24 Hour Summary of the Circulatory System Devices Panel Meeting Keystone Heart, Ltd TriGUARD 3 Cerebral Embolic Protection Device August 3, 2021

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on August 3, 2021 to discuss and make recommendations on information regarding the premarket notification (510(k)) submission for the TriGUARD 3 Cerebral Embolic Protection Device.

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.

Panel Deliberations/FDA Questions:

Question 1: Safety

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 clinical event committee (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.

In considering safety results for the two embolic protection devices compared to their respective control groups, the majority of panelists agreed that an important finding was that the point estimate rates for the safety endpoint components favored the Control group vs. the TriGUARD 3 group in the REFLECT trial, and the point estimate rates favored the Sentinel group vs. the Control group in the SENTINEL trial. The majority of panelists believed that the most appropriate groups to compare were the randomized TriGUARD 3 subjects to Phase II Control group and expressed concerns about including TriGUARD 3 Roll-in subjects in evaluating safety. Regarding CEC adjudication of safety events, the panel noted that it can be challenging to definitively determine device relatedness; they recommended that all events, independent of device-relatedness, should be the principal consideration in the evaluation of device safety.

Question 2: Effectiveness

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.

The majority of panelists believed that an important observation was that in the REFLECT trial, components of the primary effectiveness composite endpoint for the primary analysis population (eITT) trended in favor of the Control group vs. TriGUARD 3 group, and conversely, in the SENTINEL trial, neuroimaging outcomes trended in favor of the Sentinel device vs. its Control group (ITT with imputation primary analysis population). In addition, the panel voiced concern that clinical components included in the REFLECT trial primary effectiveness composite endpoint and the DW-MRI results raised the possibility of harm associated with the TriGUARD 3 device, which was not observed in the Sentinel trial. With regard to analysis cohorts, the panel noted that the PT group was a selected subgroup, and the more appropriate cohort to evaluate device effectiveness was the eITT population.

Question 3: TriGUARD 3 Device Positioning

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.

The panel expressed concerns regarding TriGUARD 3 device positioning and incomplete aortic arch vessel coverage noting that approximately 45% of TriGUARD 3 subjects had incomplete coverage, 20% no coverage, and in 10% of subjects, the TriGUARD 3 device interfered with the TAVR device. Some panelists commented that it was commendable that the sponsor made the crimper change in an effort to address device positioning challenges. Panelists noted that the Real-World Evidence (RWE) intended to evaluate the modified device may not be generalizable to the spectrum of TAVR operators and patients, and that questions remain regarding the impact of the crimper change on device positioning and vessel coverage.

Question 4: Access site and adverse events attributable to the device

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.

The panel indicated that an increased risk (bleeding and vascular complications) was not unexpected with an 8-French access sheath used to introduce the TriGUARD 3 device, but the increased risk observed in the REFLECT Phase II study was small. The panel noted that some increased risk is expected with TriGUARD 3 compared to Sentinel device given that radial access (used with the Sentinel device) is associated with less bleeding compared with femoral access (TriGUARD 3).

Question 5: Indications for Use

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

The panel stated that the proposed TriGUARD 3 device Indications for Use was not supported by the data presented. They also noted that the Indications for Use should reflect device performance demonstrated in clinical data rather than what the device is designed to do.