Panel Questions for the Advisory Committee Meeting
for the Abbott TriClip G4 System – February 13, 2024

DISCUSSION QUESTIONS

Safety

1. The Kaplan Meier estimates of freedom from MAEs (major adverse events, including cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure) at 30 days post-procedure were 98.3% for the Randomized Cohort and 100% for the Single-Arm Cohort. The individual MAE components at 30 days are shown in Table 1:

Table 1. Individual MAE Components at 30 Days Randomized Cohort Attempted Procedure (AP) Population

MAE Component	Event Rate*
Cardiovascular mortality	0.6% (1/172)
New onset renal failure	1.2% (2/172)
Endocarditis requiring surgery	0% (0/172)
Non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure	0% (0/172)

*% (no./total no.)

The CEC-adjudicated adverse event rates at 12 months for the Full Randomized Cohort are shown in Table 2:

Table 2. CEC-Adjudicated Adverse Events through 12 Months – Full Randomized Cohort Intent-to-Treat (ITT) Population

Event	Event Rate	
	Device Group (N=285)	Control Group (N=287)
All-cause mortality	8.1%	7.0%
Cardiovascular (VARC II definition)	5.3%	3.8%
Heart failure-related	3.9%	2.8%
Non-heart failure-related	1.4%	1.0%
Non-cardiovascular (VARC II definition)	2.8%	3.1%
Hospitalization	33.7%	31.0%
Heart failure hospitalization	11.2%	11.8%
Other cardiovascular hospitalization	7.7%	7.0%

Non-cardiovascular hospitalization	22.8%	19.5%
Tricuspid valve surgery	1.8%	2.4%
Tricuspid valve intervention*	2.5%	1.0%
Major bleeding (≥BARC 3a) at 30 days	3.9%	1.7%
New onset renal failure at 30 days	1.4%	0.3%
Transient ischemic attack (TIA)	0.4%	0.0%
Stroke (VARC II definition)	1.1%	1.0%
MI at 30 days (VARC II definition)	0.0%	0.0%
Endocarditis requiring surgery at 30 days	0.0%	0.0%
Non-elective cardiovascular surgery for TriClip-related adverse event post-index procedure	0.0%	0.0%
Cardiogenic shock	0.0%	0.3%

VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium; TIA: transient ischemic attack.
*Tricuspid valve intervention includes reintervention for device group and first intervention for control group.

Please discuss the clinical significance of the TriClip vs. control group major adverse event outcomes at 30 days and 12 months.

Effectiveness

2. *Primary Endpoint Results.* The primary endpoint of the TRILUMINATE pivotal trial was a hierarchical composite of time to all-cause mortality or tricuspid valve (TV) surgery, number of heart failure hospitalizations (HFH), and a ≥15 points improvement in KCCQ score from baseline at 12 months, tested using the Finkelstein-Schoenfeld (FS) method (tested at a 5% two-sided significance level). The primary analysis population was the ITT population.

   The Finkelstein-Schoenfeld test statistic result was 2.16 (2-sided p-value = 0.0311). The primary endpoint was met indicating the TriClip group was superior to the control group.

   A supplementary win ratio analysis was used to evaluate the treatment effect of the primary endpoint. For the primary analysis (n=350 randomized patients), the number of wins, losses, and ties for the TriClip group and the control group for each component of the primary endpoint are shown in Figure 1. The win-ratio point estimate was 1.44 in favor of the TriClip group, with a 95% confidence interval of 1.03-2.08.

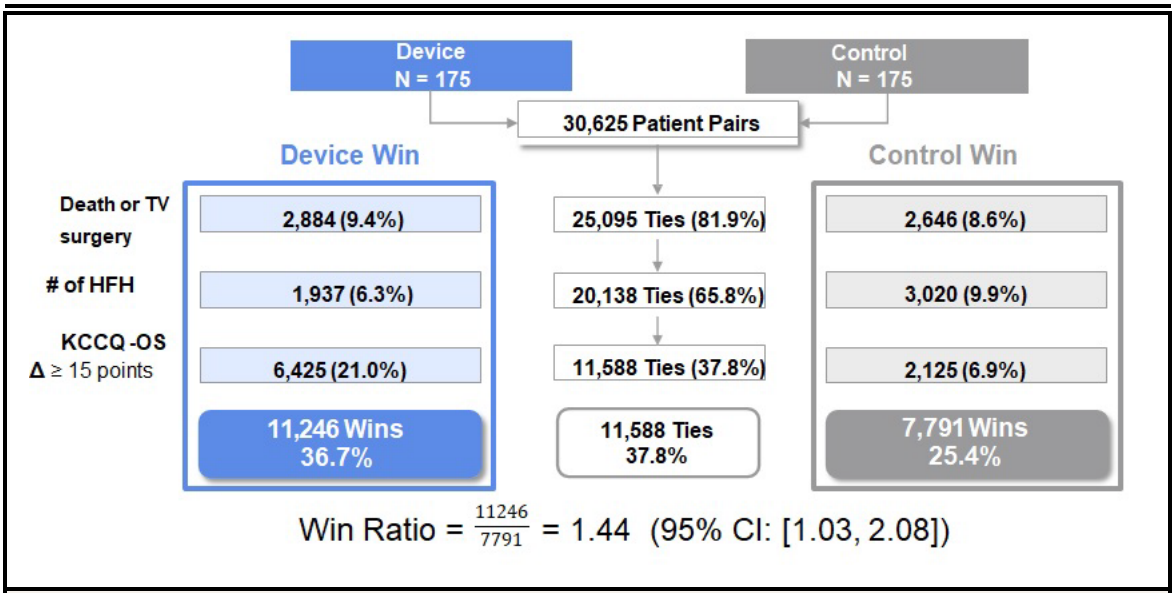

Figure 1. Win Ratio Analysis of the Randomized Cohort Primary Endpoint – ITT Population. TV: tricuspid valve; HFH: heart failure hospitalization; KCCQ-OQ: Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

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

b. The primary endpoint of the TRILUMINATE pivotal trial was met, driven by KCCQ score improvement in the device group. Mortality or tricuspid valve surgery rates were similar between treatment groups, and the HFH rate was numerically higher in the TriClip group vs. the control group. The results of the individual components of the primary endpoint were as follows:

- Kaplan-Meier estimates for freedom from all-cause mortality or tricuspid valve surgery were 90.6% and 89.4% at 12 months for the TriClip group and the control group, respectively.
- Kaplan-Meier estimates for freedom from HFH at 12 months was 84.5% for the TriClip group and 88.0% for the control group.
- Annualized HFH rates were 0.22 and 0.17 for the TriClip group and the control group, respectively.
- A significantly higher proportion of TriClip patients had a KCCQ score improvement of ≥15 points from baseline to 12 months compared to control patients (49.7% vs. 26.4%, respectively).

The win ratio analysis was repeated for the Full Randomized Cohort (N=572). The number of wins, losses, and ties for the TriClip group and the control group for each component of the primary endpoint are shown in Figure 2. The win-ratio point estimate was 1.53 in favor of the TriClip group, with a 95% confidence interval of 1.14 – 2.06.

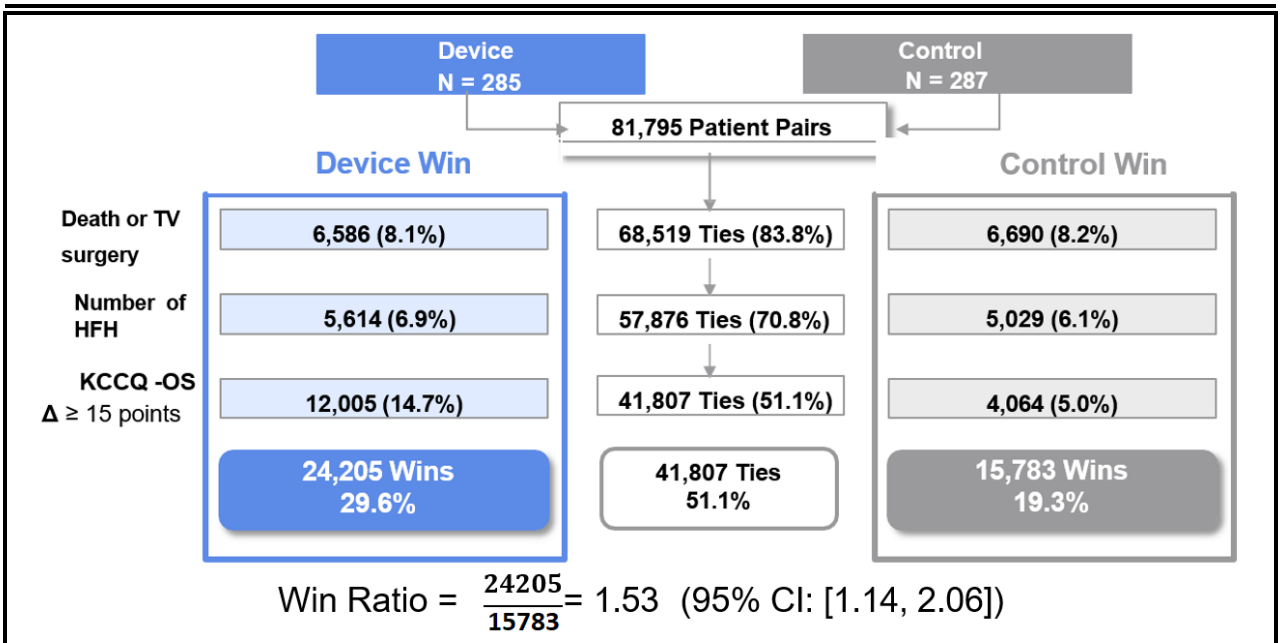

Figure 2. Win Ratio Analysis for All Available Patients – Randomized Cohort ITT Population. HFH: heart failure hospitalization; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire overall summary score; CI: confidence interval. The CI was calculated without multiplicity adjustment. The adjusted CI could be wider than presented here.

The win ratio point estimate for the full Randomized Cohort (N=572) was similar to the primary analysis cohort. The primary endpoint success continued to be driven by KCCQ improvement. In the full Randomized Cohort, the number of device wins and control wins for HFH were comparable (with very small numerical difference favoring the device group).

The TRILUMINATE pivotal trial was an unblinded (open-label) RCT. Patient reported outcomes such as the KCCQ score could be subject to the placebo effect in an unblinded trial.

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.

c. *Post hoc* analyses were performed to investigate associations between KCCQ score changes and TR severity, and between KCCQ score changes and TR severity changes. These associations are shown in Figure 3.

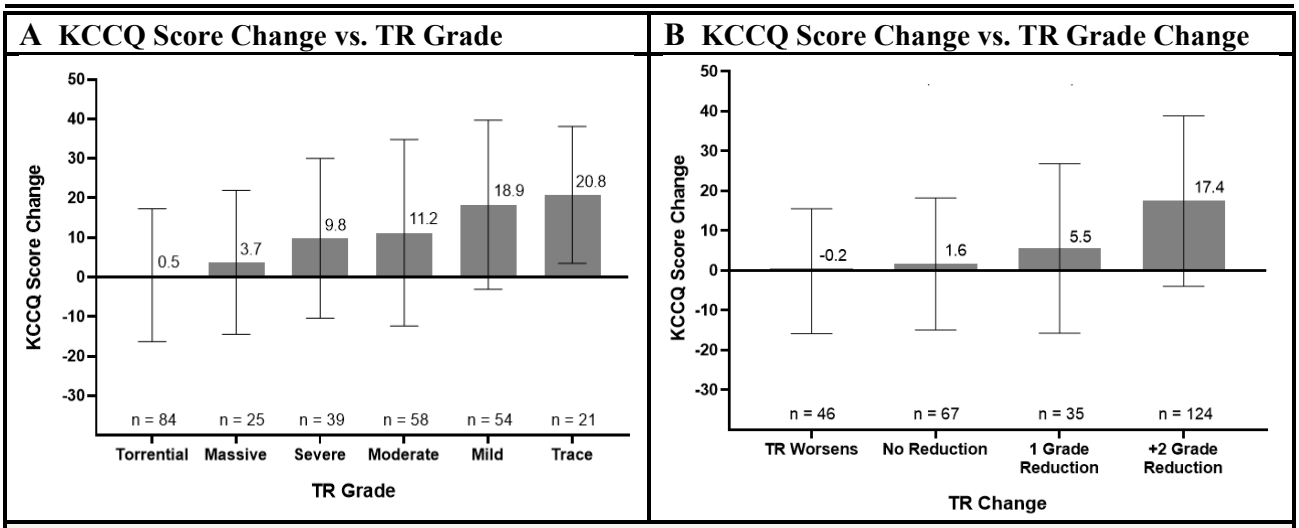

Figure 3. Association between KCCQ Score and TR at 12 Months. The error bars are standard deviations.

At 12 months, lower TR severity and greater TR severity reductions were associated with greater KCCQ score improvements. However, there were relatively wide standard deviations in KCCQ score changes at each TR severity level and in each TR severity change category.

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.

d. Among the 65 sites that contributed to the primary analysis population, 56 sites enrolled <10 patients, of which 42 enrolled <5 patients, 9 sites enrolled ≥10 patients, and one site enrolled 51 patients.

Post hoc win ratio analyses were performed to evaluate primary endpoint outcomes as a function of site enrollment for sites with ≥10 enrolled patients and sites with <10 enrolled patients. The win ratio result of the primary endpoint for the group of sites that enrolled ≥10 patients was more than two-fold higher (2.19) vs. the group of sites that enrolled <10 patients (1.06). This difference was driven by higher HFH rates and lower rates of KCCQ scores improvement in the lower enrollment site group.

The number of patients in each treatment group and the number of wins, losses, and ties in the TriClip and control groups for each component of the primary endpoint are shown in Figures 4 and 5.

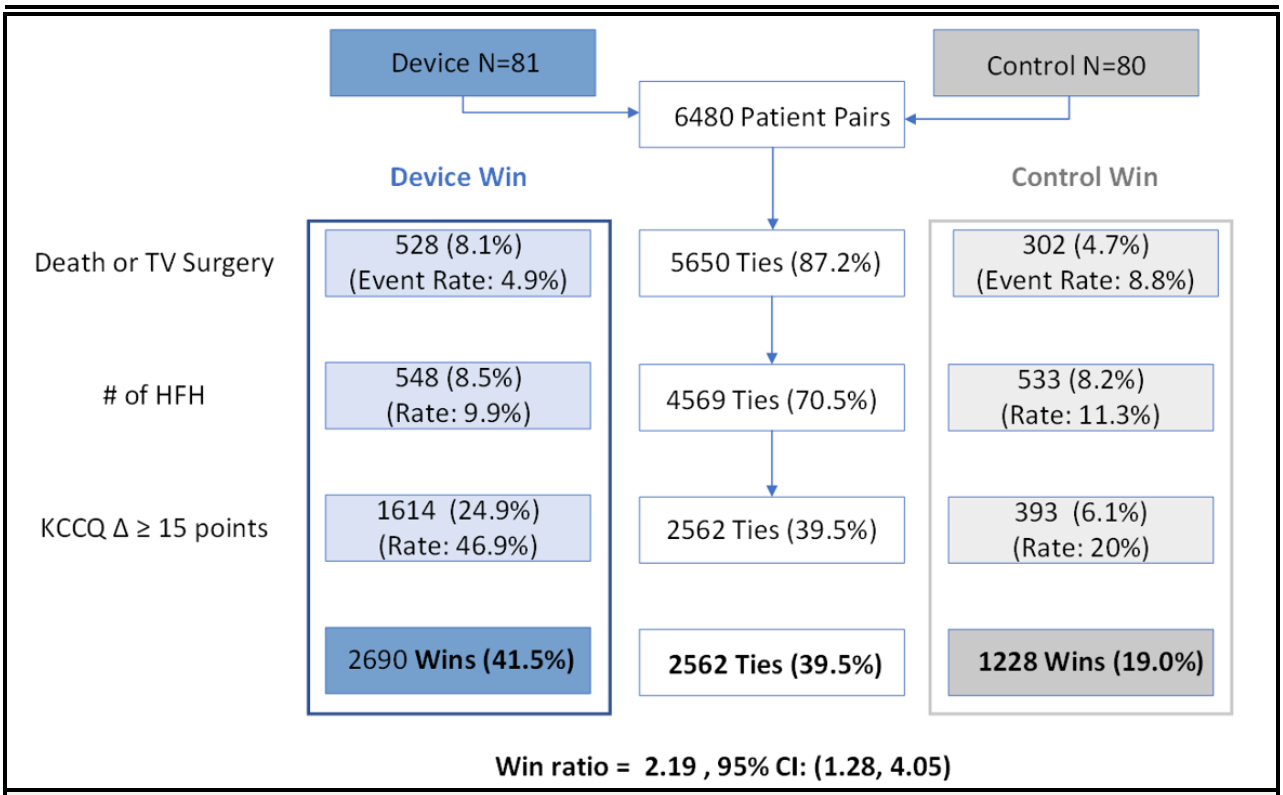

Figure 4. Win Ratio Analysis of Primary Endpoint for Sites that enrolled ≥10 Subjects - Randomized Cohort ITT Population. The confidence interval was calculated without multiplicity adjustment. The adjusted confidence interval could be wider than presented here.

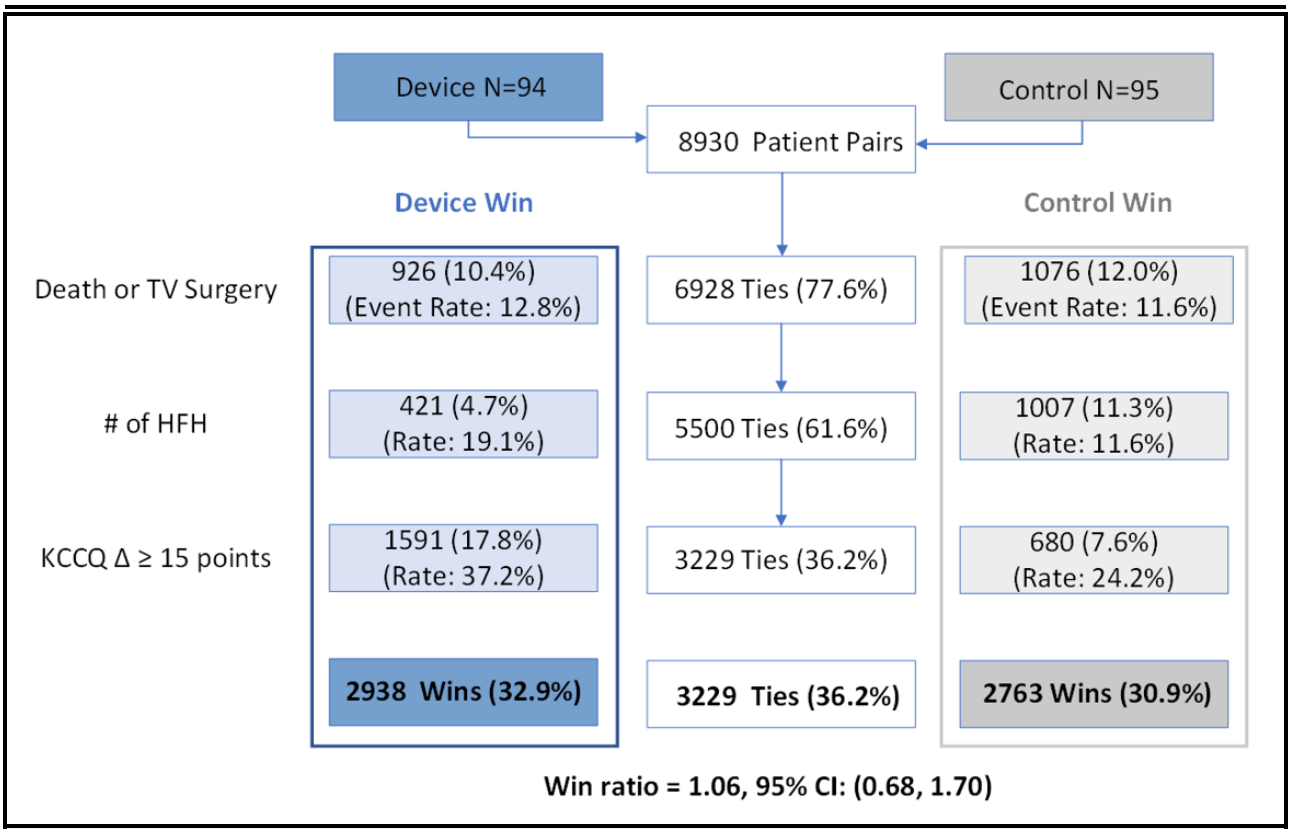

Figure 5. Win Ratio Analysis of Primary Endpoint for Sites that enrolled <10 Subjects - Randomized Cohort ITT Population. The confidence interval was calculated without multiplicity adjustment. The adjusted confidence interval could be wider than presented here.

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

3. *Descriptive Endpoint Results.* The results of key descriptive endpoints at 12 months are as follows:
    - Similar to KCCQ score changes, SF-36 score, NYHA functional class, and six-minute walk distance (6MWD) changes numerically favored the TriClip group vs. the control group.
        - The mean SF-36 physical and mental component scores increased by approximately 5 points in the TriClip group from baseline to 12 months, while the SF-36 physical and mental component scores in the control group were mostly unchanged.
        - At baseline, 59% of patients in the TriClip group and 55% in the control group were in NYHA III/IV. At 12 months, 16% of patients in the TriClip group and 40% of patients in the control group were in NYHA III/IV.

    - At 12 months, unpaired 6MWD increased by about 28 meters from baseline in the device group vs. about 13 meters in the control group (large standard deviations present).
- Annualized rates of hospitalizations for peripheral edema (0.04 vs. 0.11) and ascites (0.03 vs. 0.07) numerically favored the TriClip group vs. the control group.
- The annualized of HF hospitalization rate (0.22 vs. 0.17) was numerically higher in the TriClip group vs. the control group.
- Echocardiographic endpoints of PISA EROA, PISA regurgitant volume, and vena contracta width were reduced in the device group, which is consistent with TR reduction. There was a small (0.18 cm) reduction in mid-RVEDD in the TriClip group, and right atrial volume showed a small increase (7.78 mL) in the TriClip group.
- The MRI and CT imaging sub-study (N=82 patients at 10 sites) showed that TriClip use is associated with:
    - Favorable right atrial (RA) and right ventricular (RV) volume changes, supporting favorable RA and RV remodeling
    - Favorable changes in corrected RV ejection fraction and pulmonary forward flow

  Imaging sub-study limitations include the small sample size and uncertainty regarding long-term prognostic implications.

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

4. *Single-Arm Cohort Results.* Patients in the Single-Arm Cohort met the same enrollment criteria as the Randomized Cohort except that patients were assigned to the Single-Arm Cohort if the Eligibility Committee determined that there was a high likelihood that TR would be reduced by ≥1 grade with the TriClip device but a low likelihood that TR would be reduced to moderate or less (≤2 grades). The Single-Arm Cohort was intended to show that any reduction in TR provides health status benefit, even if TR severity was not reduced to moderate or less. TR reduction by at least 1 grade at 30 days was achieved in 98.9% (87/88) of patients, and TR reduction to moderate or less was achieved in 80% of patients.

   The primary endpoint for the Single-Arm Cohort was survival at 12 months plus a KCCQ score improvement of ≥10 points compared to baseline, tested against a 30% performance goal. In 91 patients, the primary endpoint event rate was 46.2%, with a lower 98.75% confidence limit of 34.3%, which exceeded the performance goal. Thus, the primary endpoint was met.

   CEC-adjudicated adverse event rates through 12 months are shown in Table 3. The rates of all-cause mortality, cardiovascular mortality, and heart failure hospitalization were approximately two-fold higher in the Single-Arm Cohort than in the TriClip group of the Randomized Cohort. Other event rates were comparable to the TriClip group of the Randomized Cohort.

Table 3. CEC-Adjudicated Adverse Events through 12 Months – Single-Arm Cohort AP Population.	
Event	**Event Rate N=100**
All-cause mortality	15%
Cardiovascular (VARC II definition)	11%
Heart failure-related	10%
Non-heart failure-related	1%
Non-cardiovascular (VARC II definition)	4%
Hospitalization	50%
Heart failure hospitalization	24%
Other cardiovascular hospitalization	14%
Non-cardiovascular hospitalization	26%
Tricuspid valve surgery	2%
Tricuspid valve intervention	7%
Major bleeding (greater than BARC 3a)[I]	5%
New onset renal failure[I]	0%
Transient ischemic attack (TIA)	1%
Stroke (VARC II)	0%
Myocardial infarction (VARC II definition)[I]	0%
Endocarditis requiring surgery[I]	0%
Non-elective cardiovascular surgery for TriClip-related adverse event post index procedure[I]	0%
Cardiogenic shock	1%

VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium; TIA: transient ischemic attack.
[I]Per the study CEC charter, myocardial infarction, bleeding, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip-related adverse event post index procedure were adjudicated up to 30 days post treatment visit for the device and control groups.

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.

Labeling

5. The sponsor has proposed the following indications for use statement:

   *The TriClip G4 System is indicated for the **improvement of health status** in patients with symptomatic severe tricuspid regurgitation 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**.*

   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.

Benefit/Risk

6. 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.

Post-Approval Study

7. Patients enrolled under the TriClip IDE, including those enrolled under the Continued Access Protocol (enrollment limited to 450 patients, 360 enrolled as of January 5, 2024, no study results yet available) will be followed through 5 years.

   Additionally, Abbott Medical proposes to conduct registry-based postmarket surveillance of the TriClip device through the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapy (TVT) Registry, including linkage of the TVT Registry with the Centers for Medicare and Medicaid Services (CMS) claims data. Patient outcomes will be analyzed annually through 5 years post-procedure. Patient demographics and baseline characteristics and outcomes during the first year post-procedure (including assessments performed at the index procedure, discharge, 30 days, and 12 months) will be collected through the TVT Registry. For years 2 through 5 post-procedure, outcomes (including mortality, repeat procedure for tricuspid valve-related dysfunction, and hospitalization) will be collected from the CMS claims data.

   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.

Training Program

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