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(via email)

RE: Premarket notification 510(k) for TriGUARD 3 (Keystone Heart, Ltd.)

Dear Drs. Shuren, Maisel, and Zuckerman:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, opposes Food and Drug Administration (FDA) clearance of the 510(k) premarket notification application for the TriGUARD 3 Cerebral Embolic Protection Device (hereinafter referred to as TriGUARD 3) submitted by Keystone Heart, Ltd., for use in patients undergoing transcatheter aortic valve replacement (TAVR). The sponsor proposed an indication of "designed to minimize the risk of cerebral damage by deflecting embolic debris away from the cerebral circulation during [TAVR]." The TriGUARD 3 was discussed at the August 3, 2021, meeting of the FDA's Circulatory System Devices Panel (CSDP).

Public Citizen opposes FDA clearance of the 510(k) premarket notification application for TriGUARD 3 because data from clinical trials of the device, and comparisons to its predicate

device, fail to provide evidence that TriGUARD 3 has a favorable benefit–risk profile or that it is substantially equivalent to its proposed predicate.

According to the FDA's briefing document for the August 3, 2021, CSDP meeting, the safety and effectiveness of TriGUARD 3 was based on review of clinical experience from three studies:[1]

1. **REFLECT Phase I**, a randomized (2:1) trial comparing an early version of TriGUARD HDH to unprotected TAVR, n=238 (non-randomized "roll-in", subjects included)
2. **REFLECT Phase II**, a randomized (2:1) trial comparing TriGUARD 3 to unprotected TAVR, n=220 (non-randomized "roll-in" subjects included)
3. **Netherlands Heart Registry**, an uncontrolled, observational study, n=50

Safety Assessment

The REFLECT Phase II trial was the pivotal clinical trial that provided the most important assessment of TriGUARD 3's safety and effectiveness. It was a prospective, multicenter, single-blind, 2:1 randomized, controlled trial comparing the TriGUARD 3 used during TAVR (test group) with unprotected TAVR (control group). The study enrolled a total of 179 randomized subjects, 121 in the test group and 58 in the control group, and 41 nonrandomized roll-in subjects at 18 sites in the US.[2]

The primary safety endpoint for the REFLECT Phase II trial was based on the updated Valve Academic Research Consortium (VARC-2) definition of the composite of all-cause mortality, all stroke (disabling and non-disabling), life-threatening or disabling bleeding, acute kidney injury (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 at 30 days in the TriGUARD 3 group.[3]

Although the prespecified primary safety performance goal of having a rate of the primary safety endpoint of less than or equal to 34.4% was met for the TriGUARD 3 REFLECT Phase II trial,[4] **Table 9** and **Figure 8,** excerpted below from the FDA Executive Summary for the August 3, 2021, CSDP meeting clearly show that serious adverse events related to safety of the device were far more frequent with TriGUARD 3 than in the absence of such "protection" during and following TAVR.[5] The FDA noted the following:

> 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**

[1] Food and Drug Administration. FDA Executive Summary for the Circulatory System Devices Panel on the Premarket Notification [510(k)] for Keystone Heart, Ltd TriGUARD 3 Cerebral Embolic Protection Device. August 3, 2021. https://www.fda.gov/media/151175/download. Accessed August 612, 2021.
[2] *Ibid*. PDF page 21.
[3] *Ibid*. PDF page 34.
[4] *Ibid*. PDF page 34.
[5] *Ibid*. PDF pages 35-36.

(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 [roll-in] 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 [As Treated] vs. SP[Safety Population][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).[6] [Bolded emphasis added]

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

[6] *Ibid*. PDF page 35.

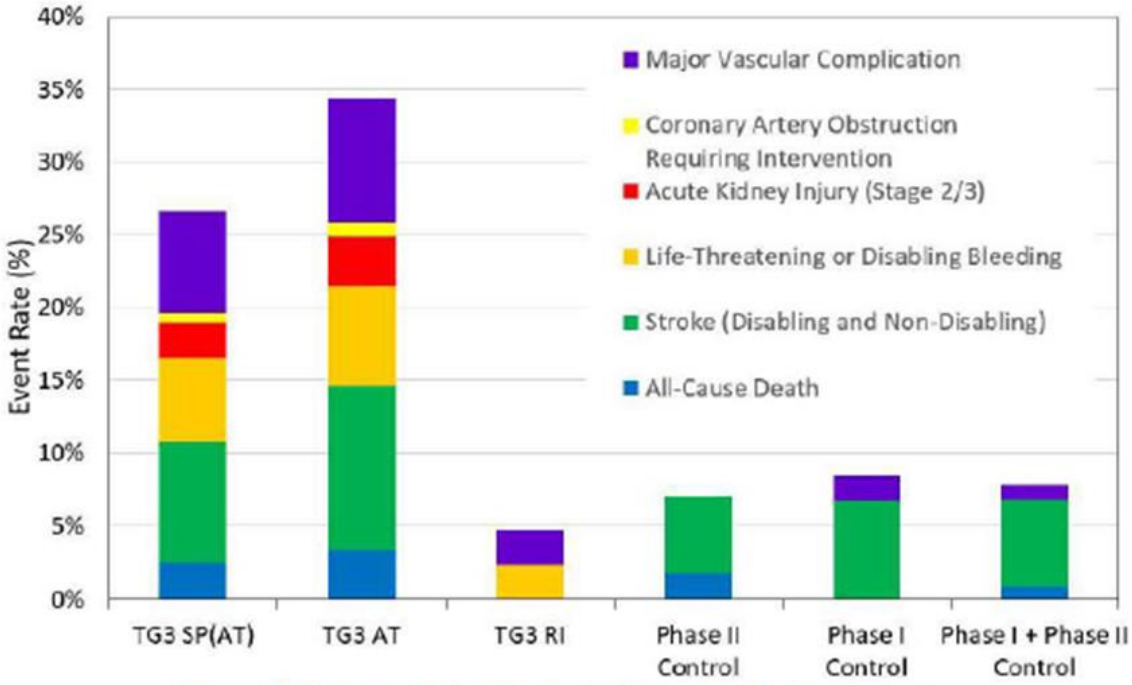


Figure 8. Primary Safety Endpoint Rates for Various Cohorts
*Note, some patients may have more than one event.

Effectiveness Assessment

The primary effectiveness endpoint for the REFLECT Phase II trial was a hierarchical composite of all-cause mortality and/or any stroke at 30 days, NIH Stroke Score (NIHSS) worsening evaluated between days two to five post-procedure, any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) evaluated between days two and five post-procedure, and total cerebral ischemic lesion volumes detected by DW-MRI evaluated between days two and five post-procedure.[7]

Tables 12 and 13, excerpted below from the FDA Executive Summary for the August 3, 2021 CSDP meeting summarize the analyses of the primary effectiveness endpoint using the efficacy intention-to-treat (eITT) and another ITT population.[8] These analyses indicated that use of TriGUARD 3 heightened rate of death and stroke within 30 days of the TAVR procedure and worsened signs of ischemic lesions in the brain including their presence or volume as measured with diffusion-weighted MRI scans.

The FDA noted the following regarding the primary effectiveness endpoint analysis for the REFLECT Phase II trial:

> 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

[7] *Ibid*. PDF page 17.
[8] *Ibid*. PDF pages 41-43.

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% Tri GUARD 3 vs. 6.7% control), higher rate of NIHSS worsening at two to five days post-procedure (14.1 % TriGUARD 3 vs. 7 .6% control), and higher mean total volume of cerebral ischemic lesions (mean 587.80 mm^3 TriGUARD 3 vs. 508.22 mm^3 control) compared to the pooled control group. The frequency of cerebral ischemic lesions was similar between the two groups (85.0% vs. 84.9%).[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

[9] *Ibid*. PDF page 41.

Table 13: REFLECT Phase II Primary Effectiveness Endpoint Components in Supplement 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
(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

So-called real-world evidence from the Netherlands Health Registry study presented by the sponsor showed that in 50 consecutive patients who underwent TAVR with the TriGUARD 3 at a single institution, 72-hour follow-up review revealed no TAVR-related stroke or transient ischemia attacks, and the TriGUARD 3 device was successfully deployed in all cases.[10] However, no controls were used. The FDA offered the following critique of this data:

> **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 TA VR 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:**

[10] *Ibid*. PDF page 52.

> **(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.**[11]
> [Emphasis in original]

Public Citizen agrees with the concerns cited by the FDA and further notes the obvious: Absent controls, this study has limited validity as a scientific indicator of safety or effectiveness.

Lack of substantial equivalence

The predicate device for the TriGUARD 3 application was the SENTINEL Cerebral Protection System (Boston Scientific) (hereinafter referred to as SENTINEL), currently the only embolic protection device commercially available in the U.S. for use during TAVR.[12]

"Substantial equivalence" between the TriGUARD 3 and the predicate device was mainly based on post-procedure cerebral ischemia volume (mm^3) derived from MRI scans. SENTINEL use was associated with a nonsignificant nominal reduction in ischemia volumes compared to controls (median volumes: 109.1 vs. 174.0, respectively, n=240, p=0.2354).[13] By comparison, this same volume indicator showed the opposite effect for TriGUARD 3 compared with controls. These results prompted the FDA to state the following:

> Effectiveness results from the SENTINEL study indicated that superiority was not demonstrated for the prespecified endpoint, and there was not a significant reduction in median total new lesion volume in protected territories (of the brain). 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…[14]

Accordingly, the sponsor appears to suggest that these joint efficacy results are consistent with the interpretation that SENTINEL and TriGUARD 3 are equivalent because neither significantly reduced signs of ischemia. Alternative interpretations, however, are that the SENTINEL device may prove superior with additional testing or that neither device is clinically effective.

Parallel comparisons of device safety summarized by the FDA in **Table 23** excerpted below from the FDA Executive Summary for the August 3, 2021, CSDP meeting seem even more

[11] *Ibid*. PDF pages 52-53.
[12] *Ibid*. PDF page 14.
[13] *Ibid*. PDF page 55.
[14] *Ibid.* PDF page 56.

damaging to the sponsor's claim of substantial equivalence to the predicate device. The most notable difference highlighted by the FDA was the following:

> 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).[15]

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)

[15] *Ibid.* PDF page 59.

A lack of substantial equivalence between the two devices is further demonstrated by the following differences in the design attributes:

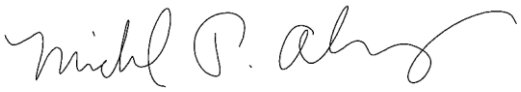
(1) TriGUARD 3 is inserted using a larger protective sheath than SENTINEL (8F versus 6F).
(2) TriGUARD 3 is inserted through the femoral artery, whereas SENTINEL is inserted via the radial or brachial arteries.
(3) TriGUARD 3 is composed of a single large membrane designed to filter three aortic arch outflows, whereas SENTINAL is composed of two smaller and separate membranes that aim to filter only the proximal right brachiocephalic and left common carotid arteries.[16]

Conclusions

In closing, the available data indicates that TriGUARD 3 is unsafe and is not substantially equivalent to SENTINEL. Moreover, it is unacceptable that the FDA considers 510(k) premarket notification to be an appropriate pathway for marketing such invasive cerebral embolic protection devices. Such high-risk medical devices should be categorized as Class III devices and subject to premarket approval application requirements. We therefore urge the FDA to deny premarket clearance for TriGUARD 3.

Thank you for considering our comments on this important public health matter.

Sincerely,



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[16] *Ibid.* PDF pages 14-15.