FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

24 Hour Summary of the Circulatory System Devices Panel Meeting

February 13, 2024

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee for the Food and Drug Administration met on February 13, 2024, to discuss, make recommendations, and vote on the information regarding the premarket approval (PMA) application for the Abbott Medical TriClip G4 System. The proposed Indication for Use statement is as follows: The TriClip G4 System is indicated for the improvement of health status in patients with symptomatic severe tricuspid regurgitation (TR) despite being treated optimally with medical therapy, who are at intermediate or greater risk for surgery and in whom tricuspid valve edge-to-edge repair is appropriate as determined by a heart team.

Panel Deliberations/FDA Questions:

Question 1: Safety

Please discuss the clinical significance of the TriClip vs. control group major adverse event outcomes at 30 days and 12 months.
The panel agreed that the device appears to be safe considering the multiple comorbidities of the patient population and risks associated with complex interventional cardiology procedures. The panel noted that further data are needed to address potential risks associated with future reinterventions (e.g., right heart catheterization and pacemaker or ICD implantation) when TriClip devices are in place but suggested that this issue should be better addressed in postmarket studies.

Question 2: Primary Endpoint Results

a. Please discuss the clinical significance of the primary endpoint results.

The panel generally acknowledged that the Kansas City Cardiomyopathy Questionnaire (KCCQ) score improvement was clinically significant and that the KCCQ score changes were unlikely due to a placebo effect alone. Panelists expressed uncertainty about why the improvement in KCCQ score did not translate to improvement in mortality and heart failure hospitalization (HFH) rates and were not associated with reduced medication use. The panel suggested several possible explanations: (1) study duration not long enough to show reduced mortality and HFH; (2) HFH for right sided heart failure occurs less frequently vs. left-sided heart failure; and (3) the patient population enrolled in the pivotal trial may have been less sick compared to general

patients with severe TR. Additionally, panelists noted that responder data suggest that patients with higher KCCQ scores at baseline showed less improvement, but there is some uncertainty about which patients in the heterogeneous patient population have the most favorable responses to the TriClip treatment.

b. Please discuss the strengths and limitations of the primary endpoint results considering KCCQ score improvement favoring the device group (and potential placebo effects) and the lack of reduced mortality and HFH rates through 12 months in the TriClip group vs. the control group.

The panel agreed that a placebo effect or patient bias was likely present but concluded that a placebo effect does not fully account for the observed magnitude of KCCQ score improvement. Panelists based this conclusion on the durability of the KCCQ score improvement through 12 months, the association of KCCQ score improvement with TR reduction, and imaging data showing cardiac reverse remodeling. Panelists reiterated that the lack of correlation between KCCQ score improvement and mortality, or heart failure hospitalization improvement may be related to the lower risk population, and the duration of the study may not have been sufficient to show improvement in these endpoints.

c. Please discuss the clinical significance of TR severity and KCCQ changes at 12 months in supporting benefits of the TriClip device and mitigating potential placebo effects in an open-label trial.

The panel noted that although the standard deviations around KCCQ score changes associated with TR reduction were wide, this was not unexpected in view of the clinical complexity of the enrolled patients. Panelists suggested that the association between KCCQ score improvement and TR reduction is intuitive, biologically plausible, and consistent with MitraClip experience. That the study showed no reduction in diuretic usage if the patients were feeling better was an unexpected finding that remains unexplained.

d. Please discuss the primary endpoint outcome variability as a function of site enrollment and implications on the generalizability of the primary endpoint results.

Lower volume centers achieved the same TR reduction as higher volume centers, but panelists noted that the win ratio results in low volume centers were less favorable to the TriClip group because of higher rates of mortality or TV surgery and HFH. The panelists discussed potential differences in baseline covariates in patients treated at high vs. low volume sites, and whether the patients received the same medical care. The panel did not find evidence of differences in the technical aspects of the TriClip procedure at the high vs. low volume sites. The differences in outcomes between higher and lower volume centers remained unexplained, and the Panel suggested further study of patient management in the postmarket setting.

Question 3: Descriptive Endpoint Results

Please discuss the clinical significance of these clinical and imaging outcomes.

The panel agreed that the clinical and imaging outcomes generally support and are consistent with KCCQ score improvement, significant TR reduction, and evidence for reverse RV remodeling in TriClip patients.

Question 4: Single-Arm Cohort Results

Please discuss the clinical significance of the Single-Arm Cohort results, their value-added to the Randomized Cohort results, and the implications on defining the TriClip intended use population.

The panel noted that the Single-Arm Cohort met its primary endpoint, and about 80% of patients had TR reduction to moderate or less, which was higher than anticipated since those patients were determined during screening to have a low likelihood of TR reduction to moderate or less. The panel also noted that although there was no comparator group, the adverse event rates (e.g., bleeding rate) were higher than the device group of the Randomized Cohort. In general, the panel acknowledged that the Single-Arm Cohort was selected to include patients that were at higher risk vs. the Randomized Cohort. The panel discussed that the technical success rate and TR reduction were still favorable despite more patients having torrential TR, and that these results should be considered when defining the indicated population.

Question 5: Labeling

a. **Please discuss whether the available clinical data support the proposed indications for use.**
b. **Please discuss whether the phrases "improvement of health status" and "as determined by a heart team" should be modified or further defined.**

The panel generally agreed that the available clinical data support the proposed indications for use. Panelists had mixed opinions on the phrase "improvement of health status." Some panelists suggested using more specific language including more objective measures to ensure that the expected benefit is clear, while others suggested that "improvement of health status" accurately represented the observed KCCQ outcomes. The panel suggested replacing the term "heart team" with "a multidisciplinary structural heart team" to better ensure appropriate expertise involved in patient selection. The panel also suggested better defining the patient population to reflect the cohort that was studied in the pivotal trial, including the large percentage of patients who were NYHA Class II/III and the high prevalence of patients with atrial fibrillation. Many panelists raised general concerns about the potential for patients outside of the studied population to be treated with the device in the real-world setting (indication creep).

Question 6: Benefit/Risk

Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile of the device.

The panel generally considered the risks associated with TriClip to be low, and the main benefit is related to health status improvement as measured by KCCQ score. Panelists noted that patients have limited alternatives, so the favorable safety profile provides reasonable assurance in a favorable benefit/risk profile despite some uncertainty regarding device effectiveness. The panel suggested that TriClip may be a good treatment option for patients with poor right ventricular function who are not good candidates for valve replacement. Concerns were raised again about whether the treatment would limit future intervention options such as surgical valve repair and transcatheter valve replacement. The panel also emphasized the need to ensure the therapy is used in the appropriate patients and avoid indication creep.

Question 7: Post-Approval Study

a. **Please discuss the strengths and limitations of the proposed single arm registry-based study design for the post-approval study.**
b. **Please discuss whether sample sizes for specific subgroups or underrepresented minority patient populations should be prespecified and evaluated in the post approval-study.**

The panel agreed that registry-based postmarket data have value. They agreed that postmarket surveillance is critically important for such a novel device and should include evaluation of health status benefit including both heart failure symptoms and quality of life. They emphasized the need to collect long-term (i.e., 2-5 years) KCCQ data in the current patient population with as much specificity as possible, which would allow assessment of the correlation of KCCQ with harder endpoints. Panelists acknowledged the challenges of collecting such data in the postmarket registry setting. Panelists suggested collecting data on left ventricular dysfunction, atrial fibrillation, and more specific symptom-related data such as incidence of ascites, edema, and fatigue. There were no concerns with the single arm-design. The panel also suggested collecting data to assess whether the device prevents future interventions such as pacemaker implantation. The panel also emphasized the value of and need for collecting data in diverse patient populations.

Question 8: Training Program

Please discuss key elements recommended in the operator training program for the TriClip procedure.

The panel emphasized the importance of proctoring, identifying centers for excellence, and building a multidisciplinary heart team that supports training of operators and includes staff responsible for TriClip patient treatment and follow-up care. Panelists proposed four key elements that should be included in a training program: Prior site experience with MitraClip, training to support appropriate patient selection, training to support tricuspid valve imaging and credentialing of the imaging team and building a multidisciplinary heart failure team to support patient management post-TriClip implantation.

VOTE:

The Panel voted on the safety, effectiveness, and benefit-risk profile of the Abbott TriClip G4 system.

Voting Question 1:

Is there reasonable assurance that the Abbott TriClip G4 System is safe for use in patients who meet the criteria specified in the proposed indication?

The panel voted as follows:

- Yes: 14
- No: 0
- Abstain: 0

Voting Question 2:

Is there reasonable assurance that the Abbott TriClip G4 System is effective for use in the patients who meet the criteria specified in the proposed indication?

The panel voted as follows:

- Yes: 12
- No: 2
- Abstain: 0

Voting Question 3:

Do the benefits of the Abbott TriClip G4 System outweigh the risk for use in the patients who meet the criteria specified in the proposed indication?

The panel voted as follows:

- Yes: 13
- No: 1
- Abstain: 0

Contact: Akinola Awojope, DrPH, MPH.
Designated Federal Officer
(301) 636-0512
Akinola.Awojope@fda.hhs.gov

Transcripts may be downloaded from:

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OR

Food and Drug Administration
Freedom of Information Staff (FOI)
5600 Fishers Lane, HFI-35
Rockville, MD 20851
(301) 827-6500 (voice), (301) 443-1726