SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Tricuspid Valve Repair Device, Percutaneously Delivered
Device Trade Name:	TriClip G4 System
Device Procode:	NPS
Applicant Name and Address:	Abbott Medical 177 County Road B East St. Paul, MN 55117 USA
Date of Panel Recommendation:	February 13, 2024
Premarket Approval Application (PMA) Number:	P230007
Date of FDA Notice of Approval:	April 1, 2024
Breakthrough Device:	Granted breakthrough device status on November 19, 2020, because the device can provide for more effective treatment of an irreversibly debilitating disease; as well as represents a breakthrough technology, offers significant advantages over existing approved or cleared alternatives, and is in the best interest of patients.

II. INDICATIONS FOR USE

The TriClip G4 System is indicated for improving quality of life and functional status in patients with symptomatic severe tricuspid regurgitation despite optimal medical therapy, who are at intermediate or greater risk for surgery and in whom transcatheter edge-to-edge valve repair is clinically appropriate and is expected to reduce tricuspid regurgitation severity to moderate or less, as determined by a multidisciplinary heart team.

III. CONTRAINDICATIONS

The TriClip G4 System is contraindicated in patients with the following conditions:

- Intolerance, including allergy or untreatable hypersensitivity, to procedural anticoagulation.
- Untreatable hypersensitivity to implant components (nickel-titanium alloy,
- cobalt-chromium alloy).
- Active endocarditis or other active infections of the tricuspid valve.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TriClip G4 System labeling.

V. DEVICE DESCRIPTION

The TriClip G4 System is designed to repair the native tricuspid valve without open heart surgery by grasping and bringing together (coapting) the tricuspid valve leaflets to reduce tricuspid regurgitation (TR). The device, as shown in Figure 1, is composed of the TriClip Steerable Guide Catheter (SGC), the TriClip G4 Delivery System (TDS), and Accessories.

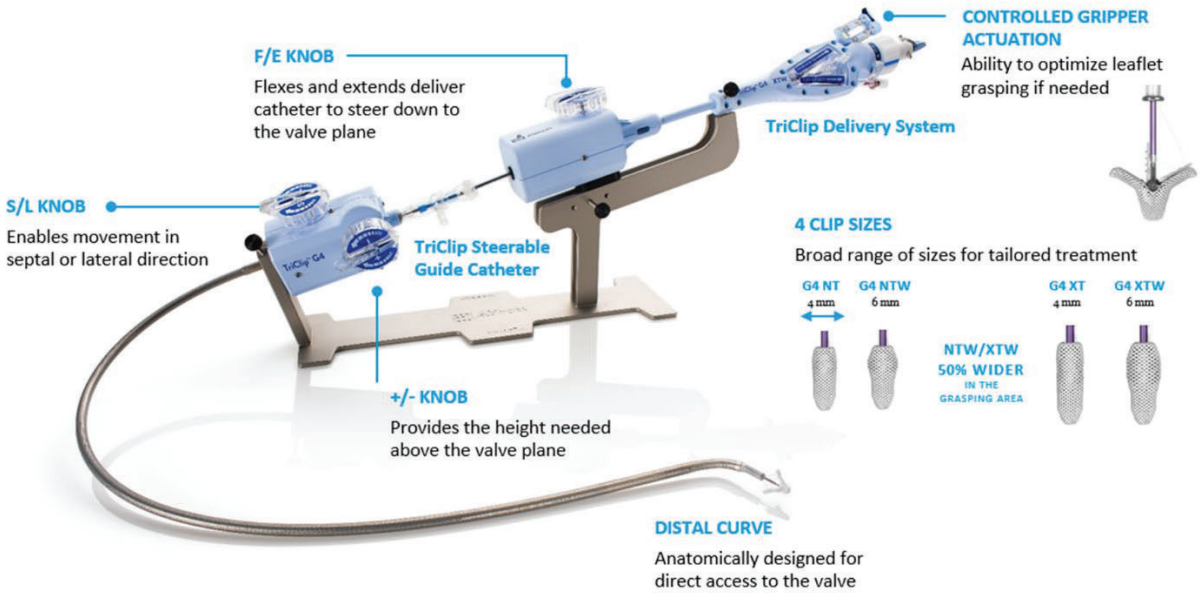


Figure 1. TriClip G4 System and Stabilizer Accessory.

TriClip Steerable Guide Catheter

The TriClip Steerable Guide Catheter's primary function is to access the right atrium, maneuver to the target location above the tricuspid valve and position the TriClip G4 Delivery System.

TriClip G4 Delivery System

The TriClip G4 Delivery System (TDS) is used to deliver, position, and place the implant of the TriClip G4 System on the tricuspid valve leaflets. The TDS is comprised of the Delivery Catheter, the Steerable Sleeve, a handle, and the TriClip G4 Implant. The user interface on the TDS allows for the adjustment of the implant to the desired position for implantation, which are open, closed or inverted.

The Delivery Catheter controls the actuation and deployment of the TriClip G4 Implant. The Delivery Catheter is controlled using the Arm Positioner, Gripper Levers, Actuator Knob, and Lock Lever.

The Steerable Sleeve facilitates the navigation and positioning of the TriClip G4 Implant in the appropriate location above the tricuspid valve.

The Implant grasps and coapts the tricuspid valve leaflets resulting in fixed approximation of the leaflets throughout the cardiac cycle. It is available in four sizes (NT, XT, NTW, XTW) and can be locked, unlocked, and repeatedly opened and closed to allow for repositioning of the implant to the target location.

Accessories

The Accessories are intended to support the TriClip G4 System during the procedure. The Accessories consist of the Stabilizer, the Support Plate, and the Lift. The Lift and the Support Plate are used outside of the sterile field to provide a stable platform during the procedure. The Stabilizer is used in the sterile field to support and position the TriClip Steerable Guide Catheter and the TriClip G4 Delivery System during the procedure.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternative TR treatments including medical therapy, surgery, and transcatheter tricuspid valve replacement. Each alternative has its own advantages and disadvantages. A patient should discuss these alternatives with his/her physician to select the treatment that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The TriClip G4 System is commercially available in the European Union, Argentina, Australia, Canada, Colombia, Costa Rica, Ecuador, Indonesia, Israel, Lebanon, Malaysia, Mexico, New Zealand, Russia, Saudi Arabia, Singapore, Taiwan, Thailand, Turkey, and United Kingdom. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the TriClip G4 System.

- Allergic reactions or hypersensitivity to latex, contrast agent, anaesthesia, device materials and drug reactions to anticoagulation, or antiplatelet drugs
- Additional treatment or surgery due to device-related complications
- Bleeding
- Nausea or vomiting
- Pain
- Pericardial effusion
- Stroke/cerebrovascular accident (CVA) and transient ischemic attack (TIA)
- System organ failure:
    - Cardio-respiratory arrest

- Blood disorders (including coagulopathy, hemolysis, and heparin induced thrombocytopenia (HIT))
- Cardiac arrhythmias (including conduction disorders, atrial arrhythmias, ventricular arrhythmias)
- Cardiac ischemic conditions (including myocardial infarction, myocardial ischemia, unstable angina, and stable angina
- Cardiac perforation
- Cardiac tamponade
- Chest pain
- Death
- Dyspnea
- Edema
- Embolization (device or components of the device)
- Endocarditis
- Fever or hyperthermia
- Fluoroscopy and transesophageal echocardiogram (TEE)-related complications:
    - Skin injury or tissue changes due to exposure to ionizing radiation
    - Esophageal irritation
    - Esophageal perforation
    - Gastrointestinal bleeding
- Hypotension or hypertension
- Infection including:
    - Septicemia
    - Worsening heart failure
    - Pulmonary congestion
    - Respiratory dysfunction, failure, or atelectasis
    - Renal insufficiency or failure
    - Cardiogenic or anaphylactic shock
- Thrombosis
- Tricuspid valve complications, which may complicate or prevent later surgical repair, including:
    - Chordal entanglement or rupture
    - Single leaflet device attachment (SLDA)
    - Dislodgement of previously implanted devices
    - Tissue damage
    - Tricuspid valve stenosis
    - Worsening, persistent or residual tricuspid regurgitation
- Vascular access complications which may require additional intervention, including:
    - Wound dehiscence,
    - Bleeding at the access site
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation or rupture, vascular occlusion
    - Embolism (air, thrombus)
    - Peripheral nerve injury
- Venous thrombosis (including deep vein thrombosis) and thromboembolism (including pulmonary embolism)

For specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Nonclinical laboratory studies on the TriClip G4 System were performed in accordance with, but not limited to, ISO 5910:2018, *Cardiovascular implants and extracorporeal systems - Cardiac valve repair devices*, along with relevant FDA guidance documents.

1. Biocompatibility

Biocompatibility of the TriClip G4 System was assessed in accordance with *ISO 10993-1, Biological Evaluation of Medical Devices - Part 1: Evaluation and testing within a risk management process*, and the FDA Guidance for Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*. The required testing for each component was determined based on the nature and duration of body contact per ISO 10993-1. The test articles consisted of patient-contacting device components after exposure to all manufacturing processes, including sterilization.

Testing to support the TriClip G4 implant was leveraged from the commercially available MitraClip G4 implant testing. The TriClip G4 implant is identical to the MitraClip G4 implant in formulation, geometry, sterilization, and manufacturing processes. The biocompatibility test results to support the TriClip G4 implant are summarized in Table 1.

Table 1. Summary of TriClip G4 Clip Biocompatibility Assessment

Biological Effect per ISO10993-1	Test Method	Results
Cytotoxicity	Colony assay	Non-cytotoxic
Sensitization	Guinea pig maximization	Non-sensitizing
Irritation/Intracutaneous Reactivity	Intracutaneous reactivity	Non-irritating
Pyrogenicity	Material-mediated rabbit pyrogen	Non-pyrogenic
Systemic Toxicity	Acute Systemic Toxicity	No biologically significant signs of systemic toxicity
	Subchronic Systemic Toxicity	No biologically significant signs of systemic toxicity
Implantation	Implant 13 Weeks - IM	Non-irritant
	Implant 4 Weeks - IM	Slight local irritant
	Implant 13 Weeks - IM	Local tissue inflammatory or tissue toxicity response (e.g., degenerative or necrotic changes) to the test article in all animals was significantly stronger with test articles than negative control
Implant Toxicity	Implant Toxicity 4 Weeks - IM	Non-irritant, and no patterns of systemic toxicity
	Implant Toxicity 13 Weeks - IM	Non-irritant, and no patterns of systemic toxicity

Biological Effect per ISO10993-1	Test Method	Results
Hemocompatibility	Hemolysis – Direct Contact and Extract	Non-Hemolytic
	Complement Activation Assay – SC5b-9	Equivalent to comparison and/or reference material
	Prothrombin Time	Clotting time greater than or not statistically significantly lower than the clotting time of the negative control and negative reference control
	Partial Thromboplastin Time	Clotting time greater than or not statistically significantly lower than the clotting time of the negative control and negative reference control
	Platelet & Leukocyte	The mean percentage value of the platelet cell counts was within 80 to 120% of the negative control
Genotoxicity	Ames – Bacterial Reverse Mutation	No biologically significant increases in reversion rates
	In vitro Mouse Lymphoma	Non-genotoxic, non-clastogenic
	Chromosomal Aberration	No biologically significant increases in aberrations rates
	In vivo Mouse micronucleus	Non-mutagenic

Testing to support the TriClip G4 delivery system was leveraged from the commercially available MitraClip G4 delivery system testing. The TriClip G4 delivery system is similar to the MitraClip G4 delivery system in terms of formulation, geometry, sterilization, and manufacturing processes, and minor differences are not expected to impact the biocompatibility device profile. The biocompatibility test results to support the TriClip G4 delivery system are summarized in Table 2.

Table 2. Summary of TriClip G4 TDS (excluding Clip), TriClip G4 Delivery Catheter, and Steerable Guide Catheter Biocompatibility Assessment

Biological Effect per ISO10993-1	Test Method	Results
Cytotoxicity	Cytotoxicity – MEM Elution Assay	Non-cytotoxic
	Cytotoxicity – Colony	Non-cytotoxic

Biological Effect per ISO10993-1	Test Method	Results
	Assay	
Sensitization	Sensitization – Guinea Pig Maximization	Non-sensitizing
Irritation	Irritation –Intracutaneous Reactivity	Non-irritant
Pyrogenicity	Material-Mediated Pyrogen	Non-pyrogenic
Systemic Toxicity	Acute Systemic Toxicity	No biologically significant signs of systemic toxicity
Hemocompatibility	Hemolysis – Direct Contact and Extract	Non-Hemolytic
	Complement Activation Assay – SC5b-9	Equivalent to comparison and/or reference material
	Partial Thromboplastin Time	Clotting time greater than or not statistically significantly lower than the clotting time of the negative control and negative reference control
	Platelet & Leukocyte	The mean percentage value of the platelet cell counts was within 80 to 120% of the negative control

2. Bench Testing

A summary of the bench testing results is provided in Table 3.

Table 3. Summary of TriClip G4 System Bench Testing

Test	Purpose	Results
Catheter dimensions	Quantitatively assess the dimensions (lengths, outer diameters, inner diameters) of the Steerable Guide Catheter (SGC), Dilator, Steerable Sleeve, Delivery Catheter and Clip	Steerable Guide Catheter, Dilator, Steerable Sleeve, Delivery catheter and Clip dimensions met all design requirements and acceptance criteria.
Curves and Steering Performance	Quantitatively assess curve positioning and steerability of the SGC and Sleeve curves	All curves met design requirements and acceptance criteria.
Clip Reliability	Confirm the Clip is able to open, lock and unlock, maintain the locked position, and raise and lower Grippers the required number of times under	Tested Clip Delivery Systems met all reliability requirements and acceptance criteria.

Test	Purpose	Results
	simulated use conditions	
Delivery Catheter Stability	Quantitatively assess the stability of the Delivery Catheter during Clip positioning	The Delivery Catheter met all design requirements and acceptance criteria.
Clip Deployment	Quantitatively assess the forces on the system when the Clip is deployed from the catheter	All deployment forces met all design requirements and acceptance criteria.
Tensile Strengths	Quantitatively assess the tensile strength of the SGC, Dilator, Steerable Sleeve and Delivery Catheter bonds	All bonds met all tensile strength design requirements and acceptance criteria.
Torsional Strengths	Quantitatively assess the torsional strength of the SGC, Dilator, Steerable Sleeve and Delivery Catheter bonds	All bonds met all torsional strength design requirements and acceptance criteria.
Delivery Catheter Functionality	Quantitatively assess the forces delivered to the by the catheter during actuation of the Clip and deployment	The Delivery Catheter met all design requirements and acceptance criteria.
Hemostasis	Confirm the catheters do not leak	The catheters met all design requirements and acceptance criteria.
Clip Functionality	Quantitatively assess the forces required to operate the Clip	The Clip met all design requirements and acceptance criteria.
Particulate	Evaluate the size and count of particulate generated by the TriClip System	Size and count of particulate generated were within acceptable limits.
Clip Finite Element Analysis	Determine mechanical stress/strain during worst-case *in vivo* loading conditions of the tricuspid valve. Results are used to assess the fatigue life of the device	Worst-case tricuspid valve loading conditions for TriClip G4 were derived, and no implant structural component fractures were predicted at 600 million cycles of life under worst-case valvular loading conditions.
Clip Fatigue Resistance	Assess durability of the Clip with *in vitro* long-term benchtop testing	Worst-case fatigue loading conditions were conservatively applied during accelerated Clip durability testing. All tested Clips remained locked, resisted opening, and were free of any fractures throughout 15 years (600 million cycles) of applied worst-case cardiac loading cycles.
Clip Corrosion	Evaluate Clip corrosion resistance	Acceptable corrosion resistance was

Test	Purpose	Results
Resistance		demonstrated per ASTM F2129 with breakdown potential (Eb) and breakdown gap (Eb-Er) test results that exceeded recommended acceptability thresholds from the literature.
MRI Compatibility Testing	Evaluate magnetic resonance imaging (MRI) safety and compatibility of the implant and ensure that the implant can be safely scanned at 1.5 Tesla and 3.0 Tesla field strengths	The TriClip G4 implants were determined to be Magnetic Resonance Conditional under the conditions listed in the device labeling.

3. Sterilization

The TriClip G4 System (TriClip G4 Delivery System and TriClip Steerable Guide Catheter) and the Silicone Pad and Fasteners are sterilized via ethylene oxide (EtO) in accordance with *EN ISO 11135-1:2014, Sterilization of health care products – Ethylene oxide – Requirements for development, validation and routine control of a sterilization process for medical devices*. The validated EtO sterilization process demonstrated a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The TriClip G4 Stabilizer, Lift, and Support Plate are provided separately as non-sterile and must be cleaned, disinfected, and/or sterilized prior to each use.

4. Packaging and Shelf-Life

The TriClip G4 System is provided to the end user in two packages, one for the TriClip G4 Delivery System and one for the TriClip Steerable Guide Catheter. The TriClip G4 Delivery System and TriClip Steerable Guide Catheter are individually packaged. The Silicone Pad and Fasteners are single use components and are included in the TriClip SGC packaging.

The TriClip G4 Delivery System and TriClip Steerable Guide Catheter packaging systems both include a thermoformed internal tray and lid. The device is placed in the tray, and the tray/lid is individually pouched in a Tyvek/Nylon pouch and heat sealed. The sealed pouch is placed in a shelf carton. The Stabilizer, Lift, and Support Plate are provided separately.

The packaging validation for the sterile components of the TriClip G4 system was conducted per *EN ISO 11607-1:2020, Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems* and *EN ISO 11607-2:2020, Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes*. The packaging validation demonstrated that the packaging system was able to maintain a sterile barrier after exposure to temperature, distribution conditioning, and accelerated aging.

The shelf life is 12 months for the TriClip G4 Delivery System and 18 months for the TriClip SGC as demonstrated by packaging integrity and product functional testing on aged samples.

B. Animal Studies

The TriClip G4 System underwent Good Laboratory Practice-compliant preclinical *in vivo* evaluations in a porcine model as summarized in Table 4. Preclinical testing of the TriClip G4 System was conducted through 90 days. Evaluation through 20 weeks was leveraged from previous studies of the MitraClip implant through at least 20 weeks, which demonstrated that the device is well encapsulated and endothelialized by 90 days. The TriClip implant is identical to the MitraClip implant in formulation, geometry, sterilization, and manufacturing processes.

Table 4: Summary of TriClip G4 Animal Studies

Chronic 30-Day and 90-Day Study	
Sample size / animal model	15 adult pigs (to achieve a sample size of at least N=6 animals at 30 days and N=6 at 90 days that reach the terminal time point)
Test articles	15 MitraClip NT clips (delivered on the tricuspid valve repair system)
Technique	The animals in the 90-day group had a sedated follow up at the 30-day time point. At both the follow up and termination procedures echocardiography and fluoroscopy was performed. At the designated time point (either 30 or 90 days), the animals were euthanized and sent to necropsy for gross evaluation and tissue harvest.
Objective	The purpose of this study was to demonstrate the safety of the TriClip implant at 30 Day (±2 days) and 90 Day (±2 days) post implant. The objective was to demonstrate safety through systemic and histological evaluation. Endpoints included: - Overall animal health (moribundity) - Device deployment and hemodynamics - Tissue response to the device
Results	There was one procedural death, one early termination, and one early death. The pre-determined safety endpoints acceptance criteria were met for all 12 animals (both the 30-day and the 90-day test groups).
Conclusion	There were no observed clinically relevant adverse gross or histological changes in the myocardium or tricuspid valves attributed to the test article. Although there were two early deaths in the study (one death prior to the early termination and one early termination), no definite cause of death was determined and, in both cases, tissue responses to the clips were typical for the time points and appeared unrelated to the cause of death.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study, the TRILUMINATE Pivotal trial (NCT03904147), to establish a reasonable assurance of safety and effectiveness of the TriClip G4 System for patients with symptomatic severe TR despite optimal medical therapy (OMT). The study was conducted under IDE# G170118. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The TriClip System and TriClip G4 System (a next-generation system) were used in the TRILUMINATE Pivotal trial. Minor design changes were made to the TriClip G4 Delivery System compared to the TriClip Delivery System, but the same TriClip Steerable Guide Catheter was used with both generations. The TriClip G4 System added two additional clip sizes compared to the TriClip system, resulting in a total of four clip length and width options with similar designs and no difference in materials or principle of operation. The minor changes and additional implant sizes were not anticipated to impact TRILUMINATE Pivotal trial outcomes.

A. Study Design

The TRILUMINATE Pivotal trial was a prospective, multicenter, randomized (1:1), controlled clinical trial designed to test the superiority of transcatheter tricuspid repair using the TriClip device plus OMT (device group) vs. OMT alone (control group) in subjects with severe symptomatic TR who were determined by the site's local heart team to be at intermediate or greater risk for mortality or morbidity with open heart surgery. In addition to the Randomized Cohort, the trial also included a Single-Arm Cohort. After being enrolled into the trial, subjects were assigned to a cohort based on the following criteria:

- Randomized Cohort: High likelihood that the TriClip could reduce TR to moderate or less (i.e., less than or equal to grade 2).
- Single-Arm Cohort: High likelihood that the TriClip could reduce TR by at least 1 grade but a low likelihood that TR will be reduced to moderate or less.

This determination was based on multiple considerations, including but not limited to:

- Baseline TR severity
- The presence of cardiovascular implantable electronic device (CIED) leads across the tricuspid valve
- The coaptation gap width

A Cardiac Computed Tomography/Magnetic Resonance Imaging (CT/MRI) imaging sub-study (referred to as imaging sub-study) was conducted for a maximum of 100 subjects to provide insights into cardiac reverse remodeling and quantitative measurements to assess TR severity and the effect of TR changes on clinical endpoints.

The TRILUMINATE Pivotal trial utilized: an independent Eligibility Committee (EC), which confirmed that the subject met enrollment criteria, assessed anatomic suitability for the

TriClip device, and assigned eligible patients to the Randomized or Single-Arm Cohort; an Echocardiography Core Laboratory (ECL), which reviewed screening echocardiography images to confirm patient eligibility and assessed TR severity, right ventricular measurements, and other measures at baseline and follow-up; a Clinical Events Committee (CEC), which adjudicated all adverse events per pre-established definitions; and a Data Monitoring Committee (DMC), which monitored the safety of subjects throughout trial. The study was unblinded except for the research staff administering Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk test, SF-36, and New York Heart Association (NYHA) functional classification assessments.

The trial was to enroll up to 550 patients in the Randomized Cohort and up to 200 patients in the Single-Arm Cohort. Up to 3 roll-in patients per implanter could be enrolled at sites with implanters who did not have prior or recent experience using the TriClip device.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the TRILUMINATE Pivotal trial was limited to patients who met the following inclusion criteria:

- In the judgment of the site local heart team, subject has been adequately treated per applicable standards (including medical management) and stable for at least 30 days as follows:
    - Optimized medical therapy for TR treatment (e.g., with diuretics)
    - Medical and/or device therapy for mitral regurgitation, atrial fibrillation, coronary artery disease and heart failure

  The EC confirmed that the subject has been adequately treated medically.
- Subject was symptomatic with severe TR despite optimal medical ± device treatment. TR severity was determined by the assessment of a qualifying transthoracic echocardiogram (TTE) and confirmed by the ECL. The ECL also requested a transoesophageal echocardiogram (TEE) to confirm TR etiology. Note: If any cardiac procedure(s) occurred after eligibility was determined, TR severity was re-assessed 30 days after the cardiac procedure(s).
- The site heart team cardiac surgeon concurred that the patient was at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.
- NYHA Functional Class II, III or ambulatory class IV
- In the judgment of the TriClip implanting Investigator, femoral vein access was feasible and could accommodate a 25 Fr catheter.
- Age ≥18 years at time of consent.
- Subject provided written informed consent prior to any trial related procedure.

Patients were not permitted to be enrolled in the TRILUMINATE Pivotal trial if they met any of the following exclusion criteria:

- Systolic pulmonary artery pressure (sPAP) >70 mmHg or fixed pre-capillary pulmonary hypertension as assessed by right heart catheterization (RHC).
- Severe uncontrolled hypertension: Systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure DBP) ≥110 mm Hg .
- Prior tricuspid valve procedure that would interfere with placement of the TriClip device.

- Indication for left-sided heart intervention (e.g., for severe aortic stenosis, severe mitral regurgitation) or pulmonary valve correction in the prior 60 days. Note: Patients with concomitant mitral and tricuspid valve disease had option of undergoing MR treatment and waiting 60 days prior to being reassessed for the trial.
- Pacemaker or ICD leads that would prevent appropriate placement of the TriClip device.
- Tricuspid valve stenosis, defined as a tricuspid valve orifice of ≤1.0 cm^2 and/or a mean gradient ≥5 mmHg as measured by the ECL.
- Left ventricular ejection fraction (LVEF) ≤20%
- Tricuspid valve leaflet anatomy which may preclude clip implantation, proper device positioning on the leaflets or sufficient reduction in TR. This may include:
    - Evidence of calcification in the grasping area.
    - Presence of a severe coaptation defect (> 2cm) of the tricuspid leaflets.
    - Severe leaflet defect(s) preventing proper device placement.
    - Ebstein Anomaly - Identified by having a normal annulus position while the valve leaflets are attached to the right ventricular walls and interventricular septum.
- Tricuspid valve anatomy not evaluable by TTE and TEE.
- Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated).
- MI or known unstable angina within prior 30 days.
- Percutaneous coronary intervention within prior 30 days.
- Hemodynamic instability defined as systolic blood pressure (SBP) <90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
- Cerebrovascular accident (CVA) within the prior 90 days.
- Chronic dialysis.
- Bleeding disorders or hypercoagulable state.
- Active peptic ulcer or active gastrointestinal (GI) bleeding.
- Contraindication, allergy, or hypersensitivity to dual antiplatelet and anticoagulant therapy.
  Note: Contraindication to either antiplatelet or anticoagulant therapy (individually not both therapies) was not an exclusion criterion.
- Ongoing infection requiring antibiotic therapy (if temporary illness, patients could enroll 30 days after discontinuation of antibiotics with no active infection).
- Known allergy or hypersensitivity to device materials.
- Evidence of intracardiac, inferior vena cava (IVC), or femoral venous mass, thrombus, or vegetation.
- Life expectancy of less than 12 months.
- Subject currently participating in another clinical trial that had not yet reached its primary endpoint.
- Subject currently participating in another clinical investigation for valvular heart disease(s).
- Pregnant or nursing subjects and those who planned pregnancy during the clinical investigation follow-up period. Female subjects of child-bearing potential were required to have a negative pregnancy test done within 7 days of the baseline visit per site standard

test. Female patients of childbearing potential instructed to use safe contraception (e.g., intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release). It was accepted, in certain cases, to include subjects having a sterilized regular partner or subjects using a double barrier contraceptive method.

- Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

2. Follow-up Schedule

All subjects were required to have a treatment visit within 14 days of randomization (within 14 days of the baseline visit for Single-Arm Cohort subjects). At this visit, device group patients underwent the TriClip procedure, and control group patients were seen by a heart failure specialist and underwent a physical exam, including vital signs, cardiac health status, and evaluation of heart failure medications.

The follow-up time points were at 30 days, 6 months, and 12 months from the date of the treatment visit and will continue annually through 5 years. The device group patients were also assessed at hospital discharge.

Baseline and follow-up visit assessments included physical assessments, medical history laboratory tests, imaging studies, and health status surveys. Adverse events and complications were recorded at all visits.

3. Statistical Analysis Populations

The analysis populations for the TRILUMINATE Pivotal trial are shown in Table 5.

Table 5: Statistical Analysis Populations

Analysis Population	Definition
Randomized Cohort	
Intent-to-Treat (ITT)	All patients randomized in the trial.
As-Treated (AT)	ITT patients grouped by treatment received.*
Per Protocol (PP)	ITT patients who received assigned randomized treatment according to protocol and followed all major study requirements.
Attempted Procedure (AP)	Patients randomized to the device group with an attempted TriClip procedure (i.e., femoral vein puncture performed).
Single-Arm Cohort	
Attempted Procedure (AP)	Patients with an attempted TriClip procedure (i.e., femoral vein puncture performed).

*Patients randomized to the device group who died or had heart failure hospitalization prior to the TriClip procedure were considered to be in the Control group regardless of randomization. Patients randomized to the device group who died or had heart failure hospitalization after (but not prior to) a TriClip procedure are considered to be in the device group regardless of randomization. Patients who did not experience death or heart failure hospitalization at any time during follow-up were assigned to the group that constituted >50% of their follow-up duration.

4. Randomized Cohort Clinical Endpoints

Primary Endpoint

The primary safety and effectiveness endpoint was a hierarchical composite of the following components at 12 months:

1. Time to all-cause death or tricuspid valve surgery
2. Number of heart failure (HF) hospitalizations
3. An improvement of ≥15 points in KCCQ score from baseline

The hypothesis for the primary endpoint was as follows:

H_0: None of the components are different between the Treatment and Control group
H_1: At least one component is different between the Treatment and Control group

The alternative hypothesis that the device group was superior to the control group in at least one component of the primary endpoint was tested using the Finkelstein-Schoenfeld methodology (Finkelstein et al. 1999)[1] at a two-sided significance level of 5%.

A sample size of 350 randomized patients was simulated to provide approximately 83% power to reject the null hypothesis at a two-sided significance level of 5%.

The 350 randomized ITT patients was defined as the Primary Analysis Population.

As a supplementary analysis, the win-ratio method (Pocock et al. 2012)[2] was used to evaluate the treatment effect of the composite endpoint. In this analysis, each pair of patients from the device group and the control group were compared in the order of the hierarchy defined above, and the win ratio was defined as the number of winners divided by the number of losers in the device group.

An adaptive design with sample size re-estimation was planned when the first 150 randomized patients completed the 12-month follow-up visit. At that time, an independent statistician was unblinded to the interim data and calculated the conditional power for the primary endpoint. The interim analysis concluded that the original 350-patient sample size would provide adequate power to assess the primary endpoint.

Secondary Endpoints

Four powered secondary safety and effectiveness endpoints were assessed hierarchically at 12 months (see Table 6)

Table 6. Ordered List of Secondary Endpoints for Hierarchical Testing (Randomized Cohort)

Order	Secondary Endpoint	Null and Alternative Hypotheses	Analysis Population	Significance Level
1	Freedom from MAEs at 30 days post-procedure	$H_0: P_D(MAEs) \leq 90\%$ $H_1: P_D(MAEs) > 90\%$	AP	2.5% (one-sided)
2	Change in KCCQ score at 12 months over baseline	$H_0: \mu_D(\Delta KCCQ) - \mu_C(\Delta KCCQ) = 0$ $H_1: \mu_D(\Delta KCCQ) - \mu_C(\Delta KCCQ) \neq 0$	ITT	5% (two-sided)
3	TR reduction to moderate or less at 30-day visit	$H_0: P_D(TR \leq 2) - P_C(TR \leq 2) = 0$ $H_1: P_D(TR \leq 2) - P_C(TR \leq 2) \neq 0$	ITT	5% (two-sided)
4	Change in 6MWD at 12 months over baseline	$H_0: \mu_D(\Delta 6MWD) - \mu_C(\Delta 6MWD) = 0$ $H_1: \mu_D(\Delta 6MWD) - \mu_C(\Delta 6MWD) \neq 0$	ITT	5% (two-sided)

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; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance; AP: attempted procedure; ITT: intent-to-treat; H_0: null hypothesis; H_1: alternative hypothesis; P_D(MAEs): proportion of TriClip patients free from MAEs; μ_D(ΔKCCQ) and μ_C(ΔKCCQ): mean KCCQ score change in TriClip and control patients; P_D TR≤2) and P_C(TR≤2): proportion of TriClip and control

patients with ≤moderate TR; μ_D(Δ6MWD): mean 6MWD change in TriClip and control patients.

Additional Outcomes

Additional outcomes assessed for the Randomized Cohort included the following:

- Technical success at exit from procedure room: alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a clip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure
- Device success at 30-days post-procedure: alive with original intended clip(s) in place, and no additional surgical or interventional procedures related to access or device since completion of the original procedure, and intended performance of the clip(s) i.e., ≥1 grade improvement in TR severity, no embolization, single leaflet device attachment, absence of para-device complications)
- Procedural success at 30-days post-procedure: device success, and no device- or procedure-related serious adverse event
- Echocardiographic parameters of tricuspid valve and cardiac function
- Clinical and functional parameters

5. Single-Arm Cohort Clinical Endpoints

Primary Endpoint

The primary safety and effectiveness endpoint was survival at 12 months plus a KCCQ score improvement of ≥10 points compared to baseline, tested in the AP population.

The null (H_0) and alternative (H_1) hypotheses for the primary endpoint were as follows:

$H_0: P_D \leq 30\%$
$H_1: P_D > 30\%$

where 30% was a performance goal based on the expected TriClip patient survival rate and the KCCQ result observed in the COAPT trial control group (NCT01626079; Stone et al. 2018)[3]. A sample size of 100 patients was estimated to provide 90% power to reject the null hypothesis at a one-sided significance level of 2.5%.

Secondary Endpoints

Five powered secondary safety and effectiveness endpoints were assessed hierarchically at 12 months (see Table 7).

Table 7. Ordered List of Secondary Endpoints for Hierarchical Testing – Single-Arm Cohort.

Order	Secondary Endpoint	Null and Alternative Hypotheses	Analysis Population	Significance Level
1	TR reduction by at least one grade at 30 days post-procedure	H_0: $P_D(\Delta TR \geq 1) \leq 50\%$ H_1: $P_D(\Delta TR \geq 1) > 50\%$	AP	2.5% (one-sided)
2	Freedom from MAEs at 30 days post-procedure	H_0: $P_D(MAEs) \leq 80\%$ H_1: $P_D(MAEs) > 80\%$	AP	2.5% (one-sided)
3	Change in 6MWD at 12 months over baseline	H_0: $\mu_D(\Delta 6MWD) \leq 0$ H_1: $\mu_D(\Delta 6MWD) > 0$	AP	2.5% (one-sided)
4	Freedom from all-cause mortality and tricuspid valve surgery at 12 months	H_0: $P_D(Survival) \leq 65\%$ H_1: $P_D(Survival) > 65\%$	AP	2.5% (one-sided)
5	Recurrent HF hospitalizations at 12 months	H_0: $\lambda_D(PRE) \leq \lambda_D(POST)$ H_1: $\lambda_D(PRE) > \lambda_D(POST)$	AP	2.5% (one-sided)

TR: tricuspid regurgitation; 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; 6MWD: 6-minute walk distance; AP: attempted procedure; HF: heart failure; H_0: null hypothesis; H_1: alternative hypothesis; P_D ΔTR≥1): proportion of TriClip patients with TR reduction by at least 1 grade; P_D(MAEs): probability of freedom from any MAE; μ_D Δ6MWD): mean 6MWD change; λ_D(PRE) and λ_D(POST): annualized event rates for recurrent HF hospitalizations within 12 months pre- and post-procedure.

B. Accountability of PMA Cohort

The database for this PMA included data collected through April 24, 2023. A total of 936 eligible patients were enrolled between August 21, 2019 and June 29, 2022 at 68 investigational sites in the US, Canada, and Europe. Of these patients, 901 were approved by the Eligibility Committee and were randomized or had an attempted procedure, including 141 in the Roll-in Cohort, 572 in the Randomized Cohort, and 188 in the Single-Arm Cohort. Patient accountability is shown in Figure 2. As planned, the primary endpoint analysis was performed on the first 350 patients (296 in the US, 38 in Canada, and 16 in Europe) in the Randomized Cohort and the first 100 patients with an attempted procedure in the Single-Arm Cohort.

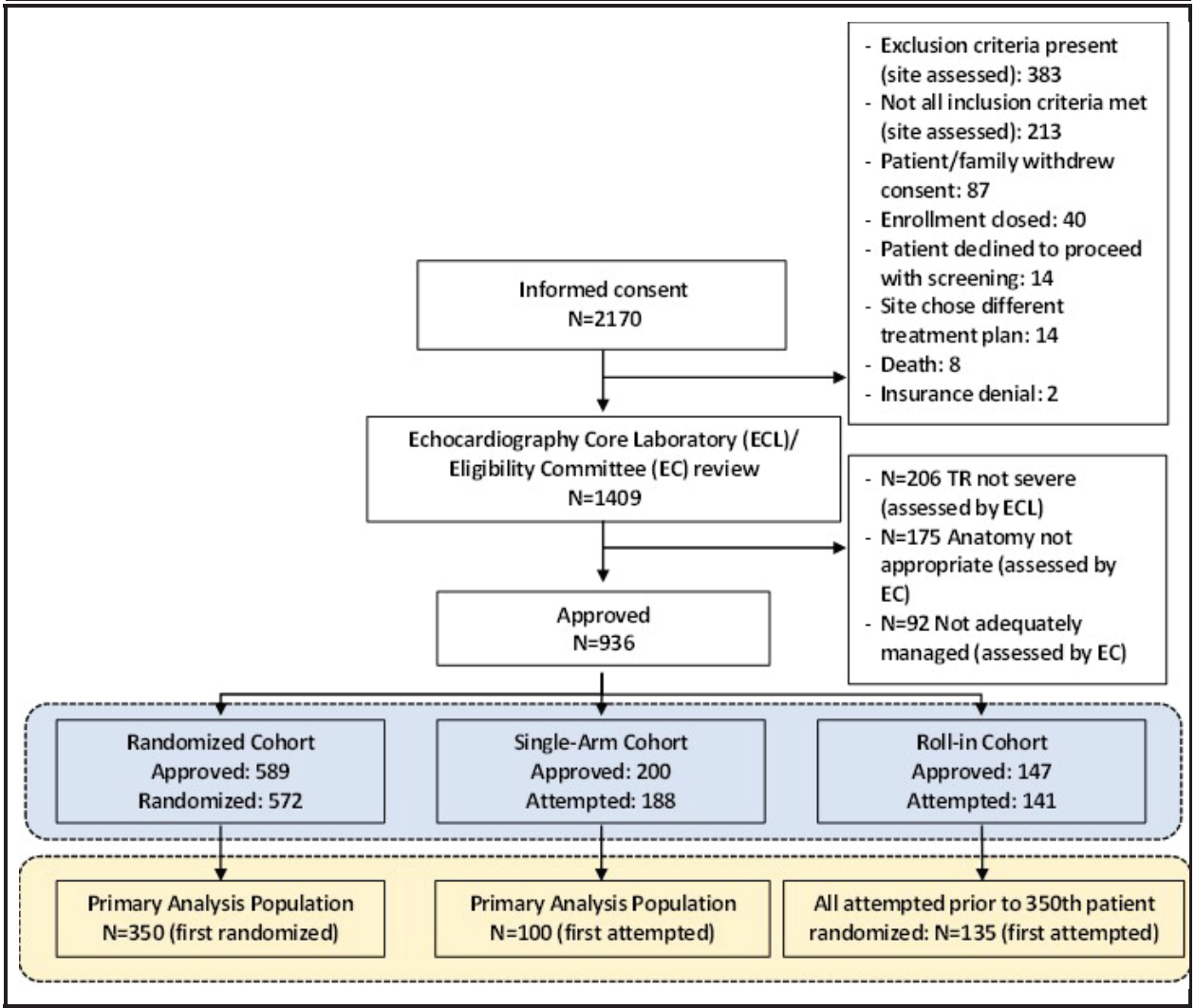


Figure 2. Patient Accountability.

At the time of database lock, of the Randomized Cohort patients eligible for the for the 1-year visit, 100% in the device group and 99% in the control group completed the visit (Table 8, Figure 3.) In the single-arm cohort, 96% of eligible patients completed the 1-year visit (Figure 4).

Table 8. Visit Compliance.

	Device Group			Control Group			Single-Arm Cohort		
Visit	**Expected Visits**	**Actual Visits**	**Compliance[1]**	**Expected Visits**	**Actual Visits**	**Compliance[1]**	**Expected Visits**	**Actual Visits**	**Compliance[1]**
Baseline	175	175	N/A	175	175	N/A	100	100	N/A
Index Procedure or Treatment Visit	172	172	100%	174	174	100%	100	100	100%
Discharge (Device group only)	172	172	100%	-	-	-	100	100	100%
30-Day Visit	170	168	99%	172	162	94%	97	96	99%
6-Month Visit	157	155	99%	158	155	98%	90	89	99%
12-Month Visit	152	152	100%	152	150	99%	84	81	96%
Overall Follow-up[2]	**823**	**819**	**99%**	**656**	**641**	**98%**	**471**	**466**	**99%**

[1]Compliance calculated as Actual/Expected, where Expected excludes subject withdrawal.

[2]Overall follow-up includes discharge through 12-month visit (excludes baseline visit).

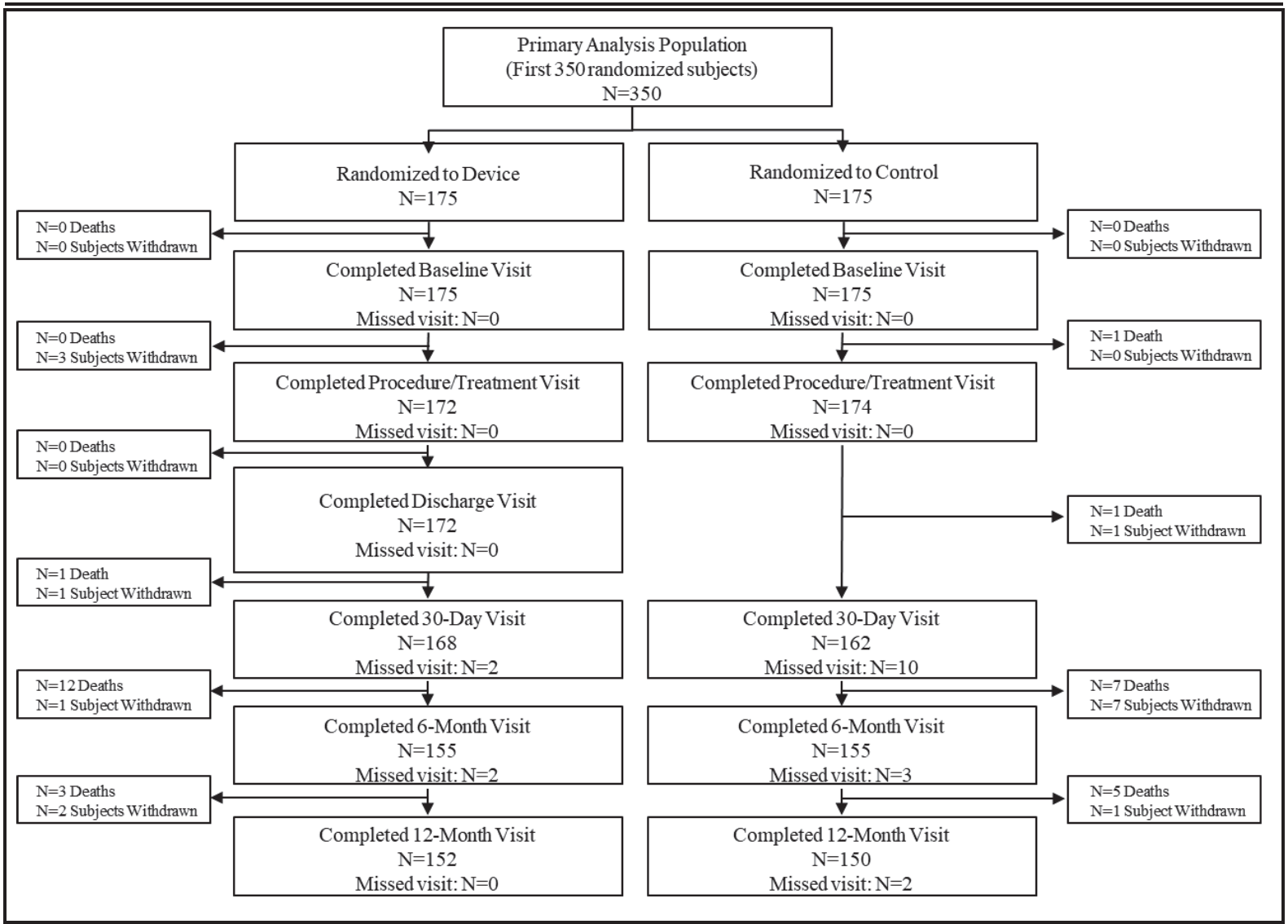


Figure 3. Disposition of Subjects – Randomized Cohort.

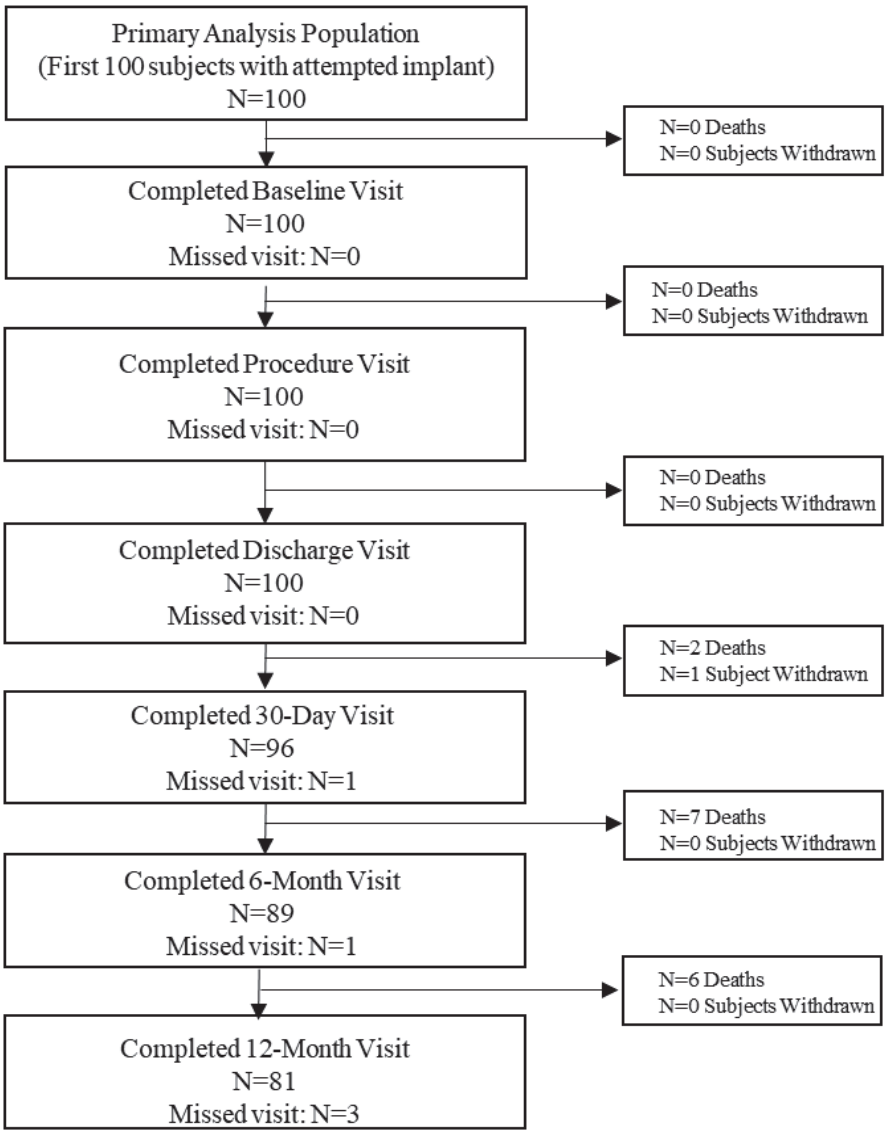


Figure 4. Disposition of Subjects – Single Arm Cohort.

C. Study Population Demographics and Baseline Characteristics

Patient demographics and baseline characteristics for the primary analysis population of the Randomized Cohort and Single-Arm Cohort are shown in Table 9.

In both the randomized and single-arm cohorts, the majority of patients were Caucasian and just over half were female. Over 90% of Randomized Cohort patients had functional TR and atrial fibrillation, and most patients were in NYHA functional class II/III with an average KCCQ score in the mid-50s. Torrential TR was present in approximately half of the patients in both the device and control groups. Medication use at baseline was similar between the two randomized groups. In all, demographics and baseline characteristics were similar between Randomized Cohort Device and Control groups.

Compared to the Randomized Cohort, a higher proportion of Single-Arm Cohort patients had torrential TR (74.0% vs. 50.9%), CIED-related TR (5.1% vs. 0%), a pacemaker or defibrillator (35.0% vs. 16.0%), and larger coaptation gaps (7.4 ± 2.7 vs. 5.5 ± 1.8 mm). Some baseline covariate differences were expected between the Randomized and Single-Arm cohorts as TR severity and complex tricuspid anatomy were considered when assigning patients to each cohort.

Table 9. Demographics and Baseline Characteristics – Primary Analysis Population.

Demographics and Baseline Characteristics	Summary Statistic*		
	Randomized Cohort (N=350)		Single-Arm Cohort (N=100)
	Device (N=175)	Control (N=175)	
Demographics			
Age	78.0 ± 7.4 (175)	77.8 ± 7.2 (175)	80.4 ± 6.2 (100)
Sex			
Male	44.0% (77/175)	46.3% (81/175)	47.0% (47/100)
Female	56.0% (98/175)	53.7% (94/175)	53.0% (53/100)
Race			
Caucasian	85.1% (149/175)	81.7% (143/175)	87.0% (87/100)
Black/African American	4.0% (7/175)	5.7% (10/175)	7.0% (7/100)
Asian	4.0% (7/175)	4.0% (7/175)	3.0% (3/100)
American Indian/Alaska Native	0.6% (1/175)	0.0% (0/175)	0.0% (0/100)
Native Hawaiian/Pacific Islander	0.0% (0/175)	0.0% (0/175)	0.0% (0/100)
Declined or unable to disclose	6.3% (11/175)	8.6% (15/175)	3.0% (3/100)
Ethnicity			
Hispanic or Latino	2.9% (5/175)	5.1% (9/175)	4.0% (4/100)
Not Hispanic or Latino	93.1% (163/175)	87.4% (153/175)	94.0% (94/100)

Declined/unknown	4.0% (7/175)	7.4% (13/175)	2.0% (2/100)
Body mass index (BMI, kg/m^2)	27.0 ± 5.8 (175)	26.9 ± 5.2 (175)	26.3 ± 5.3 (100)
Medical history			
Atrial fibrillation	87.4% (153/175)	93.1% (163/175)	93.0% (93/100)
Chronic obstructive pulmonary disease	10.9% (19/175)	13.7% (24/175)	22.0% (22/100)
CRT/CRT-D/ICD/permanent pacemaker	16.0% (28/175)	13.7% (24/175)	35.0% (35/100)
Dyslipidemia	66.9% (117/175)	52.6% (92/175)	64.0% (64/100)
Hypertension	81.1% (142/175)	80.6% (141/175)	83.0% (83/100)
Liver disease	6.3% (11/175)	9.1% (16/175)	3.0% (3/100)
Renal disease	35.4% (62/175)	35.4% (62/175)	36.0% (36/100)
Peripheral vascular disease	9.1% (16/175)	10.3% (18/175)	11.0% (11/100)
Prior aortic valve intervention	15.4% (27/175)	15.4% (27/175)	11.0% (11/100)
Prior mitral valve intervention	25.7% (45/175)	24.0% (42/175)	36.0% (36/100)
Echocardiography measurements			
TR severity			
Trace	0.0% (0/173)	0.0% (0/165)	0.0% (0/96)
Mild	0.0% (0/173)	0.0% (0/165)	0.0% (0/96)
Moderate	2.3% (4/173)	1.2% (2/165)	0.0% (0/96)
Severe grade 3 (severe)	25.4% (44/173)	29.7% (49/165)	9.4% (9/96)
Severe grade 4 (massive)	21.4% (37/173)	18.2% (30/165)	16.7% (16/96)
Severe grade 5 (torrential)	50.9% (88/173)	50.9% (84/165)	74.0% (71/96)
TR etiology			
Functional	94.8% (165/174)	92.9% (158/170)	85.9% (85/99)
Degenerative	2.3% (4/174)	1.2% (2/170)	5.1% (5/99)
Mixed	2.9% (5/174)	5.9% (10/170)	4.0% (4/99)
Pacer-related	0.0% (0/174)	0.0% (0/170)	5.1% (5/99)
Coaptation gap (mm)	5.5 ± 1.8 (137)	5.2 ± 1.7 (142)	7.4 ± 2.7 (75)
Health status			
KCCQ overall summary score	56.0 ± 23.4 (175)	54.1 ± 24.2 (174)	54.5 ± 22.6 (99)
6MWD (m)	240.5 ± 117.1 (164)	253.6 ± 129.1 (169)	237.7 ± 120.4 (97)
NYHA functional class			
Class I	0.0% (0/175)	0.0% (0/175)	0.0% (0/100)

Class II	40.6% (71/175)	44.6% (78/175)	41.0% (41/100)
Class III	57.1% (100/175)	52.0% (91/175)	53.0% (53/100
Class IV	2.3% (4/175)	3.4% (6/175)	6.0% (6/100)
Medication use			
Beta-blockers	72.6% (127/175)	73.1% (128/175)	74.0% (74/100)
ACE-I or ARBs	42.3% (74/175)	45.1% (79/175)	41.0% (41/100)
Vasodilators	10.9% (19/175)	12.0% (21/175)	12.0% (12/100)
Diuretics	97.1% (170/175)	98.9% (173/175)	98.0% (98/100)

CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; ICD: implantable cardioverter-defibrillator; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance; NYHA: New York Heart Association; ACE-I: angiotensin-converting enzyme 1; ARBs: angiotensin receptor blockers.
*Continuous measures – Mean ± standard deviation (total no.); Categorical measures - % (no./total no.)

D. Safety and Effectiveness Results

The analysis of safety and effectiveness were primarily based on the Randomized Cohort of 350 patients available for the 12-month evaluation. The key safety outcomes for this study included mortality, need for tricuspid valve surgery, and major adverse event rates as assessed by the primary and secondary endpoints. All CEC-adjudicated adverse effects are reported in Table 13 for the Randomized Cohort and Table 23 for the Single-Arm Cohort. The key effectiveness outcomes included number of heart-failure hospitalizations, improvement in KCCQ score, TR reduction and 6-minute walk distance (6MWD) as assessed by the primary and secondary endpoints and summarized below.

1. Primary Endpoint – Randomized Cohort

The Randomized Cohort primary safety and effectiveness endpoint analysis results are shown in Table 10. The Finkelstein-Schoenfeld test statistic result was 2.16 with a 2-sided p-value of 0.0311, which is less than the pre-specified two-sided significance level of 0.05. Thus, the primary endpoint was met indicating the device group was superior to the control group.

Table 10. Primary Analysis Result – Randomized Cohort ITT Population.

Primary Endpoint	Test Statistic	p-Value (2-sided)	Significance Level (2-sided)	Result
Finkelstein-Schoenfeld analysis	2.16	0.0311	0.05	Superiority endpoint met

The supplemental win ratio analysis is shown in Figure 5. The win ratio of the device group vs. the control group was 1.44 (95% confidence interval of 1.03 - 2.08). The number of wins in the device group and control group were similar for death or TV surgery, and there were slightly more wins in the control group for heart failure

hospitalization (6% in the device group vs 10% in the control group). The primary endpoint success was driven by KCCQ score improvement of at least 15 points, which had 21% wins in the device group and 7% wins in the control group.

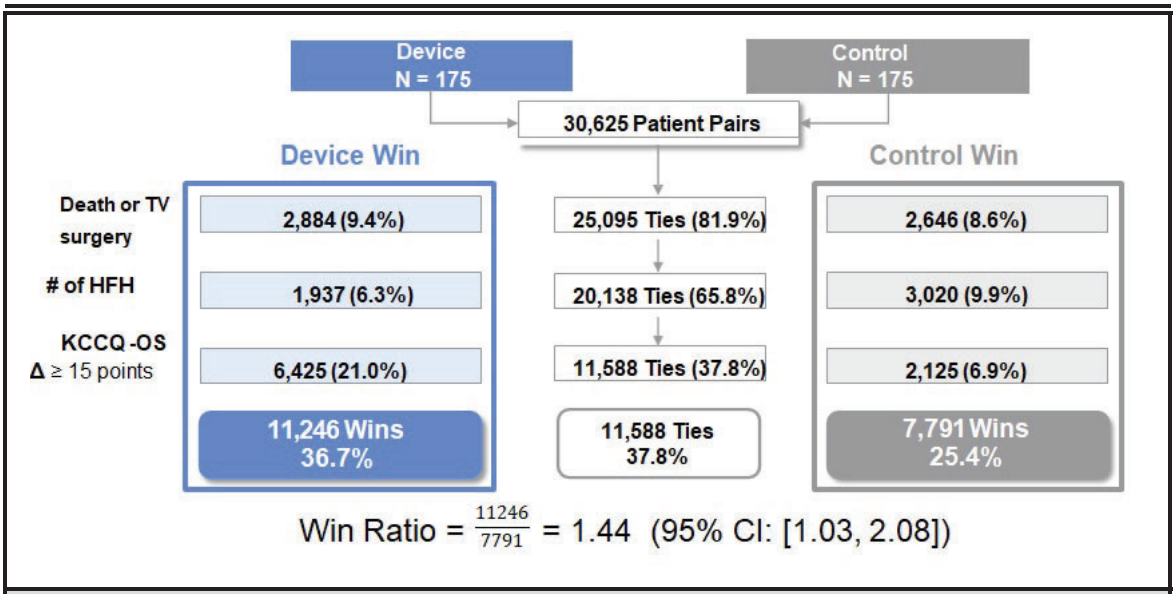


Figure 5. Win Ratio Analysis of the Randomized Cohort Primary Endpoint – ITT Population. TV: tricuspid valve; HFH: heart failure hospitalization; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

2. Secondary Endpoint – Randomized Cohort

The results of the powered secondary safety and effectiveness endpoints are shown in Table 11. The endpoints of freedom from major adverse events (MAEs) at 30 days post-procedure, change in KCCQ score at 12 months vs. baseline, and TR reduction to moderate or less at 30 days were met. There was a numerically smaller reduction in 6MWD at 12 months in the device group vs. the control group (-8.12 vs. -25.17 meters), but the difference was not statistically significant, and standard deviations were large. Therefore, the 6MWD endpoint was not met.

Table 11. Summary of Powered Secondary Endpoint Results – Randomized Cohort ITT Population (Paired).

Order	Secondary Endpoint	Summary Statistics		p-Value	Result
		Device Arm	Control Arm		
1	Freedom from MAEs at 30 days post-procedure	98.3% [96.3%, 100%]*	-	< 0.0001	Endpoint met
2	Change in KCCQ score at 12 months over baseline	12.34 (1.75)†	0.61 (1.75)†	< 0.0001	Endpoint met

3	TR reduction to moderate or less at 30-day visit	87.0% (141/162)‡	5.4% (8/147)‡	<0.0001	Endpoint met
4	Change in 6MWD at 12 months over baseline‖ (meters)	-8.12 (10.50)†	-25.17 (10.31)†	0.2482	**Endpoint not met**

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; TR: tricuspid regurgitation; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance.
*Kaplan-Meier estimate [95% confidence interval]
†Least square means (standard error) from analysis of covariance (ANCOVA) model
‡% (no./total no.)
‖A KCCQ overall score of 0 and a 6MWD of 0 meter were imputed for subjects who had a heart failure related cardiovascular death or tricuspid valve surgery prior to 12 months.

The individual MAE component rates at 30 days are shown in Table 12. Of the MAEs, one case of new onset renal failure was adjudicated as procedure-related but not device-related. A second new onset renal failure case and the one cardiovascular mortality were adjudicated as neither procedure nor device related.

Table 12. Results of Individual MAE Components at 30 Days – Randomized Cohort 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.)

3. Adverse Events – Randomized Cohort

CEC-adjudicated adverse events through 12 months (unless otherwise noted) are shown in Table 13 for the Randomized Cohort. Rates of HF hospitalizations, cardiovascular mortality, and tricuspid valve reintervention at 12 months as well as major bleeding and new onset renal failure at 30 days were numerically higher in the device group vs. the control group.

Table 13. CEC-Adjudicated Adverse Events through 12 Months – Randomized Cohort ITT Population.

Event	Summary Statistics	
	Device Arm (N=175)	Control Arm (N=175)
All-cause mortality	8.6% (15, 15, 0, 0, 1)[*]	7.4% (13, 13, 0)[†]
Cardiovascular (VARC II definition)	6.3% (11, 11, 0, 0, 0)	4.6% (8, 8, 0)
Heart failure-related	4.0% (7, 7, 0, 0, 0)	2.9% (5, 5, 0)
Non-heart failure-related	2.3% (4, 4, 0, 0, 0)	1.7% (3, 3, 0)
Non-cardiovascular (VARC II definition)	2.3% (4, 4, 0, 0, 1)	2.9% (5, 5, 0)
Hospitalization	36.0% (111, 63, 2, 7, 2)	34.3% (100, 60, 0)
Heart failure hospitalization	14.9% (35, 26, 1, 2, 0)	11.4% (8, 20, 0)
Other cardiovascular hospitalization	9.1% (17, 16, 1, 5, 0)	9.1% (21, 16, 0)
Non-cardiovascular hospitalization	21.7% (59, 38, 0, 0, 2)	21.1% (51, 37, 0)
Tricuspid valve surgery	1.7% (3, 3, 2, 2, 0)	3.4% (6, 6, 0)
Tricuspid valve intervention[‡]	2.3% (4, 4, 3, 4, 0)	1.7% (3, 3, 0)
Major bleeding (≥BARC 3a)[I]	5.7% (10, 10, 0, 3, 0)	1.7% (3, 3, 0)
New onset renal failure[I]	2.3% (4, 4, 0, 1, 0)	0.6% (1, 1, 0)
Transient ischemic attack (TIA)	0.6% (1, 1, 0, 0, 0)	0.0% (0, 0, 0)
Stroke (VARC II definition)	1.7% (3, 3, 0, 0, 0)	1.7% (4, 3, 0)
Myocardial infarction (VARC II definition)[I]	0.0% (0, 0, 0, 0, 0)	0.0% (0, 0, 0)
Endocarditis requiring surgery[I]	0.0% (0, 0, 0, 0, 0)	0.0% (0, 0, 0)
Non-elective cardiovascular surgery for TriClip-related adverse event post index procedure[I]	0.0% (0, 0, 0, 0, 0)	0.0% (0, 0, 0)
Cardiogenic shock	0.0% (0, 0, 0, 0, 0)	0.6% (1, 1, 0)

[*]Event rate (no. of events, no. of subjects, no. of device-related events, number of procedure-related events, number of COVID-19-related events); event rate = no./total no. Number of COVID-19-related events includes related or possibly related events; this excludes events with unknown relatedness.
[†]Event rate (no. of events, no. of subjects, number of COVID-19-related events).
[‡]Tricuspid valve intervention includes reintervention for device group and first intervention for control group.
[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.
VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium; TIA: transient ischemic attack.

Table 14 provides site-reported procedure- or device-related serious adverse events from the treatment visit through 1 year. Procedure- or device-related serious adverse events occurred in 3.5% (6/172) of subjects.

Table 14. Listing of Site-reported Procedure/Device Related Serious Adverse Events from treatment visit through 1 Year (Primary Analysis Population) (Attempted Procedure Population, n=172)

Subject	Description
1	Access site bleeding
	Hypotension with tachycardia secondary to acute blood loss
2	Access site complication
3	Access site complication – thrombin injection for pseudoaneurysm
	Access site complication – surgical repair of pseudoaneurysm
4	TV surgery due to unsuccessful TriClip procedure
5	Re-intervention due to SLDA
6	Heart failure due to volume overload

4. Other Randomized Cohort Observations

Procedural Endpoints:

Technical success was achieved in 98.8% of TriClip subjects, device success in 88.9%, and procedural success in 87.0% (see Table 15).

Table 4. Results of Procedural Endpoints – Randomized Cohort AP Population.

Endpoints	Results
Technical success (at exit from procedure room)	98.8% (170/172)
Device success (at 30 days post-procedure)	88.9% (144/162)
Procedural success (at 30 days post-procedure)	87.0% (141/162)

Technical success was not achieved in 2 subjects due to inability to successfully deploy the TriClip device. Device success could not be evaluated in 10 subjects due to missing TR grade assessment. In addition, device success was not achieved in 18 subjects due to single leaflet device attachment (n=11), no reduction in TR (n=3), surgery/intervention within 30 days post procedure (n=3), and death within 30 days post procedure (n=1). Procedural success was not achieved in the same 18 subjects in whom device success was not achieved and in 3 additional subjects who experienced a

device- or procedure-related site-reported serious adverse event: single leaflet device attachment (n=1; not confirmed by the ECL), ruptured chordae (n=1), and access site complication (n=1).

Procedural Data:

The TriClip procedure was performed under general anesthesia with echocardiographic (TEE) and fluoroscopic guidance. Procedural data for the Randomized Cohort AP Population is shown in Table 16. The TriClip was successfully implanted in 170 of the 172 (98.8%) subjects with an attempted procedure in the Randomized Cohort, with approximately 85% of subjects receiving two or three TriClip devices.

Table 16. Procedural Data – AP Population

Procedural Data	**Randomized Cohort (Device Group)** (N=172)
Number of clips implanted	2.2 ± 0.7 (172)
0 clips	1.2% (2/172)
1 clip	10.5% (18/172)
2 clips	61.0% (105/172)
3 clips	24.4% (42/172)
4 clips	2.9% (5/172)
Device used	
TriClip (first-generation)	47.1% (81/172)
TriClip G4	52.9% (91/172)
Total procedure time (min)	151.0 ± 71.7 (171)
Device time (min)	89.7 ± 66.4 (168)
Fluoroscopy exposure (min)	31.9 ± 23.5 (171)

*Continuous measures – Mean ± standard deviation (total no.); Categorical measures - % (no./total no.)

TR Severity:

TR severity for the Randomized Cohort ITT Population is shown in Figure 6 . In the device group, the proportion of subjects with greater than moderate TR was 97% at baseline, which decreased to 13% at 30 days and 12% at 12 months. In the control group, TR severity was greater than moderate in 99% of subjects at baseline and remained greater than moderate in 95% of subjects at 30 days and 92% at 12 months.

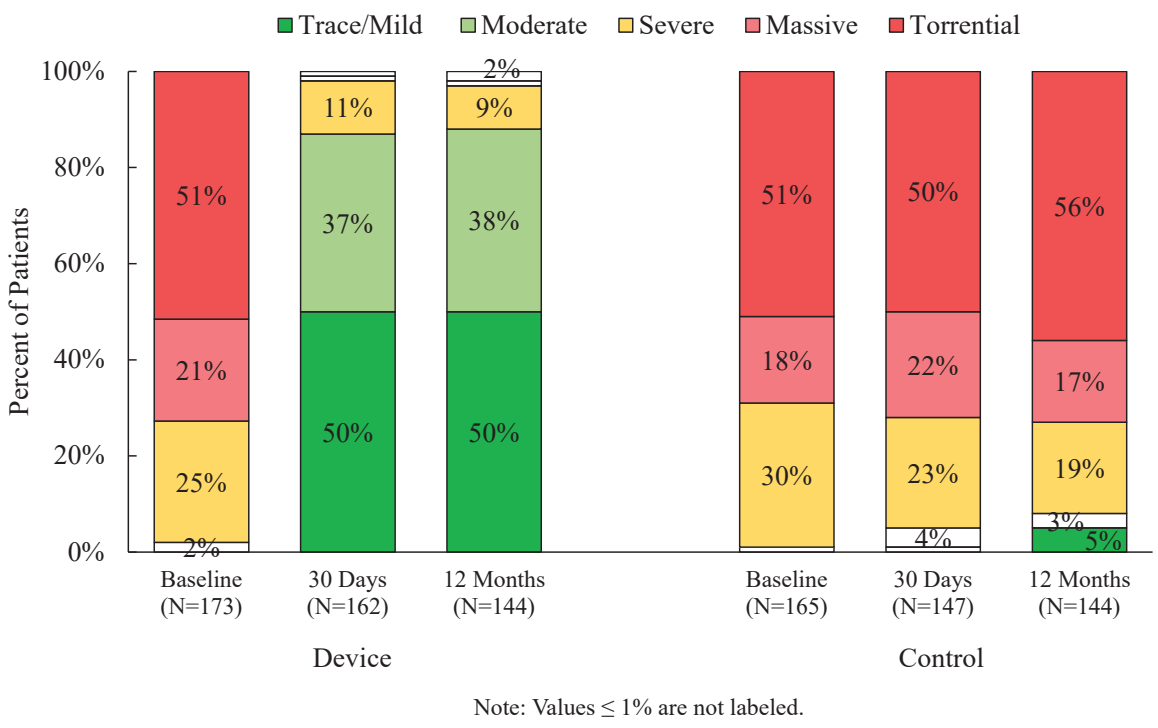
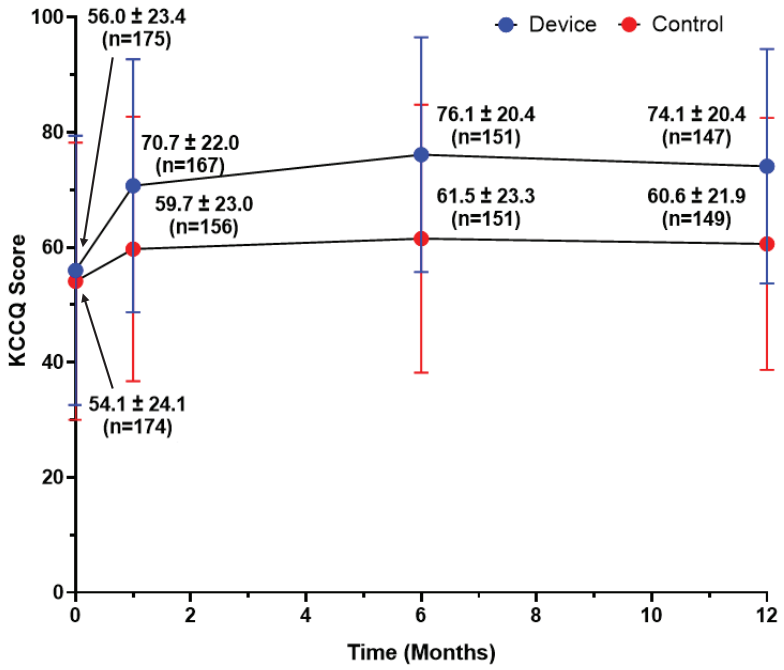


Figure 6. TR Severity Visit – Randomized Cohort ITT Population (Unpaired).

KCCQ Score:

KCCQ scores and score changes through 12 months are shown in Figure 7 for the Randomized Cohort ITT Population. On average, the KCCQ score increased by 15.2 points in the device group vs. 4.8 points in the control group through 12 months.

A KCCQ Score



B KCCQ Score Change

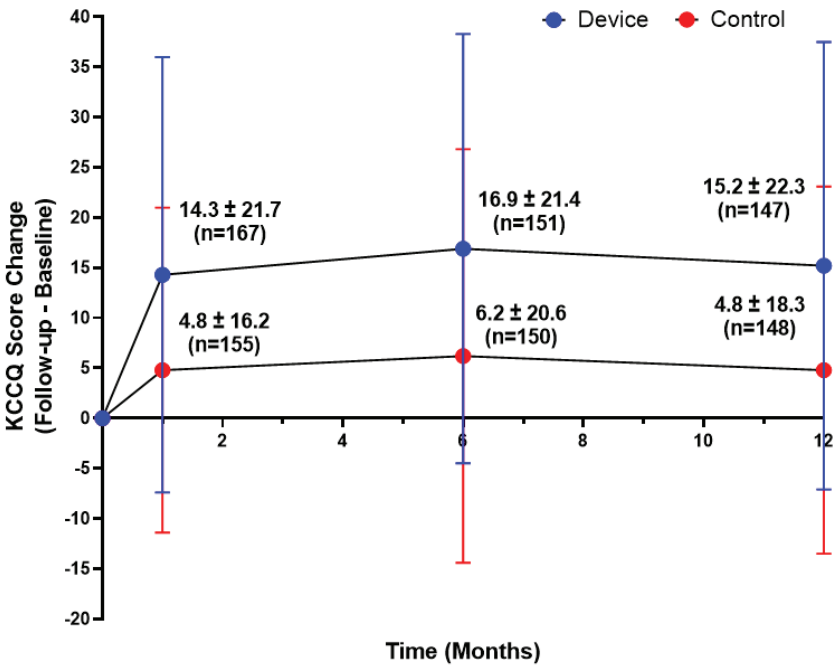


Figure 7. KCCQ Score by Visit – Randomized Cohort ITT Population (Unpaired). The error bars are standard deviations.

Association between KCCQ Score and TR:

Post hoc analyses were performed to investigate the associations between KCCQ score changes and TR severity and between KCCQ score changes and TR severity changes at 12 months. These analyses were conducted to provide evidence that the KCCQ score improvement observed in the study was not solely the result of a placebo effect. The associations are shown in Figure 8. Lower TR severity and greater TR severity reductions were generally associated with greater KCCQ score improvements.

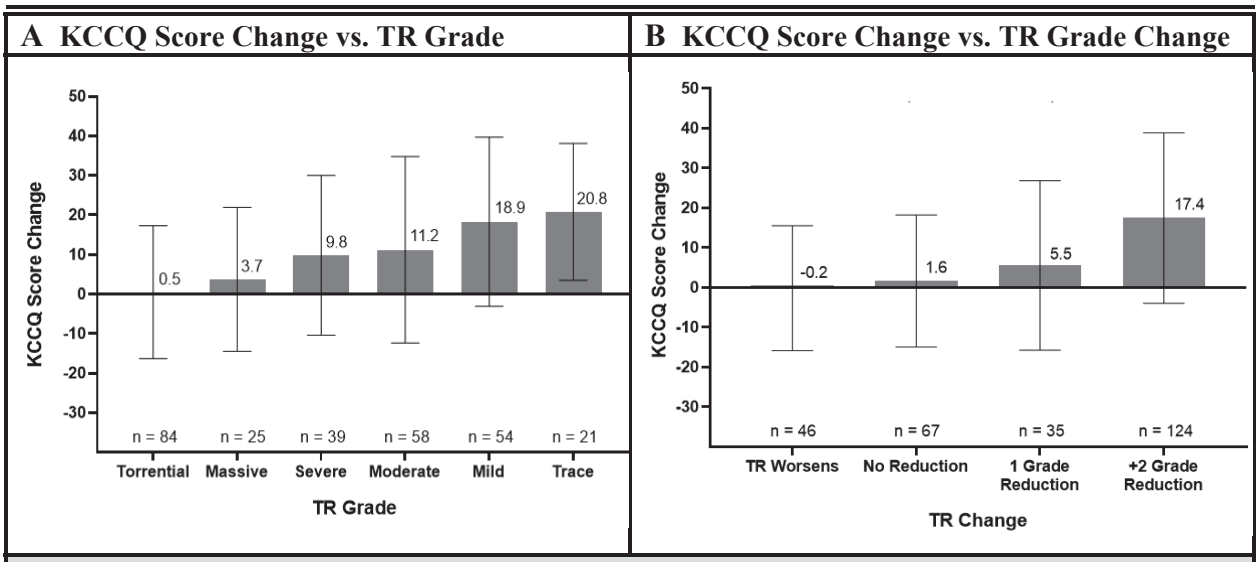


Figure 8. Association between KCCQ Score and TR at 12 Months. The error bars are standard deviations.

SF-36 Score:

SF-36 scores through 12 months are shown in Figure 9 for the Randomized Cohort ITT Population. The mean physical component score increased by about 5 points through 12 months compared to the baseline in the device group, while remaining mostly unchanged from baseline through 12 months in the control group. A similar trend was seen in the mental component score. In some studies, SF-36 score changes similar to the changes observed in the device group have been interpreted as clinically significant.

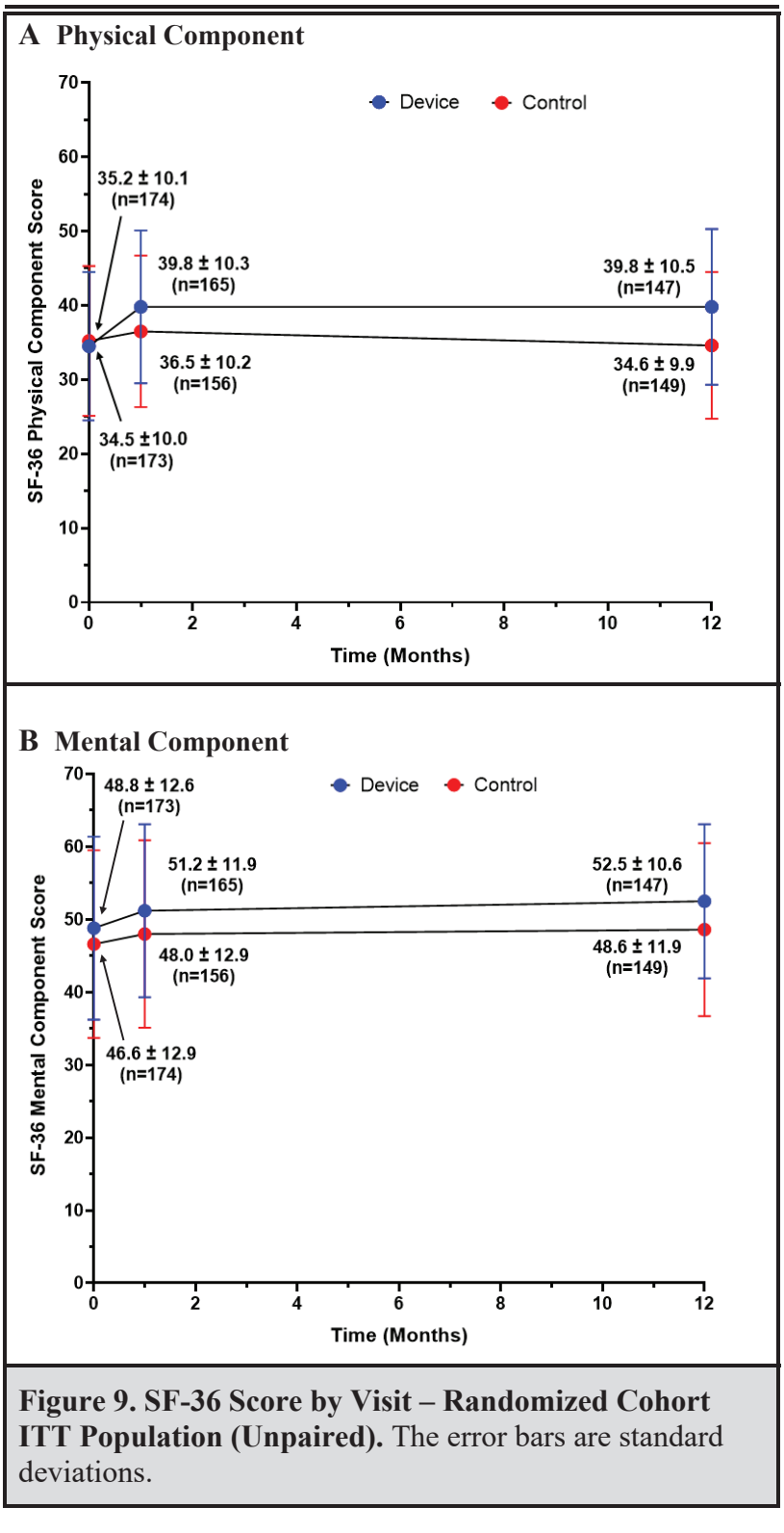


Figure 9. SF-36 Score by Visit – Randomized Cohort ITT Population (Unpaired). The error bars are standard deviations.

NYHA Functional Class:

The results for NYHA classification by visit are shown in Figure 10 for the Randomized Cohort ITT Population. At baseline, 59% of subjects in the device group and 55% in the control group were in NYHA III/IV. At 12 months, fewer device subjects were in NYHA III/IV than the control subjects (16% vs. 40%).

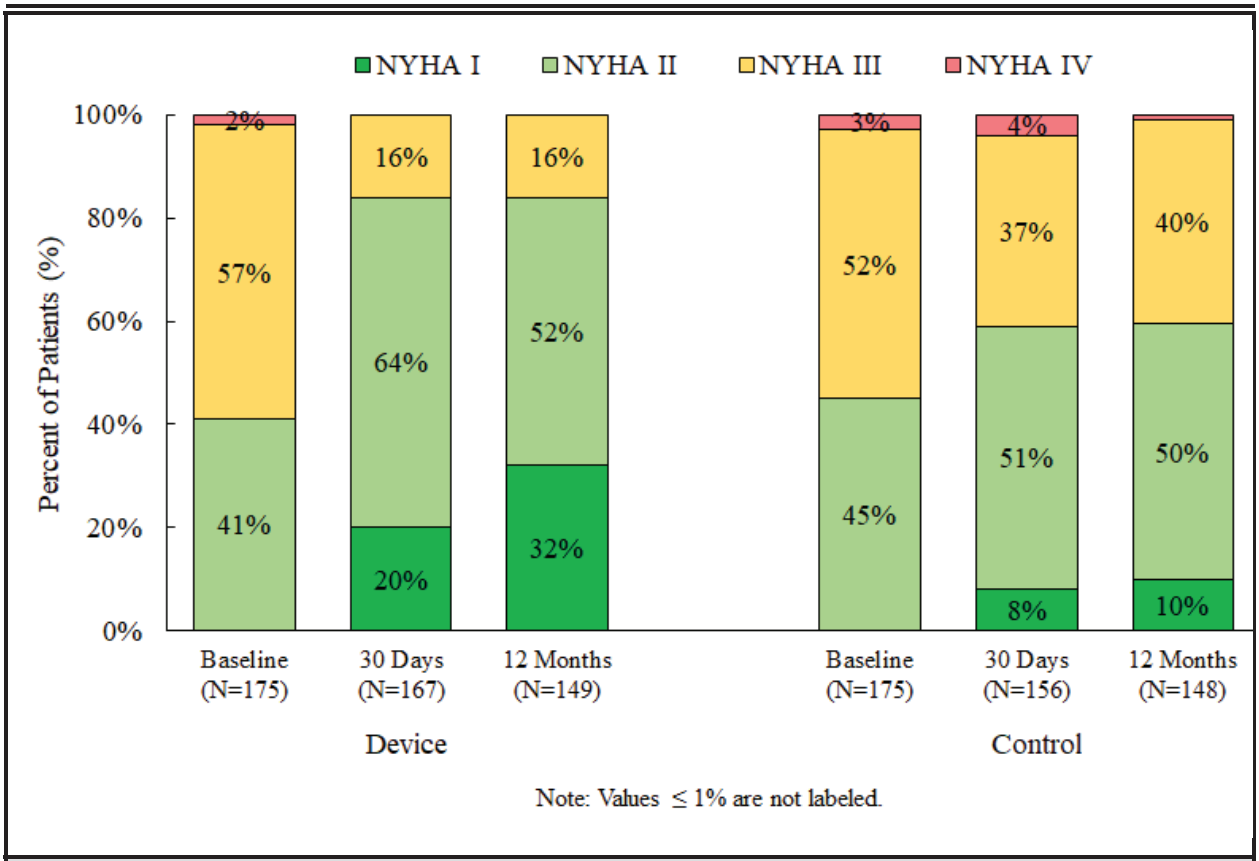


Figure 10. NYHA Functional Class by Visit – Randomized Cohort ITT Population (Unpaired).

Echocardiographic Parameters:

PISA EROA, PISA regurgitant volume, and vena contracta width all showed substantial decreases from baseline to 12 months in the device group and were minimally changed in the control group (Table 17). There were no notable changes in cardiac size or function in either treatment group at 12 months. Right atrial volume, which would be expected to decrease as a result of reduced TR due to reverse remodeling, showed an unexpected small increase in the device group.

Table 17. Results of Echocardiographic Endpoints – Randomized Cohort ITT Population (Paired Analysis).

Echocardiographic Endpoint Change from Baseline to 12 Months	Device Arm (N=175)	Control Arm (N=175)	Difference [95% CI]*
ΔTricuspid annulus diameter (end-diastole, apical 4Ch, cm)			
Mean ± SD (n)	-0.09 ± 0.64 (140)	-0.11 ± 0.74 (135)	0.02 [-0.14, 0.19]
Median (Q1, Q3)	-0.10 (-0.50, 0.30)	-0.17 (-0.50, 0.30)	
Range (min, max)	(-1.46, 1.39)	(-3.90, 2.02)	
ΔPISA EROA (cm^2)			
Mean ± SD (n)	-0.44 ± 0.33 (115)	-0.04 ± 0.31 (127)	-0.40 [-0.48, -0.32]
Median (Q1, Q3)	-0.42 (-0.56, -0.26)	0.00 (-0.16, 0.12)	
Range (min, max)	(-2.33, 0.25)	(-1.25, 0.80)	
ΔPISA regurgitant volume calculation (mL)			
Mean ± SD (n)	-33.84 ± 20.48 (115)	-1.99 ± 23.56 (127)	-31.85 [-37.43, -26.28]
Median (Q1, Q3)	-33.20 (-44.90, -21.40)	-1.30 (-12.40, 10.21)	
Range (min, max)	(-105.20, 12.11)	(-115.90, 67.80)	
ΔVena contracta width (SL, 4Ch view, cm)			
Mean ± SD (n)	-0.52 ± 0.48 (139)	0.03 ± 0.44 (136)	-0.54 [-0.65, -0.43]
Median (Q1, Q3)	-0.48 (-0.77, -0.26)	0.00 (-0.30, 0.32)	
Range (min, max)	(-3.00, 0.97)	(-1.10, 1.40)	
ΔRV end diastolic diameter – mid (4Ch, cm)			
Mean ± SD (n)	-0.18 ± 0.73 (140)	-0.02 ± 0.85 (134)	-0.17 [-0.36, 0.02]
Median (Q1, Q3)	-0.20 (-0.60, 0.20)	0.10 (-0.50, 0.50)	
Range (min, max)	(-1.90, 2.80)	(-2.20, 2.90)	
ΔRV end diastolic diameter – base (4Ch, cm)			
Mean ± SD (n)	-0.21 ± 0.71 (142)	-0.12 ± 0.76 (134)	-0.09 [-0.26, 0.08]
Median (Q1, Q3)	-0.15 (-0.70, 0.20)	-0.10 (-0.60, 0.40)	
Range (min, max)	(-2.40, 2.70)	(-2.00, 1.90)	
ΔRight atrial volume (single plane Simpson's, mL)			
Mean ± SD (n)	7.78 ± 55.92 (140)	-2.13 ± 54.14 (136)	9.91 [-3.13, 22.95]
Median (Q1, Q3)	8.17 (-22.48, 28.25)	-4.35 (-29.90, 21.90)	
Range (min, max)	(-122.03, 276.20)	(-154.44, 181.20)	
ΔRV fractional area change (%)			
Mean ± SD (n)	-0.73 ± 8.16 (133)	-0.52 ± 7.38 (125)	-0.21

Median (Q1, Q3)	-0.50 (-6.40, 3.90)	-1.00 (-5.80, 3.90)	[-2.12, 1.69]
Range (min, max)	(-27.90, 21.22)	(-18.70, 23.00)	
ΔLV end diastolic volume (mL)			
Mean ± SD (n)	3.91 ± 25.02 (129)	-4.80 ± 23.49 (114)	8.70 [2.57, 14.84]
Median (Q1, Q3)	3.30 (-12.90, 16.30)	-4.98 (-16.80, 9.70)	
Range (min, max)	(-70.30, 94.50)	(-83.20, 52.70)	
ΔLV end systolic volume (mL)			
Mean ± SD (n)	2.31 ± 15.28 (129)	-2.93 ± 12.52 (114)	5.24 [1.72, 8.75]
Median (Q1, Q3)	0.82 (-4.80, 8.80)	-2.95 (-9.50, 4.20)	
Range (min, max)	(-37.00, 85.50)	(-65.34, 23.80)	
ΔRV TAPSE (cm)			
Mean ± SD (n)	-0.13 ± 0.45 (141)	0.00 ± 0.48 (132)	-0.13 [-0.24, -0.02]
Median (Q1, Q3)	-0.10 (-0.43, 0.10)	0.01 (-0.20, 0.30)	
Range (min, max)	(-1.40, 1.00)	(-2.27, 1.00)	
ΔCardiac output (L/min)			
Mean ± SD (n)	-0.05 ± 1.89 (136)	0.03 ± 1.40 (131)	-0.07 [-0.47, 0.33]
Median (Q1, Q3)	-0.14 (-0.98, 0.63)	-0.04 (-0.88, 0.86)	
Range (min, max)	(-4.98, 14.95)	(-3.42, 4.10)	
ΔLVOT Doppler stroke volume (mL)			
Mean ± SD (n)	-1.58 ± 17.62 (138)	-1.93 ± 16.48 (133)	0.35 [-3.73, 4.43]
Median (Q1, Q3)	-2.04 (-11.00, 7.80)	-1.50 (-11.73, 4.40)	
Range (min, max)	(-49.50, 65.00)	(-40.60, 51.70)	
ΔInferior vena cava diameter (cm)			
Mean ± SD (n)	-0.09 ± 0.56 (135)	-0.01 ± 0.56 (136)	-0.08 [-0.21, 0.05]
Median (Q1, Q3)	-0.04 (-0.48, 0.34)	0.00 (-0.34, 0.32)	
Range (min, max)	(-1.80, 1.16)	(-1.90, 1.80)	
ΔTricuspid valve diastolic mean gradient (CW, mmHg)			
Mean ± SD (n)	1.15 ± 1.28 (136)	0.07 ± 0.58 (126)	1.08 [0.84, 1.32]
Median (Q1, Q3)	0.86 (0.32, 1.89)	0.02 (-0.31, 0.43)	
Range (min, max)	(-2.80, 7.32)	(-1.11, 1.60)	

PISA: proximal isovelocity surface area (a method for estimating regurgitant volume); EROA: effective regurgitant orifice area; RV: right ventricular; LV: left ventricular: TAPSE: tricuspid annular plane systolic excursion (a measure of the RV apex to-base shortening and RV systolic function); LVOT: left ventricular outflow tract.

SD: standard deviation; CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

*By normal approximation.

5. 1-Year Outcomes for All Available Subjects in the Randomized Cohort

The trial used an adaptive design with sample size re-estimation for the Randomized Cohort. The pre-specified sample size re-estimation occurred once the first 150 randomized subjects completed 12-month follow-up, while the trial was still enrolling. The trial continued to randomize subjects until the sample size re-estimation analysis was completed and indicated that no further subject enrollment was necessary, by which point 572 subjects were randomized at 68 sites. Fifty-six subjects (29 Device, 26 Control) were pending 12-month follow-up visits at the time of data analysis.

The win ratio analysis result for all available randomized subjects was 1.53 (Figure 11), which is slightly greater than the win-ratio result for the Primary Analysis Population (1.44, Figure 4). The number of device wins and control wins for death or TV surgery continued to be similar between treatment groups for all available randomized subjects. While there were more control group wins for heart failure hospitalizations in the win ratio analysis for the Primary Analysis Population, the number of device group wins and control group wins for heart failure hospitalizations were similar for all available subjects. The win ratio continued to be driven by KCCQ score improvement, and the data for all available subjects support the Primary Analysis Population analysis.

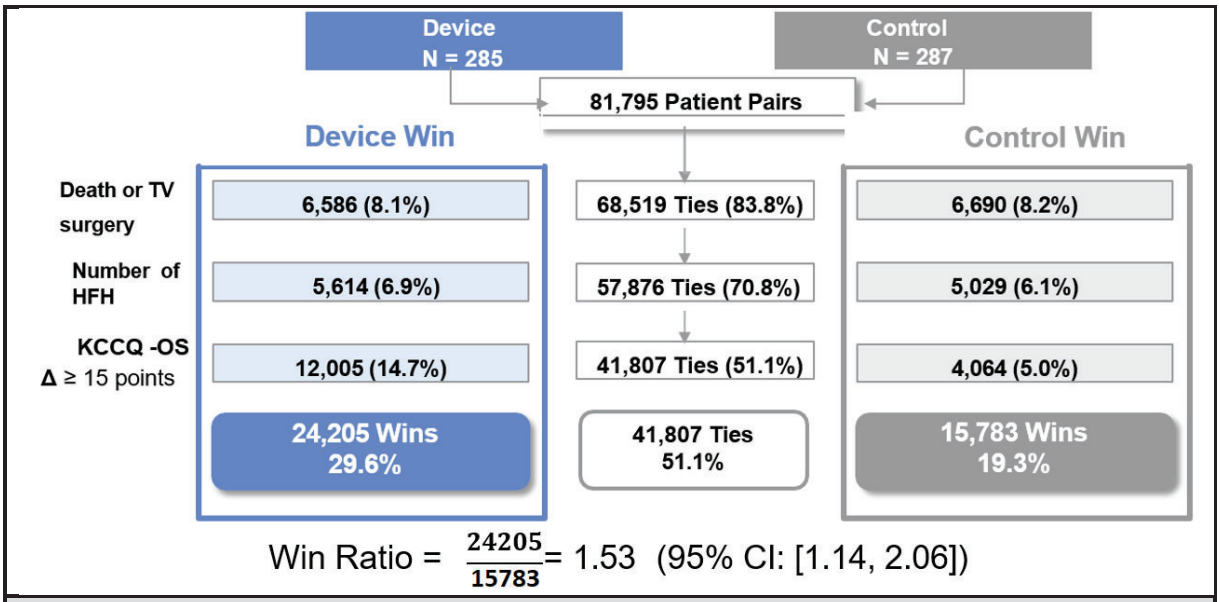


Figure 11. Win Ratio Analysis for All Available Subjects – Randomized Cohort ITT Population. HFH: heart failure hospitalization; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire overall summary score; CI: confidence interval. The CI was calculated without multiplicity adjustment. The adjusted CI could be wider than presented here.

Components of the primary endpoint for the Primary Analysis Population and Full Randomized Cohort are provided in Table 18.

Table 18. Primary Endpoint Components – Primary Analysis Population and Full Randomized Cohort

Component	Primary Analysis Population (N=350)		Full Randomized Cohort (N=572)	
	Device (N=175)	Control (N=175)	Device (N=285)	Control (N=287)
All-cause mortality or TV surgery at 12 months, Kaplan-Meier (%)[1]	9.4%	10.6%	9.9%	9.7%
Rate of heart failure hospitalizations, per patient-year[2]	0.22	0.17	0.17	0.19
Proportion with KCCQ-OS improvement ≥15 points at 12 months	50%	26%	50%	26%

[1]Kaplan-Meier estimate with Log-rank test
[2]Normal approximation for differences in Binomial proportions

Secondary endpoints were consistent in the Primary Analysis Population and Full Randomized cohorts as summarized in Table 19. Device subjects experienced a larger improvement in 6MWD than Control subjects in the Full Randomized Cohort than in the Primary Analysis Population.

Table 19. Secondary Endpoints – Primary Analysis Population and Full Randomized Cohort

Secondary Endpoints	Primary Analysis Population (N=350)		Full Randomized Cohort (N=572)	
	Device (N=175)	Control (N=175)	Device (N=285)	Control (N=287)
Freedom from MAE at 30 days	98.3%	-	98.9%	-
Moderate or less TR at 30 days	87.0%	5.4%	88.9%	5.3%
Change from Baseline to 12 months				
KCCQ-OS (imputed[a], ANCOVA), Mean ± SE	12.3 ± 1.8	0.6 ± 1.8	11.5 ± 1.6	-0.5 ± 1.6
Between-group difference, Mean [95% CI][b]	11.7 [6.9, 16.6]		11.9 [7.4, 16.4]	
KCCQ-OS (complete-case paired), Mean ± SD	15.2 ± 22.3	4.8 ± 18.3	15.2 ± 22.8	4.2 ± 18.9
Between-group difference, Mean [95% CI]	10.4 [5.7, 15.1]		11.0 [6.9, 15.2]	
6MWD (imputed[a], ANCOVA), Mean ± SE	-8.1 ± 10.5	-25.2 ± 10.3	-5.0 ± 8.7	-29.8 ± 8.4
Between-group difference, Mean [95% CI]	17.1 [-12.0, 46.1]		24.8 [1.1, 48.6]	

6MWD (complete-case paired), Mean ± SD	11.5 ± 111.4	-8.7 ± 109.7	15.1 ± 103.4	-12.1 ± 102.0
Between-group difference, Mean [95% CI]	20.3 [-7.2, 47.7]		27.2 [5.5, 48.9]	

[a] Subjects who experienced HF-related death or had TV surgery prior to 12-month visit were assigned 12-month KCCQ-OS or 6MWD of 0. Subjects who were unable to exercise due to cardiac reasons were also assigned a 6MWD of 0 meters at 12-month follow-up.
Subjects who experienced hospitalization related to COVID-19 had their follow-up information following the COVID-19 related hospitalization excluded.
[b]CI: confidence interval. The CI was calculated without multiplicity adjustment. The adjusted CI could be wider than presented here.

CEC-adjudicated adverse event rates through 12 months (unless otherwise noted) were also consistent in the Primary Analysis Population and Full Randomized cohorts. Event rates for the Full Randomized Cohort are summarized in Table 20.

Table 20. Selected CEC-Adjudicated Adverse Events through 12 Months – Full Randomized Cohort ITT Population.

Event	Summary Statistics	
	Device Arm (N=285)*	**Control Arm (N=287)†**
All-cause mortality	8.1% (23, 23, 0, 0, 1)	7.0% (20, 20, 0)
Cardiovascular (VARC II definition)	5.3% (15, 15, 0, 0, 0)	3.8% (11, 11, 0)
Heart failure-related	3.9% (11, 11, 0, 0, 0)	2.8% (8, 8, 0)
Non-heart failure-related	1.4% (4, 4, 0, 0, 0)	1.0% (3, 3, 0)
Non-cardiovascular (VARC II definition)	2.8% (8, 8, 0, 0, 1)	3.1% (9, 9, 0)
Hospitalization	33.7% (161, 96, 2, 7, 9)	31.0% (155, 89, 0)
Heart failure hospitalization	11.2% (44, 32, 1, 2, 0)	11.8% (48, 34, 0)
Other cardiovascular hospitalization	7.7% (23, 22, 1, 5, 0)	7.0% (25, 20, 0)
Non-cardiovascular hospitalization	22.8% (94, 65, 0, 0, 9)	19.5% (82, 56, 0)
Tricuspid valve surgery	1.8% (5, 5, 2, 2, 0)	2.4% (7, 7, 0)
Tricuspid valve intervention‡	2.5% (7, 7, 5, 7, 0)	1.0% (3, 3, 0)
Major bleeding (≥BARC 3a)‖	3.2% (9, 9, 0, 3, 0)	1.7% (5, 5, 0)
New onset renal failure‖	0.7% (2, 2, 0, 1, 0)	0.3% (1, 1, 0)

*Event rate (no. of events, no. of subjects, no. of device-related events, number of procedure-related events, number of COVID-19-related events); event rate = no./total no. Number of COVID-19-related events includes related or possibly related events; this excludes events with unknown relatedness.

[†]Event rate (no. of events, no. of subjects, number of COVID-19-related events).
[‡]Tricuspid valve intervention includes reintervention for device group and first intervention for control group.
[ǀ]Per the study CEC charter bleeding and new onset renal failure were adjudicated up to 30 days post treatment visit for the device and control groups.
VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium

6. Single-Arm Cohort Results

Primary Endpoint:

There were 100 subjects with an attempted TriClip procedure in the Single-Arm Cohort. The primary analysis was performed on 91 subjects, which excluded subjects who withdrew (n=1), died or were hospitalized due to COVID-19 (n=2), or missed the 12-month visit or did not complete the 12-month KCCQ assessment (n=6). The results of the primary analysis are shown in Table 19. Fifteen (15) subjects died prior to 12 months, 34 had a KCCQ score improvement of <10 points, and 42 survived with a KCCQ score improvement of ≥10 points at 12 months. The proportion of subjects who survived and experienced at least a 10-point improvement in KCCQ score at 12 months from baseline was 46.2%, with a lower 98.75% confidence limit of 34.3%, which exceeded the performance goal of 30%. Thus, the primary endpoint was met.

Table 215. Primary Analysis Results – Single-Arm Cohort.

Primary Endpoint	Rate	Lower 98.75% Confidence Limit	Performance Goal	P-value	Result
Survival with ≥10 point improvement vs. baseline in KCCQ score at 12 months	46.2% (42/91)	34.3%	30%	0.008	Endpoint Met

Secondary Endpoint:

The results of the powered secondary endpoints for the Single-Arm Cohort are summarized in Table 22. TR reduction by at least one grade at 30 days post-procedure occurred in 98.9% of subjects, and freedom from MAEs at 30 days post-procedure occurred in 100% of subjects; these endpoints were met. However, the improvement in 6MWD at 12 months from baseline (13.7±92.7) did not meet the performance goal, so the endpoint was not met. As a result, the subsequent endpoints in the pre-defined hierarchy (freedom from all-cause mortality or tricuspid valve surgery and recurrent HF hospitalizations at 12 months post-procedure) were not hypothesis-tested. Descriptively, the annualized HF hospitalization rates pre- and post-TriClip procedure were generally similar.

Table 226. Summary of Powered Secondary Endpoints – Single-Arm Cohort AP Population.

Order	Secondary Endpoint	Summary Statistics	p-Value	Result
1	TR reduction by at least one grade at 30 days post-procedure	98.9% (87/88)*	< 0.0001	Endpoint met
2	Freedom from MAEs at 30 days post-procedure	100% (99/99)*	<0.0001	Endpoint met
3	Change in 6MWD at 12 months from baseline (m)	13.7±92.7 (71)† 95% CI: [-8.3, 35.6]	0.1090	**Endpoint not met**
4	Freedom from all-cause mortality and tricuspid valve surgery at 12 months	83.7% (3.7%)‡	-	Not tested
5	Recurrent HF hospitalizations at 12 months (events/patient-year)	Pre-procedure: 0.33 [0.23, 0.46]ǀ Post-procedure: 0.36 [0.26, 0.51]ǀ	-	Not tested

TR: tricuspid regurgitation; 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; 6MWD: 6-minute walk distance; HF: heart failure.
CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.
*% (no./total no.)
†Mean ± standard deviation (total no.)
‡Kaplan-Meier estimate (standard error)
ǀAnnualized event rate [95% CI].

Safety Results:

CEC-adjudicated adverse event rates through 12 months are shown in Table 23. 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 device group of the Randomized Cohort. Other event rates were comparable to the device group of the Randomized Cohort.

Table 237. CEC-Adjudicated Adverse Events through 12 Months – Single-Arm Cohort AP Population.

Event	Summary Statistics N=100
All-cause mortality	15% (15, 15, 0, 0, 1)*
Cardiovascular (VARC II definition)	11% (11, 11, 0, 0, 0)
Heart failure-related	10% (10, 10, 0, 0, 0)

Non-heart failure-related	1% (1, 1, 0, 0, 0)
Non-cardiovascular (VARC II definition)	4% (4, 4, 0, 0, 1)
Hospitalization	50% (85, 50, 5, 4, 1)
Heart failure hospitalization	24% (33, 24, 1, 0, 0)
Other cardiovascular hospitalization	14% (17,14, 4, 3, 0)
Non-cardiovascular hospitalization	26% (35, 26, 0, 1, 1)
Tricuspid valve surgery	2% (2, 2, 1, 0, 0)
Tricuspid valve intervention	7% (7, 7, 5, 4, 0)
Major bleeding (greater than BARC 3a)[‖]	5% (5, 5, 0, 1, 0)
New onset renal failure[‖]	0% (0, 0, 0, 0, 0)
Transient ischemic attack (TIA)	1% (1, 1, 0, 0, 0)
Stroke (VARC II)	0% (0, 0, 0, 0, 0)
Myocardial infarction (VARC II definition)[‖]	0% (0, 0, 0, 0, 0)
Endocarditis requiring surgery[‖]	0% (0, 0, 0, 0, 0)
Non-elective cardiovascular surgery for TriClip-related adverse event post index procedure[‖]	0% (0, 0, 0, 0, 0)
Cardiogenic shock	1% (1, 1, 0, 1, 0)

[*]Event rate (no. of events, no. of subjects, no. of device-related events, number of procedure-related events, number of COVID-19-related events); event rate = no./total no. Number of COVID-19-related events includes related or possibly related events; this excludes events with unknown relatedness.

[‖]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.

VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium; TIA: transient ischemic attack.

7. Imaging Sub-study

A pre-planned exploratory imaging sub-study was conducted on a subset of subjects to further investigate changes in TR, right ventricular size, and right ventricular function and to gain additional insights into cardiac reverse remodeling. Ten (10) sites participated, and site selection was based on MRI/CT imaging expertise, adequate imaging equipment, and study enrollment. The imaging sub-study was to enroll 100

subjects. A total of 82 subjects enrolled and completed baseline imaging as of April 23, 2023, with 44 subjects enrolled at a single site.

MRI and CT were performed at baseline and 30 days, and CT was performed at 12 months. TR parameters were only assessed with MRI. The 30-day cardiac MRI results (Table 24) showed TR reduction in TriClip subjects consistent with the echocardiogram results. In addition, there were general trends in right ventricular reverse remodeling in TriClip subjects. However, the sample size was small, and there was large patient-to-patient variability in the results. The long-term prognostic values of the observed changes are unknown.

Table 248. Imaging Sub-Study: 30-Day Cardiac MRI Results.

Endpoint Change from Baseline to 30 Days	Randomized Cohort		Single-Arm & Roll-in Cohorts (N=12)
	Device Arm (N=27)	Control Arm (N=26)	
ΔTR volume (mL)			
Mean ± SD (n)	-34.1 ± 28.2 (27)	3.2 ± 22.1 (24)	-39.0 ± 16.3 (10)
Median (Q1, Q3)	-28.0 (-52.0, -10.0)	2.0 (-13.0, 11.5)	-43.0 (-46.0, -28.0)
Range (min, max)	(-100.0, 4.0)	(-20.0, 84.0)	(-62.0, -9.0)
ΔTR fraction (%)			
Mean ± SD (n)	-27.8 ± 16.0 (27)	-2.3 ± 21.2 (24)	-29.1 ± 14.6 (10)
Median (Q1, Q3)	-28.0 (-45.0, -13.8)	0.5 (-8.4, 6.0)	-29.5 (-37.0, -18.0)
Range (min, max)	(-52.9, 9.4)	(-66.4, 60.2)	(-56.3, -9.0)
ΔRight atrial end diastolic volume (RAEDV, mL)			
Mean ± SD (n)	-8.7 ± 23.1 (27)	-4.0 ± 38.5 (26)	-29.6 ± 27.8 (12)
Median (Q1, Q3)	-9.0 (-21.0, 8.0)	-3.0 (-16.0, 22.0)	-17.5 (-51.0, -5.5)
Range (min, max)	(-64.0, 37.0)	(-113.0, 63.0)	(-83.0, -2.0)
ΔRight ventricular mass (g)			
Mean ± SD (n)	-4.7 ± 5.2 (27)	0.0 ± 6.0 (25)	-7.2 ± 8.7 (11)
Median (Q1, Q3)	-5.0 (-9.0, 0.0)	1.0 (-4.0, 5.0)	-5.0 (-9.0, -1.0)
Range (min, max)	(-16.0, 4.0)	(-13.0, 10.0)	(-32.0, -1.0)
ΔRight ventricular ejection fraction (RVEF, %)			
Mean ± SD (n)	-5.6 ± 6.6 (27)	0.6 ± 6.1 (25)	-9.2 ± 5.6 (11)
Median (Q1, Q3)	-6.0 (-11.0, 1.0)	1.0 (-1.0, 2.0)	-10.0 (-15.0, -6.0)
Range (min, max)	(-17.0, 5.0)	(-15.0, 17.0)	(-16.0, 2.0)
ΔCorrected RVEF (%)*			
Mean ± SD (n)	8.4 ± 7.6 (27)	-0.2 ± 4.5 (24)	7.1 ± 9.3 (10)

Median (Q1, Q3)	8.1 (4.0, 15.0)	0.0 (-2.6, 2.5)	8.5 (-1.0, 14.0)
Range (min, max)	(-8.2, 20.3)	(-12.0, 8.8)	(-10.9, 18.5)
ΔRight ventricular free wall strain (%)			
Mean ± SD (n)	-2.0 ± 4.5 (27)	1.2 ± 6.1 (25)	-2.7 ± 4.8 (10)
Median (Q1, Q3)	-1.0 (-5.0, 1.0)	0.0 (-3.0, 3.0)	-2.0 (-6.0, 2.0)
Range (min, max)	(-12.0, 6.0)	(-8.0, 16.0)	(-12.0, 3.0)
ΔPulmonary forward flow (mL)			
Mean ± SD (n)	5.2 ± 13.0 (27)	0.3 ± 9.1 (24)	-1.8 ± 27.5 (11)
Median (Q1, Q3)	5.0 (-4.0, 14.0)	1.0 (-4.0, 5.0)	4.0 (-5.0, 10.0)
Range (min, max)	(-19.0, 41.0)	(-22.0, 19.0)	(-79.0, 29.0)

*Corrected RVEF: provides a more accurate measurement of forward flow by subtracting regurgitant volume from the total stroke volume for a regurgitant valve.

The 12-month cardiac CT results are shown in Table 25. Similar to the cardiac MRI results, general trends of right ventricular reverse remodeling were observed in TriClip subjects. However, sample sizes were small, and there was large patient-to-patient variability in the results. The long-term prognostic values of the observed changes are unknown.

Table 25. Imaging Sub-Study: 12-Month Cardiac CT Results.

Endpoint Change from Baseline to 12 Months	Randomized Cohort		Single-Arm & Roll-In Cohorts (N=7)
	Device Group (N=20)	Control Group (N=20)	
ΔRight atrial end diastolic volume (RAEDV, mL)			
Mean ± SD (n)	-19.5 ± 34.2 (20)	4.4 ± 35.5 (20)	-3.3 ± 23.6 (7)
Median (Q1, Q3)	-18.0 (-31.5, -4.0)	5.0 (-14.0, 23.0)	4.0 (-28.0, 21.0)
Range (min, max)	(-83.0, 45.0)	(-70.0, 99.0)	(-33.0, 23.0)
ΔTricuspid valve annular area (mm^2)			
Mean ± SD (n)	-195.0 ± 197.1 (20)	-3.0 ± 142.8 (20)	-194.3 ± 119.7 (7)
Median (Q1, Q3)	-205.0 (-305.0, -60.0)	-20.0 (-70.0, 60.0)	-160.0 (-300.0, -130.0)
Range (min, max)	(-690.0, 90.0)	(-240.0, 390.0)	(-360.0, 0.0)
ΔRight ventricular end diastolic volume (RVEDV, mL)			
Mean ± SD (n)	-35.8 ± 26.4 (20)	-1.0 ± 38.1 (20)	-42.4 ± 33.5 (7)
Median (Q1, Q3)	-38.0 (-58.5, -18.5)	-3.5 (-22.5, 12.5)	-37.0 (-56.0, -16.0)
Range (min, max)	(-74.0, 8.0)	(-61.0, 68.0)	(-103.0, 0.0)

ΔRight ventricular mass (g)			
Mean ± SD (n)	-4.7 ± 4.9 (20)	1.4 ± 6.5 (20)	-3.6 ± 5.7 (7)
Median (Q1, Q3)	-3.5 (-6.5, -1.0)	1.5 (-4.5, 5.0)	-5.0 (-7.0, -2.0)
Range (min, max)	(-16.0, 2.0)	(-10.0, 13.0)	(-10.0, 8.0)
ΔRight ventricular ejection fraction (%)			
Mean ± SD (n)	-6.9 ± 6.2 (20)	0.9 ± 5.2 (20)	-2.1 ± 7.0 (7)
Median (Q1, Q3)	-9.0 (-11.0, -2.0)	0.5 (-2.0, 4.0)	-2.0 (-8.0, 7.0)
Range (min, max)	(-16.0, 5.0)	(-10.0, 11.0)	(-11.0, 7.0)
ΔRight ventricular free wall strain (%)			
Mean ± SD (n)	-4.2 ± 7.2 (18)	-1.3 ± 5.4 (19)	-1.3 ± 6.5 (7)
Median (Q1, Q3)	-3.5 (-8.0, 2.0)	-2.0 (-5.0, 3.0)	2.0 (-8.0, 3.0)
Range (min, max)	(-20.0, 5.0)	(-14.0, 10.0)	(-13.0, 4.0)

SD: standard deviation;

8. Subgroup Analyses

Pre-specified subgroup analyses were performed on the primary endpoint components at 12 months by sex (male vs. female), baseline TR grade (severe vs. greater than severe), baseline NYHA functional class (I/II vs. III/IV), and TR etiology (primary vs. secondary). Outcomes for each component of the primary endpoint were generally consistent across subgroups except KCCQ score change by TR etiology. However, this is not considered a qualitative interaction, as the device group had a higher proportion of subjects with a KCCQ improvement of ≥15 points vs. the control group for both the primary and secondary TR etiology subgroups.

The study was not specifically powered for race subgroup. However, a subgroup analysis was also performed to investigate potential differences in outcomes based on race. The number of non-Caucasians is too small to draw any conclusions (Table 26).

Table 26. Primary Endpoint Components of Safety and Effectiveness by Race

Race	All-Cause Mortality or TV Surgery§		Heart Failure Hospitalization§		ΔKCCQ ≥15 Points§	
	Device	Control	Device	Control	Device	Control
American Indian or Alaskan Native	0/1	0/0	0/1	0/0	0/1	0/0
Asian	0/7	1/7	1/7	0/7	2/7	4/9

Black or African American	2/7	2/7	2/7	1/10	1/4	4/9
Native Hawaiian or Other Pacific Islander*	0/0	0/0	0/0	0/0	0/0	0/0
White	13/149	15/143	20/149	19/143	67/127	28/120
Not available†	1/11	0/15	3/11	0/15	3/8	5/13

KCCQ: Kansas City Cardiomyopathy
*No subjects in the race category enrolled.
†Europeans regulations did not allow the race information to be collected for subjects enrolled in Germany.
§ The numbers shown were no. of patients with events/total no. of patients.

9. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 537 investigators of which none were full-time or part-time employees of the sponsor and 9 of investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 9
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on February 13, 2024, the Circulatory System Devices Panel voted 14-0-0 (yes-no-abstain) that there is reasonable assurance the device is safe, 12-2-0 that there is reasonable assurance that the device is effective, and 13-1-0 that the benefits of the device outweigh the risks in subjects who meet the criteria specified in the proposed indication. The panel generally believed that the device was safe and that the KCCQ score improvement was not solely due to placebo effect based on the magnitude and durability of improvement and the association of KCCQ score with TR reduction. Several panelists expressed concerns about identifying the correct patient population that will benefit from the device. They emphasized the need for a robust post approval study and training program. Information from this advisory meeting can be found on FDA's website at the following: February 13, 2024: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement – 02/13/2024

B. FDA's Post Panel Action

Comments from panel members made it clear that the panel believed that approval of this device with a revised indication and robust postmarket evaluation would be appropriate and in the interest of public health. FDA worked interactively with the sponsor to revise the indications for use from what was presented at the February 13, 2024 panel meeting to the current indications for use and to develop a post-approval study strategy to generate evidence to support: (1) longer-term durability and generalizability of the treatment; (2) effectiveness of the training program; and (3) further define the characteristics of the patient population that experiences a meaningful clinical benefit.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

E. Effectiveness Conclusions

In the TRILUMINATE Pivotal trial, the primary hierarchical composite endpoint of all-cause death or tricuspid valve surgery, heart failure hospitalizations, and KCCQ improvement of at least 15 points was met ($p=0.03$) indicating that the TriClip device in addition to OMT is superior to OMT alone. The study results did not show a benefit in mortality or TV surgery or number of heart failure hospitalizations with the TriClip device. The primary endpoint success was driven by a clinically meaningful KCCQ improvement, which may be susceptible to the placebo effect in an unblinded trial. However, the durability of KCCQ improvement, association of KCCQ improvement with TR grade and TR reduction, and the results of the exploratory imaging sub-study provide evidence to support that the KCCQ improvement is not solely due to placebo effect. TriClip was successfully implanted in 98.8% of subjects in the Device group. TR reduction to moderate or less at 30 days was achieved in 87% of Device subjects compared to 4.8% of Control subjects ($p<0.0001$).

The Single-Arm Cohort primary endpoint of survival with at least a 10-point improvement in KCCQ score at 12 months was met with a rate of 46.2%. The lower

98.75% confidence limit of 34.3% exceeds the performance goal of 30% with a p-value of 0.008. TR reduction by at least 1 grade was achieved in 98.9% of subjects.

F. Safety Conclusions

The risks of the TriClip G4 System are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory and animal studies demonstrated that the TriClip G4 System met its pre-specified performance criteria and is suitable for long-term implant.

The secondary endpoint in the TRILUMINATE Pivotal Trial of freedom from major adverse events showed the rate of freedom from MAEs occurring after procedure through 30 days was 98.3% with a lower 95% confidence limit of 96.3% which was greater than the performance goal of 90% ($p<0.0001$); thus, the endpoint was met. CEC adjudicated adverse events for subjects implanted with TriClip included mortality at 1 year (8.1%), heart failure hospitalization at 1 year (11.2%), tricuspid valve surgery at 1 year (1.8%), tricuspid valve intervention at 1 year (2.5%), major bleeding at 30 days (3.9%), and new onset renal failure at 30 days (1.4%).

In the Single-Arm Cohort, the rate of freedom from MAEs at 30 days was 100%, which exceeds the performance goal of 80% (p-value <0.0001). The CEC-adjudicated adverse event rates were higher in the Single-Arm Cohort, including mortality at 1 year (15%), heart failure hospitalization at 1 year (24%), and tricuspid valve intervention at 1 year (7%), which is expected for the more advanced disease state of this cohort.

There were no occurrences of operative mortality, no device thrombus, and no device embolization in the Randomized Cohort or the Single-Arm Cohort.

G. Benefit-Risk Determination

The probable benefits of transcatheter edge-to-edge valve repair with the TriClip G4 system in subjects who meet the conditions in the indications for use include reduction in TR and clinically meaningful improvements in quality of life and functional status as measured by KCCQ.

The probable risks of the TriClip G4 system include MAEs such as cardiovascular mortality, tricuspid valve surgery or re-intervention, heart failure hospitalization, major bleeding, and new onset renal failure.

Patient perspectives considered during the review included patient reported outcomes as measured by KCCQ and SF-36.

Given the available information, the data support that for the treatment of patients with symptomatic, severe tricuspid valve regurgitation, whose symptoms and TR severity persist despite being treated optimally with medical therapy, who are at intermediate

or greater risk of mortality or morbidity with open heart surgery, and in whom the TriClip device is expected to achieve a TR reduction of moderate or less, the probable benefits outweigh the probable risks.

H. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the TriClip G4 System when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on April 1, 2024. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct two post approval studies:

1. **Continued Follow-up of the Premarket Cohort**: The study will consist of all living patients who were enrolled under the IDE, including the Continued Access Protocol investigation. The objective of this study is to characterize the clinical outcomes annually through 5 years post-procedure. Data will be collected per the study protocol, including, but not limited to, adverse event data including deaths, tricuspid valve reintervention, and heart failure related hospitalizations, echocardiographic endpoints including tricuspid regurgitation severity grade, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, SF-36 score (1 and 2 years only), New York Heart Association (NYHA) classification, and 6-Minute Walk Test (6MWT) distance. KCCQ score and TR severity grade will be collected with a minimum of 75% completeness rate each year through 5 years.

2. **Registry-Based Real-World Use Surveillance**: The surveillance will be carried out to assess the real-world performance of the TriClip G4 system and the clinical outcomes of the device in patient populations underrepresented in the TRILUMINATE Pivotal trial. It will involve all consecutive patients treated within the first 2 years following device approval or a total of 5,000 consecutively treated patients, whichever is greater, who are entered into the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry (enrollment period). For the first 1,000 consecutively treated patients at a representative subset of sites (in terms of patient volume, geographic location, and operator expertise), key data, including KCCQ score and TR severity grade, will be collected with a minimum of 75% data completeness through one (1) year. A minimum of 50% of this subset of sites will be new sites that did not participate in the TRILUMINATE Pivotal trial. Data collection will continue for underrepresented racial and ethnic groups (Black/African American, Asian, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, and Hispanic or Latino ethnicity) until each group has enrolled a minimum of 100 patients. All patients will be followed through 5 years post-procedure (follow-up duration). The clinical data through one (1) year will be collected through the TVT

Registry. The follow-up data (including all-cause mortality, stroke, tricuspid valve reintervention, and hospitalization) from year 2 through year 5 post-procedure will be obtained through linking the TVT Registry data with the Centers for Medicare and Medicaid Services (CMS) claims database.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Finkelstein DM and Schoenfeld DA. *Combining Mortality and Longitudinal Measures in Clinical Trials*. Stat Med 1999; 18:1341-54.

2. Pocock SJ, Ariti CA, Collieret TJ, et al. *The Win Ratio: a New Approach to the Analysis of Composite Endpoints in Clinical Trials Based on Clinical priorities*. Eur Heart J 2012; 33:176-82.

3. Stone GW, Lindenfeld J, Abraham WT, et al. *Transcatheter Mitral-Valve Repair in Patients with Heart Failure*. N Engl J Med 2018; 379:2307-2318.