rendering a direct comparison of effectiveness results between the studies challenging. In the SENTINEL Study, the primary effectiveness endpoint was limited to cerebral imaging assessments. In contrast, the TriGUARD Phase II REFLECT study primary effectiveness endpoint utilized a composite that included both imaging and clinical assessments. Table 5 shows the results of DW-MRI lesion volume analyses that were performed in both studies.

Table 5: Phase II TriGUARD REFLECT and SENTINEL DW-MRI Lesion Volume Results

Analysis Population	Device Group (mm^3) median (Q1, Q3) n min, max	Control Group (mm^3) median (Q1, Q3) n min, max	Treatment Difference (Test - Control)
REFLECT Phase II DW-MRI Lesion Volume			
eITT[1]	215.4 (68.1, 619.7) n=100 0 min, 5681.3 max	188.1 (52.1, 453.1) n=106 0 min, 8133.6 max	27.3
SENTINEL DW-MRI Lesion Volume (All Territories analysis)			
ITT[2]	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

1. REFLECT eITT = All randomized subjects according to treatment assigned who did not have conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI.
2. SENTINEL ITT = Patients enrolled and randomized to a treatment arm.

Q2a. Please discuss your clinical interpretation of the effectiveness results for the TriGUARD 3 vs. its Control observed in the randomized REFLECT study compared to those observed for the Sentinel vs. its control in the randomized SENTINEL trial.

Q2b. Please discuss the strengths and limitations of the effectiveness outcomes assessed in all subjects treated with the TriGUARD 3 device (the eITT analysis population) vs. the subgroup of subjects in whom the device achieved complete 3-vessel coverage during at least 2 of 3 procedural timepoints (the PT group) as they relate to TriGUARD 3 effectiveness.

3. TriGUARD 3 Device Positioning

The TriGUARD 3 device is intended to provide complete coverage of the aortic arch ostia throughout the TAVR procedure. However, complete vessel coverage with the TriGUARD 3 device was not consistently observed in the REFLECT Phase II study: 72.4% of subjects had complete 3-vessel coverage, and 19% of subjects had no vessel coverage during TAVR deployment (Table 6). When considering coverage throughout the procedure (pre-, during, and post-TAVR), 54.7% of subjects had complete 3-vessel coverage at all three timepoints. Further, predictors of complete or incomplete vessel coverage have not been identified; incomplete coverage of the aortic arch vessels variably occurred for any or all arteries at all timepoints. These findings raise the question of whether the TriGUARD 3 satisfactorily meets special control 7(iii) for secure and stable positioning throughout the TAVR procedure. Non-

coverage of aortic arch vessels was associated with a numerically increased stoke rate vs. complete or partial coverage.

In addition to positioning challenges, the rate of device interference was approximately 10%, and technical and procedure success rates were in the 70-75% range.

Table 6: Select TriGUARD 3 Secondary performance endpoints [1]

	ITT/AT [2]	Roll-In	SP[ITT] [3] ITT+Roll-in
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 Deployment			
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. Only subjects with available and discernable angiograms are included in the denominator (subjects with indiscernible angiograms are not included in the denominator).
2. ITT = All randomized subjects according to treatment assigned (randomized subject only, excludes Roll-ins)
   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.
3. SP[ITT] = All randomized and Roll-in subjects according to treatment assigned
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.

Following completion of the REFLECT study, the sponsor modified the TriGUARD 3 crimper component, which is used to load the device into the delivery sheath during device preparation. This change was intended to increase device positioning success. To assess this modification, the sponsor provided benchtop testing and real world evidence (RWE) using the modified device in 50 patients. The RWE reported successful TriGUARD 3 device deployment with correct orientation and complete cerebral coverage in all patients and no strokes or TIAs.

Important limitations of the RWE included uncertainty regarding external generalizability (only 1 site and 3 operators participated), and there were limited outcome assessments and missing data. Imaging was only provided for 34 of 50 patients during TAVR (missing data in 16 cases), and no pre-TAVR or post-TAVR images were provided to confirm that the device maintained stable position throughout the procedure. There was also uncertainty regarding: (1) the expertise of those who evaluated the primary safety and performance endpoints; (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.

Q3a. Please discuss the challenges associated with optimal placement of the TriGUARD 3 device as it relates to device effectiveness and the overall benefit-risk profile of the TriGUARD 3 compared to the Sentinel device. In your discussion, please comment on whether study data indicate that the TriGUARD 3 satisfactorily meets special control 7(iii) for secure and stable positioning throughout the TAVR procedure.

Q3b. Please discuss the strengths and limitations of the real-world evidence submitted to address device positioning issues observed in the REFLECT Phase II trial.

4. Access site and adverse events attributable to the device

The predicate Sentinel device is introduced via radial or brachial artery access. In contrast, the TriGUARD 3 device uses contralateral femoral artery access, which is also commonly used for accessory devices for diagnostic imaging and hemodynamic monitoring during TAVR procedures. Because of shared access among accessory devices, access site complications in patients receiving the TriGUARD 3 may not be clearly attributed to the embolic protection device.

The TriGUARD 3 device requires an 8F sheath compared to a 6F sheath typically used for accessory devices in the contralateral femoral artery. The rate of major vascular complication was in 8.6% (10/116) in the As-Treated (AT) TriGUARD 3 group compared to 0% (0/57) in the REFLECT Phase II control group, and life-threatening or disabling bleeding was 6.9% (8/116) in the AT TriGUARD 3 group compared to 0% (0/57) in the Phase II control group.

Major vascular complication observed in the SENTINEL study are shown above in Table 3.

Separately, the sponsor provided post-hoc analyses wherein they excluded events from the safety endpoint analysis that were adjudicated by the Clinical Event Committee 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. In so doing, the combined 30-day safety endpoint event rate fell from 15.9% (25/157) to 7.6% (12/157), life threatening or disabling bleeding fell from 5.7% (9/157) to 0.6% (1/157), and major vascular complications fell from 7.0% (11/157) to 1.9% (3/157).

Q4. Please discuss your clinical interpretation of bleeding and vascular complications in TriGUARD 3 subjects observed in the REFLECT trial, including the need for an 8F access sheath to introduce the device compared to the bleeding and vascular complications associated with the Sentinel device. In your discussion, please address benefit-risk considerations of bleeding and access site complications compared to cerebral protection.

5. Indications for Use

The sponsor has proposed the following indications for use:

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

Q5. Please discuss and make recommendations for the proposed Indications for Use.

Analysis Populations Reference Sheet

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. 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 TriGUARD 3 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.