TRICLIP™ G4 SYSTEM

CIRCULATORY SYSTEMS DEVICE PANEL

MEETING DATE: 13 FEB 2024

SPONSOR EXECUTIVE SUMMARY

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List of Abbreviations

Abbreviation	Definition
6MWT	6-Minute Walk Test
6MWD	6-Minute Walk Test Distance
ACC	American College of Cardiology
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AHA	American Heart Association
ANCOVA	Analysis of Covariance
APS	Acute Procedural Success
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor/Neprilysin Inhibitor
AT	As-treated
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
CAD	Coronary Artery Disease
CE	Conformite Europeenne (product meets applicable health, safety, and environmental regulations in the European Union, and can be commercialized)
CEC	Clinical Events Committee
CI	Confidence Interval
CIED	Cardiac Implantable Electronic Device
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
CRRT	Continuous Renal Replacement Therapy
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy with Defibrillator
cm	centimeter
CT	Computed Tomography
EACTS	European Association for Cardio-Thoracic Surgery
ECA	Anatomic Eligibility Committee
ECPM	Patient Management Eligibility Committee
ECL	Echocardiography Core Laboratory
ED	Emergency Department
EROA	Effective Regurgitant Orifice Area

ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
FS	Finkelstein-Schoenfeld
GDMT	Guideline-Directed Medical Therapy
HFH	Heart Failure Hospitalizations
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
ITT	Intention-to-Treat
IV	Intravenous
KM	Kaplan-Meier
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-OS	KCCQ Overall Summary Score
LOCF	Last Observation Carried Forward
LVEF	Left Ventricular Ejection Fraction
MAE	Major Adverse Events
MCS	Mental Component Summary
mL	milliliter
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PCS	Physical Component Summary
PISA	Proximal Isovelocity Surface Area
PMA	Pre-Market Approval
PMCF	Post-Market Clinical Follow-up
POD	Days Post-Procedure
PP	Per-Protocol
ppts	Difference in Percentage
pts	Patients
Q1	First quartile
Q3	Third quartile
RA	Right Atrium or Right Atrial
RAEDV	Right Atrial End Diastolic Volume
RAVI	Right Atrial Volume Index
RCT	Randomized Controlled Trial
RV	Right Ventricle or Right Ventricular

RVEDD	Right Ventricular End Diastolic Diameter
RVEF	Right Ventricular Ejection Fraction
SD	Standard Deviation
SE	Standard Error
SF-36	Short Form Survey Questionnaire
SLDA	Single Leaflet Device Attachment
sPAP	Systolic Pulmonary Artery Pressure
STS	Society of Thoracic Surgeons
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Transesophageal Echocardiogram
TEER	Transcatheter Edge-to-Edge Repair
TIA	Transient Ischemic Attack
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiography
TV	Tricuspid Valve
TVT	Transcatheter Valve Therapies
TTVr	Transcatheter Tricuspid Valve repair
TVRS	Tricuspid Valve Repair System
VARC	Valve Academic Research Consortium
US	United States

1 SYNOPSIS

1.1 Introduction

Abbott is seeking approval of the TriClip™ G4 System for the improvement of health status in patients with symptomatic severe tricuspid regurgitation (TR) despite being treated optimally with medical therapy, who are at intermediate or greater risk for surgery and in whom tricuspid valve edge-to-edge repair (TEER) is appropriate as determined by a heart team.

TR is failure of the tricuspid valve to close completely during systole, resulting in impaired hemodynamics, such as leakage or “regurgitation” of blood from the right ventricle to the right atrium with each contraction of the heart. Once TR is severe, symptoms are often debilitating, impacting the health status of patients; however, limited treatment options exist in the United States (US). Patients with TR experience fatigue, declining exercise capacity, swelling of the abdomen, legs, or veins of the neck, abnormal heart rhythms, and shortness of breath with activity, which can all significantly impact patients’ health status. Due to the high morbidity and mortality risk associated with tricuspid valve surgery and the lack of effectiveness of medical therapy alone, there remains a significant unmet need for the safe treatment of patients with symptomatic severe TR.

TriClip is a minimally invasive transcatheter edge-to-edge repair system for the treatment of TR. TriClip was developed based on the well-established clinical experience with Abbott’s MitraClip System, a transcatheter edge-to-edge repair technology for the treatment of mitral regurgitation. MitraClip received Conformité Européenne (CE) mark in 2008 and US FDA approval in 2013 and has been used in more than 200,000 patients worldwide. MitraClip has been used off-label for the treatment of TR since 2015, highlighting the unmet need for an approved treatment specifically for this disease. TriClip was developed using an identical clip-based technology as MitraClip, but with a differentiated delivery system and steerable guide specifically designed to access the tricuspid valve. TriClip was granted Breakthrough Device Designation because of the clear unmet need and lack of satisfactory treatment options for the treatment of TR.

The clinical development program for TriClip includes the first clinical study (TRILUMINATE CE study) initiated in 2017, a pivotal randomized controlled trial (TRILUMINATE Pivotal trial), and a post-market study in the European Union (bRIGHT study). Across all studies, the TriClip System has been shown to be highly effective in reducing TR with very low risk. Patients experienced immediate reduction in TR severity, which was accompanied by improved health status and symptom relief. The totality of the data presented in this briefing document not only confirm the safety and effectiveness of TriClip but also demonstrate that reduction in TR with TriClip is associated with a true physiological effect. Given the limited safe treatment options for

symptomatic severe TR patients, these results support a favorable benefit to risk profile of repair with TriClip.

1.2 Background and Unmet Need

TR is an abnormal condition which has both short-term and long-term consequences. TR decreases forward cardiac output and raises right-sided systemic venous pressures. This physiology will often result in hepatorenal congestion and dysfunction and, in addition, cause edema and ascites. The retrograde cardiac blood flow and volume loading also leads to further tricuspid dilatation exacerbating regurgitation over time. Published literature suggests that at least 3% of the population over 65 years old in the US (~58 million people) has significant TR and an estimated 400,000 people experience severe TR (see **Section 2.3** for details).

The most common etiology of TR is functional (or secondary), usually related to right atrial and right ventricular dilation secondary to left-sided heart disease, pulmonary hypertension, and atrial arrhythmias. TR typically progresses and is an indolent process. Once TR is severe, symptoms are often debilitating, impacting the physical and social functioning and quality-of-life of patients. Early symptoms include peripheral edema, fatigue, changes in appetite, and shortness of breath. Additionally, TR can lead to more serious complications such as ascites, liver and renal dysfunction, rhythm disorders, and right heart failure (Otto et al. 2021, Beckhoff et al. 2018, Fender et al. 2018, Hahn 2023). Resolution of symptoms and reversing the sequalae of chronic severe TR safely are the primary consideration for TR intervention.

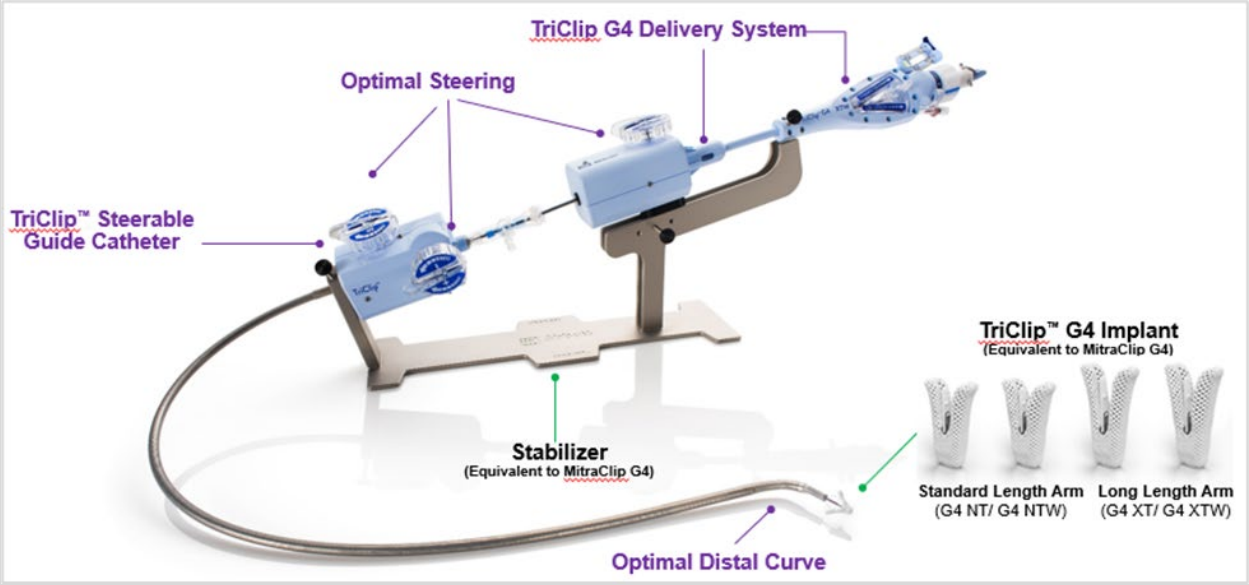
In the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of valvular heart disease (Otto et al., 2021), the only current Class 1 indication for the treatment of TR is in patients undergoing left-sided valve surgery. All other indications are Class 2, reflecting the status of the evidence for intervention in the setting of TR with no other valvular disease. Surgical treatment of TR is associated with poor outcomes and is rarely performed in the US. While medical therapy has a role, medical therapy alone is often ineffective in reducing TR. This leaves TR patients with limited options and a population that is largely undertreated. These patients need a safe and effective treatment option to reduce their symptoms and improve their overall health status.

1.3 Product Overview

The TriClip System is a first-of-its-kind minimally invasive transcatheter edge-to-edge tricuspid repair system that reduces the backflow of blood caused by TR. The TriClip System is comprised of the following components (see **Figure 1-1**):

- The Steerable Guide Catheter which allows for access to the right atrium (RA), with optimal steering for the tricuspid valve.
- The Clip Delivery System which delivers and deploys the implant, with optimal distal curve for easier access to the tricuspid valve.

Figure 1-1: TriClip G4 System



TriClip operates in a similar fashion as MitraClip but was specifically designed to access and treat the tricuspid valve. The TriClip device is available in four implant sizes to accommodate different patient anatomies.

1.4 TRILUMINATE Pivotal Trial

1.4.1 Trial Overview

The TRILUMINATE Pivotal trial is a prospective, multicenter, randomized (1:1), controlled trial to assess the superiority of TriClip in addition to medical therapy (Device group) compared to medical therapy alone (Control group). The trial enrolled symptomatic patients with severe TR despite being optimally treated with medical therapy for TR or other cardiac conditions and who were determined by the site's local heart team to be at intermediate or greater estimated risk for mortality with tricuspid valve (TV) surgery. With the recent development of transcatheter solutions, the traditional "severe" category has been stratified into severe (severe 3), massive (severe 4), and torrential (severe 5) to better assess changes in TR (Hahn and Zamorano 2017). The trial excluded patients whose symptoms could be attributed to conditions other than TR, i.e., patients with left ventricular ejection fraction (LVEF) ≤ 20%, severe pulmonary hypertension, severe uncontrolled systemic hypertension, or patients indicated for left-sided or pulmonary valve correction.

The trial was designed with two cohorts (**Figure 1-2**):

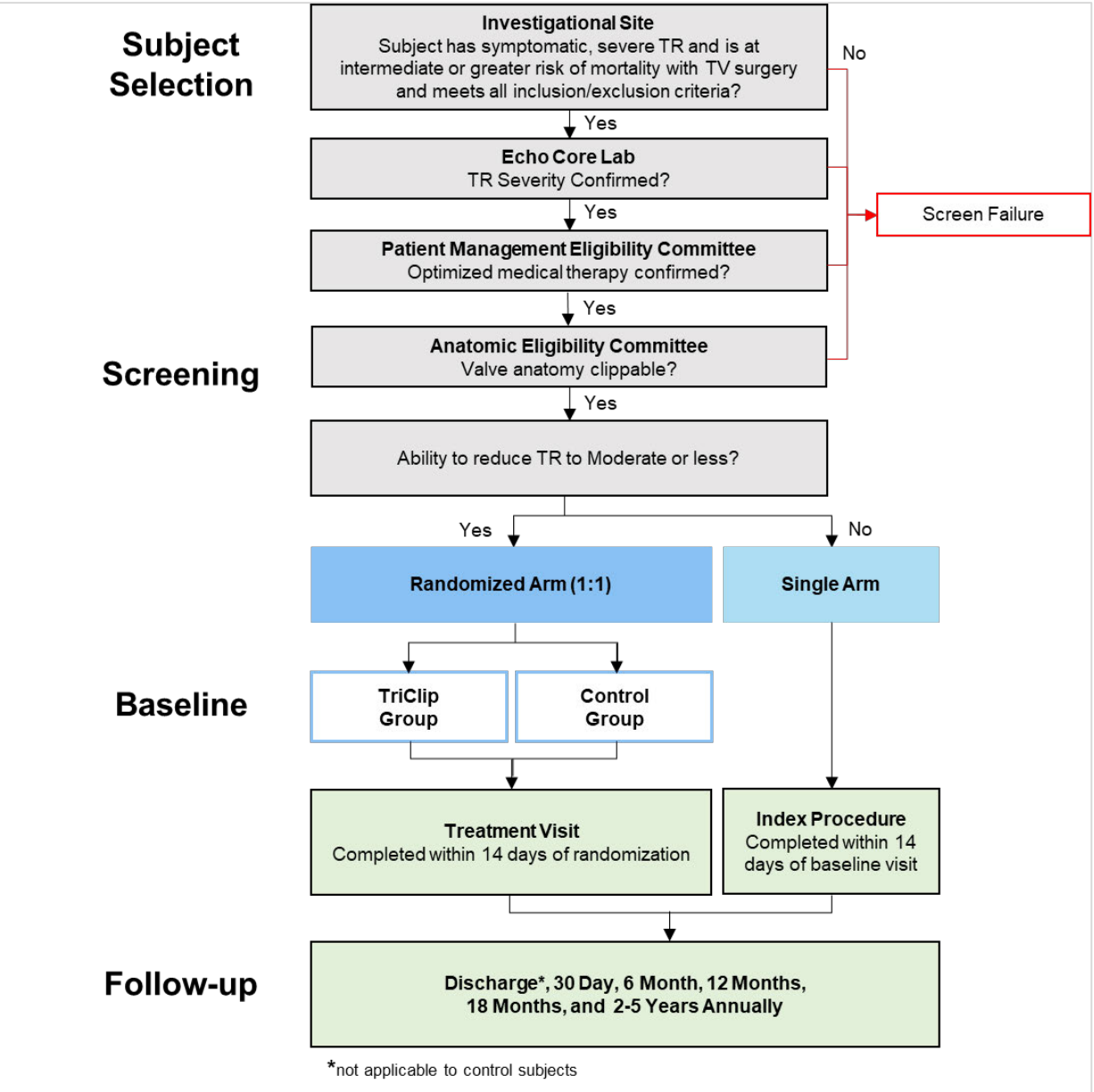
- Randomized cohort, which included patients with tricuspid valve anatomic characteristics deemed by the independent trial eligibility committee to have a high likelihood of achieving TR reduction to moderate or less with TriClip

- Single-arm cohort, which included patients with tricuspid valve anatomic characteristics deemed to have a low likelihood of achieving moderate or less TR but a high likelihood of achieving TR reduction of ≥ 1 grade with TriClip.

Prior to enrolling in the Randomized or Single-arm cohorts, up to 3 Roll-in patients were permitted per implanter without prior TriClip experience.

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

Figure 1-2: Trial Flow Chart



1.4.2 Visit Schedule

Following the baseline visit and randomization, patients were required to complete a Treatment visit (within 14 days of randomization), discharge visit (Device group only), and visits at 30 days, 6 months, 12 months, 18 months, and annually through 5 years. At the Treatment visit, Device patients underwent the index TriClip procedure and Control patients were seen by the heart failure specialist and underwent a physical examination, including vital signs, cardiac health status and evaluation of heart failure medications. Patients underwent transthoracic echocardiography (TTE) examination at all follow-ups, except at 18 months, and all echocardiography data including TR severity

at baseline and follow-up visits were assessed by an independent Echocardiography Core Laboratory (ECL). If TR remained severe (as assessed by the ECL) in a Control patient after completing the 12-month visit and the patient's anatomy remained appropriate for TriClip therapy (as assessed by the Anatomic Eligibility Committee), crossover TriClip procedure was allowed.

1.4.3 Primary and Secondary Endpoints

The primary endpoint of the Randomized cohort was a hierarchical composite at 12 months, with the objective to demonstrate superiority of the Device group over the Control group. The components of the primary endpoint included (listed in hierarchical order):

1. Time to all-cause death or tricuspid valve (TV) surgery
2. Number of heart failure hospitalizations (HFH)
3. Improvement of ≥15 points in Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS) from baseline

The primary endpoint was assessed on the Intention-to-Treat (ITT) population using the Finkelstein-Schoenfeld (FS) method (Finkelstein and Schoenfeld 1999), a nonparametric statistical test which evaluates endpoints in a hierarchical order determined by clinical importance. The objective was to demonstrate superiority of the Device group over the Control group. Upon the World Health Organization's declaration of the COVID-19 pandemic, and with approval from the FDA, Abbott updated the primary endpoint analysis in the statistical analysis plan as follows: for patients who experienced death or any hospitalization adjudicated by the independent Clinical Events Committee (CEC) as related to COVID-19, this event, and all subsequent data, if any, were censored in the primary endpoint analysis.

Secondary endpoints for the Randomized cohort were tested in a prespecified sequence as follows:

- **Secondary Endpoint #1:** Freedom from major adverse events (defined as cardiovascular mortality, new-onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for a TriClip device-related adverse event) at 30 days
- **Secondary Endpoint #2:** Change in KCCQ-OS at 12 months
- **Secondary Endpoint #3:** TR reduction to moderate or less at 30 days post procedure as assessed by TTE
- **Secondary Endpoint #4:** Change in 6-minute walk test distance (6MWD) at 12 months

Due to the uncertainty in trial design parameters at the time of trial design, the Randomized cohort had an adaptive design with sample size re-estimation planned when the first 150 patients completed 12-month follow-up. The trial randomized a total of 572 patients prior to completion of the sample size re-estimation, which indicated that

350 patients (Primary Analysis Population) with 12-month follow-up were adequate for the determination of superiority of treatment with TriClip over control.

The primary endpoint for the Single-arm cohort was survival at 12 months with improvement in KCCQ-OS ≥10 points from baseline, compared to a performance goal. The Single-arm cohort had a group sequential design with maximum sample size of 200 patients with an interim analysis to be conducted when the first 100 patients completed 12 months of follow-up.

Statistical assumptions and adaptive design details are described in **Section 6**.

1.5 Primary Analysis Population Results

1.5.1 Baseline Characteristics

The mean age of the Randomized cohort was approximately 78 years and 55% were female. At baseline, more than half of the cohort (57%) were in New York Heart Association (NYHA) Class III or IV, with mean baseline KCCQ-OS of 55.1 ± 23.8. The most common comorbidities included atrial fibrillation (90%), hypertension (81%), and renal disease (35%). Baseline demographics and medical history details are provided in **Section 7.3**.

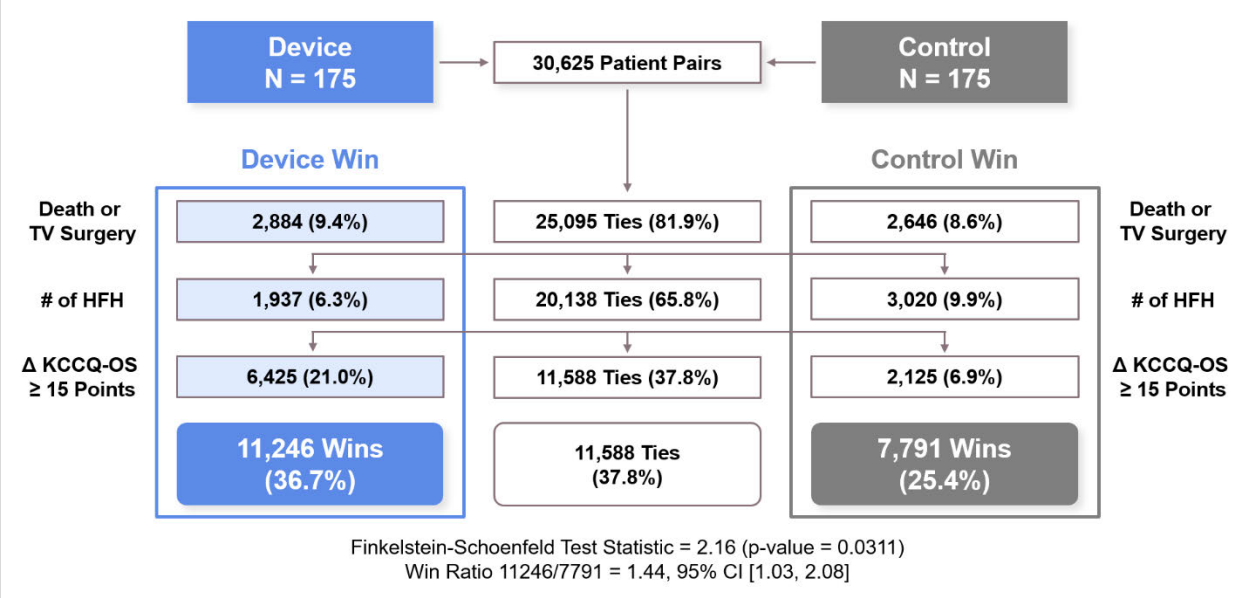
1.5.2 Effectiveness Results

1.5.2.1 Primary Endpoint Results

The trial met its primary endpoint (**Figure 1-3**), with FS p=0.0311. There were 11,246 “wins” for the Device group and 7,791 for the Control group, resulting in a win ratio (i.e., ratio of number of wins for Device to number of wins for Control) of 1.44 with 95% confidence interval [1.03, 2.08].

Please note that the results presented in this briefing document are slightly different from those reported in Sorajja et al. 2023 which used an earlier data cut-off.

Figure 1-3: Primary Endpoint (Intention-to-Treat, Primary Analysis Population, N=350)



As described in **Section 7.4**, death/TV surgery (Device: 9.4%, Control: 10.6%) and HFH rates (Device: 0.22, Control: 0.17 per patient-year) at 12 months were comparable between the Device and Control groups, therefore, the primary endpoint results were driven by the KCCQ-OS component. In the Device group, 50% of patients experienced KCCQ-OS improvement by ≥ 15 points, compared to 26% in the Control group. Additionally, Device patients experienced improvement over Control patients across all individual domains of the Kansas City Cardiomyopathy Questionnaire (KCCQ), with the quality-of-life and social limitation domains showing the largest improvement (See **Section 7.5.1** for details).

The 12-month rates for both death/TV surgery and HFH were lower than anticipated. It is important to note that when the trial was designed, the 12-month mortality rate for patients with severe TR was reported to be between 7% and 52% (See **Section 6.6.3**). The trial reported a 12-month all-cause mortality rate of 7.7% (Control group) and 8.8% (Device group), consistent with Topilsky et al. 2014. The HFH rate was also lower than the anticipated rate of 0.5 HFH/patient-year but within the range of rates reported in other transcatheter device trials for TR (Kitamura et al. 2021[1], Kodali et al. 2023[2]).

Despite the lower than anticipated rates of death/TV surgery and HFH and no notable differences between Device and Control groups, the trial met the endpoint showing a

[1] Study reported 20% of patients experienced rehospitalization for heart failure after receiving a Pascal TEER device.
[2] Study reported 10.2% of patients experienced a HFH at 1 year after being implanted with the Evoque transcatheter tricuspid valve.

significant improvement in KCCQ-OS for TriClip patients compared to patients on medical therapy alone. As demonstrated in **Section 9**, the results in the Full Randomized Cohort of 572 patients reinforce the conclusions from the Primary Analysis Population.

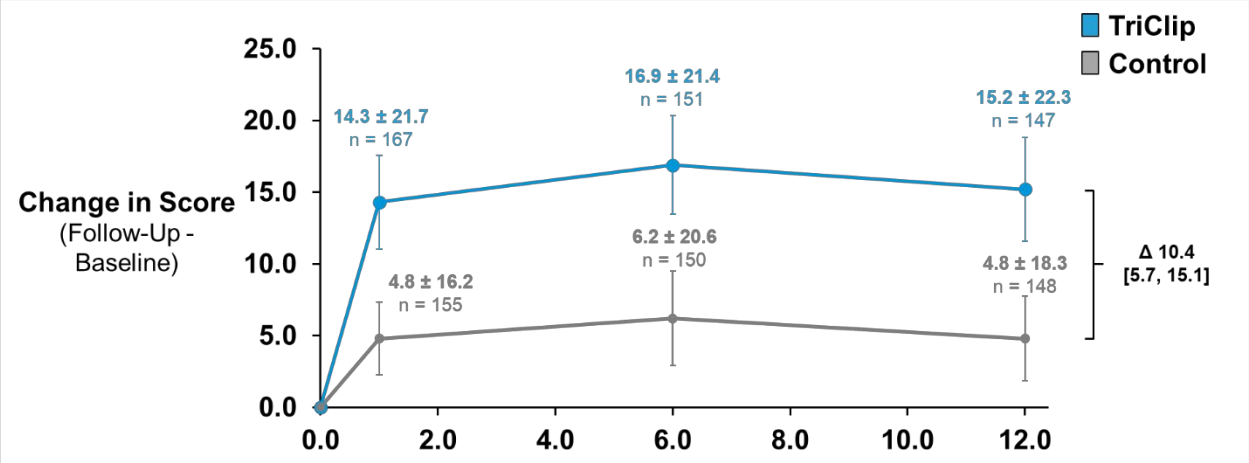
In summary, TriClip in conjunction with medical therapy was superior to medical therapy alone, demonstrating a significant benefit in health status.

1.5.2.2 Secondary Endpoint Results

KCCQ-OS (Secondary Endpoint #2[3]):

The secondary endpoint of change in KCCQ-OS at 12 months was intended to quantify the health status benefit. The endpoint was met, with the KCCQ-OS improvement in the Device group being significantly greater than that in the Control group (changes of 12.34 vs. 0.61 points, p<0.0001 in pre-specified analysis which imputed 0 KCCQ-OS values for patients who experienced heart failure related death or underwent TV surgery prior to 12 months). In complete-case paired analysis shown in **Figure 1-4**, KCCQ-OS change from baseline was larger in the Device group over the Control group at 30 days and sustained through 6 and 12 months.

Figure 1-4: KCCQ-OS Change Over Time (Complete-Case Paired Analysis, Primary Analysis Population, N=350)



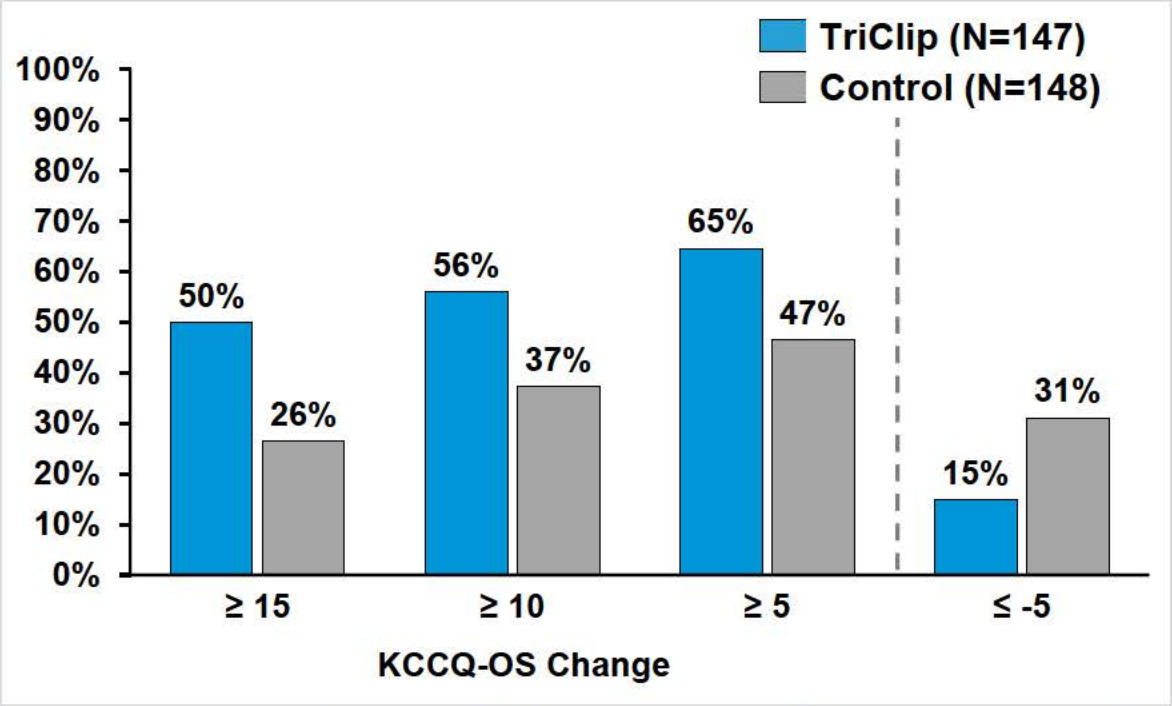
Numbers shown are Mean ± SD (n); Error bars represent 95% CI (not adjusted for multiple testing). Numbers in square brackets represent 95% CI for the between-group difference in change from baseline to 12 months.

Figure 1-5 shows the proportion of Device and Control patients with KCCQ-OS change at 12 months of ≥15 points, ≥10 points, ≥5 points and ≤-5 points. Regardless of the cutoff used to define KCCQ-OS improvement, a higher proportion of Device patients than Control patients experienced improvement. Additionally, a lower proportion of

[3] See **Section 1.5.3** for Secondary Endpoint #1 result

Device patients had worsening of KCCQ-OS by at least 5 points than Control patients (15% vs. 31%).

Figure 1-5: Proportion of Patients with Change in KCCQ-OS at 12 Months (Paired Analysis, Primary Analysis Population, N=350)



Dotted line represents cutoff for positive KCCQ-OS change threshold (left) versus negative KCCQ-OS change threshold (right)

Responder analysis in **Table 1-1** showed that patients who experienced the largest improvement in KCCQ-OS (≥ 15 points) had the lowest baseline KCCQ-OS (46.8 points) and there is an increasing trend as the cut point changes from 15 points to 10 points (49.1 points) and 5 points (50.6 points), with patients who experienced a reduction in KCCQ-OS of more than 5 points having the highest baseline KCCQ-OS (76.6 points).

Table 1-1: KCCQ-OS at Baseline for Randomized Device Group for Different Cut Points for Change in KCCQ-OS at 12 Months (N=147, Paired Data)

	Change in KCCQ-OS ≥ 15 points (N=73, 50%)	Change in KCCQ-OS ≥ 10 points (N=83, 56%)	Change in KCCQ-OS ≥ 5 points (N=95, 65%)	Change in KCCQ-OS ≤ -5 points (N=22, 15%)
Baseline KCCQ-OS Mean ± SD	46.8 ± 17.7	49.1 ± 18.8	50.6 ± 19.9	76.6 ± 13.0

TR Reduction (Secondary Endpoint #3):

The secondary endpoint of TR reduction to moderate or less at 30 days was intended to support the clinical objective of TriClip which is to reduce TR and provide a mechanism of action to support primary endpoint results. The endpoint was met, with 87% of Device patients achieving moderate or less TR at 30 days compared to only 5.4% of Control patients ($p<0.0001$).

The substantial reduction in TR severity to moderate or less at 30 days in Device patients was sustained to 12 months (89%) (**Figure A-2** in **Appendix 1**).

6MWD (Secondary Endpoint #4):

The secondary endpoint of change in 6MWD at 12 months was intended to assess whether TR reduction improved exercise capacity. The endpoint was not met ($p=0.2482$), although the between-group difference of Δ17.1 meters favored the Device group. The difference was larger in the Full Randomized Cohort (Δ24.8 meters) favoring the Device group, as shown in **Section 9**, with 95% confidence interval that does not overlap 0 (confidence interval calculated without multiplicity adjustment).

NYHA Class (Descriptive Endpoint):

The proportion of patients categorized as NYHA functional class I/II improved from 46% at baseline to 84% at 12 months for the Device group versus 47% to 59% for the Control group, indicating significant symptomatic benefit from the device. See **Figure A-1** in **Appendix 1** for details.

In summary, the trial showed a clinically meaningful and sustained reduction in TR with the TriClip device, accompanied by significant improvements in health status and symptoms compared to medical therapy alone.

1.5.3 Safety Results

Freedom from Major Adverse Events (MAE) at 30 Days (Secondary Endpoint #1):

The trial demonstrated that TriClip has a favorable safety profile. Freedom from MAE at 30 days after the TriClip procedure was 98.3%, with the lower limit for the 95% confidence interval of 96.3%, which was greater than the performance goal of 90% ($p<0.0001$). Components of the endpoint are shown in **Table 1-2**.

Table 1-2: Components of Major Adverse Events at 30 Days following TriClip Procedure – (Treated Device Patients, N=172)

MAE Component	n (%)
Any MAE	**3 (1.7%)**
Cardiovascular death[a]	1 (0.6%)
New onset renal failure[b]	2 (1.2%)
Endocarditis requiring surgery	0 (0%)
Non-elective cardiovascular surgery for TriClip device-related AE post-index procedure	0 (0%)

[a] Adjudicated by CEC as not procedure- or device-related
[b] One event was adjudicated by CEC as procedure-related and neither event as device-related

Through 12 months, TV surgery/intervention, stroke, transient ischemic attack (TIA) and cardiogenic shock all occurred at low and comparable rates between the Device and Control groups. There were no procedural deaths, device embolization or device thrombosis in the Device group. The need for new permanent pacemaker implantation was low and comparable between Device and Control groups through 30-days post Treatment visit (0.7% and 1.3% in Device and Control group) and through 12 months post randomization (3.6% and 3.4% in Device and Control groups, respectively), indicating no increased risk of conduction disturbances with TriClip therapy. See **Section 8** for details.

In summary, the trial met the secondary safety endpoint, with 98.3% of patients being free of MAE at 30 days, no procedural mortality, no endocarditis, no non-elective cardiovascular surgery for TriClip related adverse events, and very low rates of cardiovascular death and new onset renal failure. The safety profile of TriClip is particularly important to highlight given the limited treatment options for patients with symptomatic severe TR.

1.6 Full Randomized and Single-Arm Cohorts Primary Results

1.6.1.1 Full Randomized Cohort Results

The trial randomized a total of 572 patients (Full Randomized Cohort) prior to completing the sample size re-estimation. Preliminary results on this cohort reinforce the conclusions of the Primary Analysis Population (Note: at the time of this analysis, 56 patients are pending 12-month follow-up).

The p-value for the FS analysis is 0.0042 and the win ratio estimate in this cohort is higher than in the Primary Analysis Population, with tighter confidence interval (win ratio: 1.53 [1.14, 2.06]) - p-value and confidence interval not adjusted for multiple testing. The between-group difference in KCCQ-OS in the Full Randomized Cohort (Δ11.9 points with imputation and Δ11.0 in complete-case paired analysis) is consistent with that observed in the Primary Analysis Population (Δ11.7 points with imputation and Δ10.4 in complete-case paired analysis).

At 30 days, 88.9% of Device patients experienced TR reduction to moderate or less compared to 5.3% of Control patients. Between-group differences in 6MWD favoring the Device group in the Full Randomized Cohort are larger than in the Primary Analysis Population (Δ24.8 vs. Δ17.1 meters with imputation; Δ27.2 vs. Δ20.3 meters in complete-case paired analysis) with 95% confidence interval that does not overlap 0. The safety profile of TriClip in this larger cohort remains favorable with 98.9% freedom from MAE rate at 30 days. Details on the Full Randomized Cohort are provided in **Section 9**.

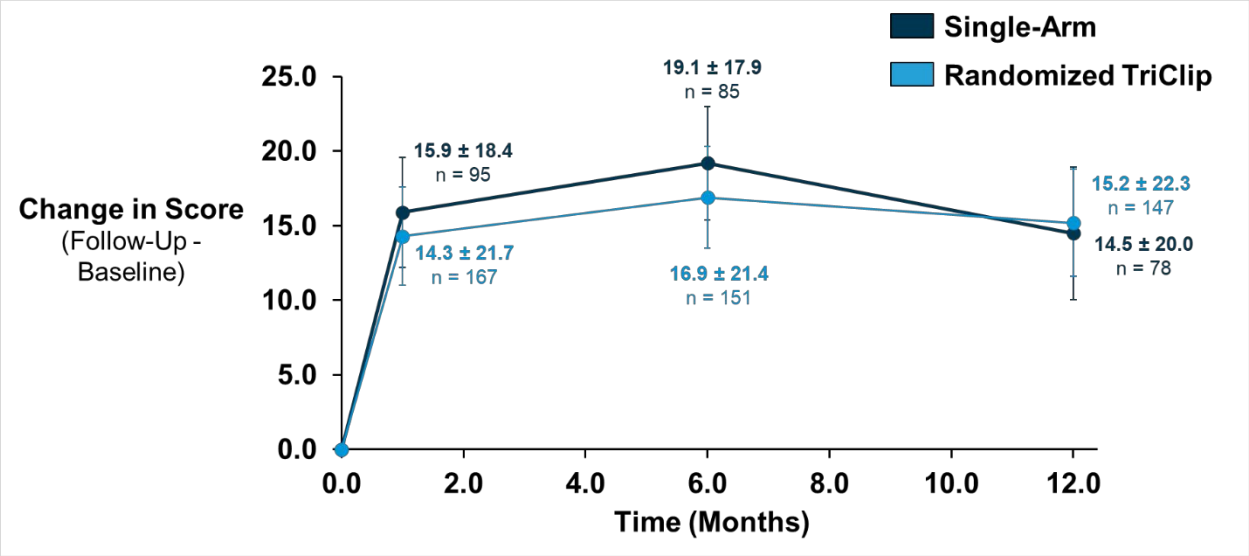
In summary, preliminary results on the Full Randomized Cohort confirm the safety and effectiveness of the TriClip device and reinforce the conclusions of the Primary Analysis Population.

1.6.1.2 Single-Arm Cohort Primary Results

TriClip demonstrated reduction in TR to moderate or less at 30 days in 80% of patients in the Single-arm cohort composed of patients with more complex anatomic characteristics compared to the Randomized cohort (i.e., larger coaptation gaps: 7.4 ± 2.7 mm vs. 5.4 ± 1.8 mm, more torrential TR: 74.0% vs. 50.9%, and higher incidence of pacing or implantable cardioverter defibrillator leads: 35.0% vs. 14.9%).

The primary endpoint of survival at 12 months with ≥ 10-point improvement in KCCQ-OS was met, with 46.2% of patients meeting the endpoint, which met the performance goal of 30% (p=0.0008). Although patients in the Single-arm cohort were older (by approximately 2 years) with higher risk characteristics and had more advanced disease than the Randomized cohort (larger right atrial volume by 33.6 mL and larger right ventricular end diastolic dimension-mid by 0.3 cm), the safety profile of TriClip in this cohort was comparable to that in the Device group of the Randomized cohort. None of the Single-arm patients experienced MAEs at 30 days and other adverse events occurred at very low rates, consistent with the Device group of the Randomized cohort. These patients also experienced the same magnitude of health status benefit as the Device group of the Randomized cohort through 12 months (**Figure 1-6**). Details on the Single-arm cohort are provided in **Section 10**.

Figure 1-6: KCCQ-OS Change in the Single-arm Cohort (N=100) and Randomized Cohort - Device Group (N=175)



Error bars represent 95% CI (not adjusted for multiple testing).

To summarize, TriClip is a safe and effective therapy option for anatomically complex patients including those deemed not likely to have TR reduced to moderate or less. The results in the Single-arm cohort confirm the favorable benefit/risk profile of TriClip even in more anatomically complex patients with more advanced disease.

1.7 Addressing Potential Bias in an Open-Label Trial

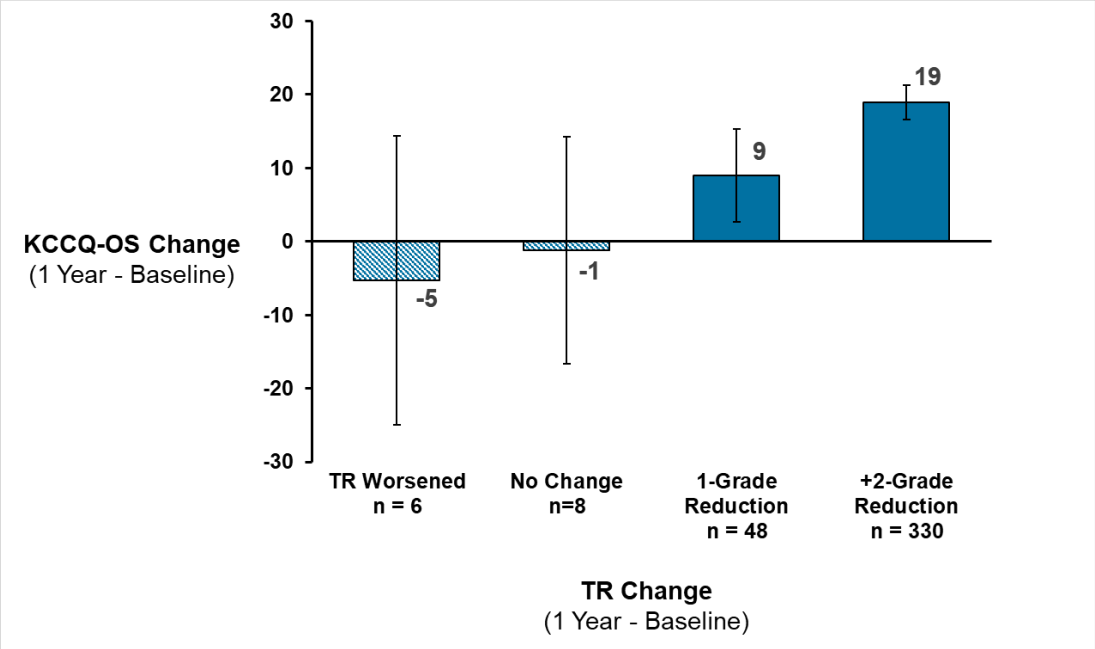
As the TRILUMINATE pivotal trial results are based on an open-label design and the trial met the primary endpoint driven by a patient-reported outcome (KCCQ-OS) alone, it can be hypothesized that patients' responses to the KCCQ may have been influenced by their knowledge of randomization and treatment received ("placebo effect"). The following additional analyses and reasoning support a true treatment effect with TriClip.

- *Substantial and Sustained Reduction in TR to Moderate or Less*
  TriClip was designed with the intent of reducing TR and the trial demonstrated substantial TR reduction in most patients. Despite the presence of massive or torrential TR at baseline in 71% of patients in the Randomized cohort, the device showed substantial and clinically meaningful reduction in TR to moderate or less at 30 days in 87% of patients compared to 5.4% in the Control group ($p<0.0001$). Reduction in TR to moderate or less with TriClip was sustained, with 89% of Device patients having moderate or less TR at 12 months. The ability of TriClip to substantially reduce and sustain the reduction in TR was further supported by the reduction of TR to moderate or less at 12 months in 79% of the more anatomically complex Single-arm patients where 91% of patients had massive or torrential TR at baseline. The reduction in TR measured by echocardiography was confirmed via Cardiac MRI in the Cardiac Imaging sub-study, which showed substantially reduced

regurgitant volume and regurgitant fraction measurements in the Device group but not in the Control group (**Section 11.1**).

- *Association between KCCQ-OS and TR Grade Change*
  Device patients were aware of treatment but likely unaware of the magnitude of TR change and/or how this may translate to effectiveness of treatment, therefore an association between TR grade change and change in KCCQ-OS supports that the health status improvement with TriClip reflects a real treatment benefit. When assessing only TriClip patients across all cohorts in the trial (Randomized, Single-arm, Roll-in), there is a clear association between KCCQ-OS change and TR grade change (**Figure 1-7**) at 12 months. Such an association cannot be a "placebo effect" since all patients were aware of receiving treatment with TriClip.

Figure 1-7: KCCQ-OS Change versus TR Grade Change at 12 Months (Randomized Device group, Single-arm Cohort, Roll-in Cohort)



Note: Patients who had TV surgery prior to 12 months are excluded.
Error bars represent 95% CI (not adjusted for multiple testing).
Striped bars represent data from <10 patients.

- *Magnitude of Health Status Benefit*
  As discussed in the Arnold et al. 2023's health status analysis from the TRILUMINATE Pivotal trial, the observed treatment benefit of 10.4 points in the trial is larger than the expected magnitude of a "placebo effect" (~5-6 points).
- *Durability of Health Status Benefit*
  The treatment benefit in terms of KCCQ-OS improvement at 30 days was sustained through 6 months and 12 months. Such changes are unlikely to be sustained

through multiple follow-up visits if awareness of treatment group was the only factor influencing the response to the KCCQ.

- *Anatomical Changes (Reverse Remodeling)*
  The Cardiac Imaging sub-study demonstrated:
  - Significant reduction in right ventricular end diastolic volume (RVEDV) via Cardiac MRI: At 30 days, RVEDV decreased substantially (-32.1 ± 33.5 mL) in the Device group while no improvement was seen in the Control group (3.3 ± 31.9 mL).
  - Significant improvement in Effective right ventricular ejection fraction (RVEF) via Cardiac MRI: At 30 days, Device patients experienced an increase in Effective RVEF of 8.4 ± 7.6 percentage points while no improvement was seen in the Control group (-0.2 ± 4.5 percentage points).
  - Sustained reduction in RVEDV via Cardiac CT: At 12 months, RVEDV showed reduction in the Device group (-35.8 ± 26.4 mL reduction from baseline) whereas no improvement was seen in the Control group (-1.0 ± 38.1 mL).

  See **Section 11** for details.

- *Physiological Changes (Biomarkers)*
  Analyses conducted on cardiac, liver, and renal function biomarkers showed that the odds of at least 15% improvement in several biomarkers (liver and renal) favored Device over Control. These analyses support that TR reduction is associated with improved liver and renal function. See **Section 12.5** for details.

Conclusions

The magnitude, durability and consistency of improvement in health status with the TriClip device compared to medical therapy alone cannot be solely due to patient's knowledge of treatment group as the change in health status was strongly associated with changes in TR grade. The benefits of TR reduction were observed in other objective measures such as right heart size and function and biomarkers, which cannot be attributed to patients' knowledge of treatment received. These analyses indicate a true treatment effect with TriClip.

1.8 Benefit-Risk Summary

Severe TR is a progressive disease associated with debilitating symptoms, physical and social limitations, and poor quality-of-life. Patients with TR experience fatigue, declining exercise capacity, swelling of the abdomen, legs, or veins of the neck, abnormal heart rhythms, and shortness of breath with activity, which can significantly impact patients' health status. While these patients have the option to undergo TV surgery, few patients with severe TR undergo surgery due to high rates of morbidity and perioperative mortality associated with surgery. Medical therapy, which is limited to diuretics, is often ineffective in reducing TR. The high operative risk associated with TV surgery and the lack of effectiveness of medical therapy alone has left patients with severe TR largely

untreated. The TriClip device was designed to offer patients with symptomatic severe TR a safe, minimally invasive option to reduce TR, amelioration of symptoms, and improvement in cardiac function and health status. TriClip was granted Breakthrough Device Designation by the FDA because of the clear unmet need and the lack of satisfactory treatment options.

The TRILUMINATE Pivotal trial met both the primary endpoint and the secondary safety endpoint, demonstrating that the device is safe and effective. The TriClip procedure was very safe with no operative mortality or urgent cardiac surgery for TriClip-related adverse events, and extremely low rates of cardiovascular mortality and new onset renal failure. Through 12 months, there were no device embolizations or device thromboses, and the need for new permanent pacemaker implantation was low and comparable between Device and Control groups. The trial demonstrated that TriClip effectively and substantially reduced TR in most patients to moderate or less at 30 days. The reduction in TR at 30 days following TriClip implantation was sustained at 12 months, accompanied by significant improvements in health status and heart failure symptoms measured by NYHA class compared to medical therapy alone. Importantly, the reduction in TR was associated with a corresponding improved health status measured by the KCCQ. The data from the Cardiac Imaging sub-study confirmed that TR reduction in the Device group was accompanied by clinically significant reverse cardiac remodeling that was sustained through 12 months and improved effective right ventricular ejection fraction. Such reverse remodeling was not noted in the Control group, confirming the mechanism of action for the health status improvement in the Device group over the Control group. The results also showed positive trends in liver and renal biomarkers favoring TriClip. Therefore, the health status improvement with TriClip is supported by physiological and anatomical changes. These data provide supporting evidence for a mechanistic explanation for the health status improvement for patients receiving the device. Collectively, despite the absence of improvement in death and HFH, the analyses indicate that the health status improvement with the TriClip device in this open-label trial is a true treatment benefit and cannot be attributed solely to the knowledge of treatment received.

The conclusions of the Primary Analysis Population were supported by the Single-arm cohort and were reinforced by the Full Randomized Cohort (N=572). The device demonstrated a consistent safety and effectiveness profile across all cohorts. Furthermore, the magnitude of benefit in health status observed across all cohorts is larger than that expected for a “placebo effect”. Importantly, although improvement in 6-Minute Walk Distance was not demonstrated in the Primary Analysis Population, the Full Randomized cohort demonstrated significant improvement favoring TriClip.

Patients with TR tend to be elderly with right heart dilation and it is important to intervene when the right heart has the capacity for reverse remodeling and patients can benefit from reduction in TR and associated improvement in health status.

In summary, TriClip was highly effective and safe in reducing TR, which led to significant improvements in health status at one year, without the high procedural risk often associated with tricuspid valve surgery or the limitations of medical therapy. The TriClip device offers a safe, compelling, and reliable treatment option with little to no added risk. With the favorable benefit to risk profile of the TriClip System, a historically undertreated population will have a safe and effective treatment option.

2 TRICUSPID REGURGITATION BACKGROUND

SUMMARY

- TR is an abnormal physiological condition, which has both short-term and long-term consequences. TR decreases forward cardiac output, raises right-sided systemic venous pressures, and often results in hepatorenal congestion and dysfunction.
- TR is an indolent process, and if left untreated, can progress and lead to debilitating symptoms, which can severely impact the patients' health status.
- Early symptoms of TR include peripheral edema, fatigue, changes in appetite, and shortness of breath. In the longer term, TR can lead to more serious complications such as liver and renal dysfunction, and right heart failure.
- Resolution of symptoms and reversing the sequalae of chronic severe TR is the primary goal for TR intervention.
- The high operative risk of isolated tricuspid valve surgery and the lack of effectiveness of medical therapy alone has left patients with severe TR largely untreated. These patients need a safe and effective treatment option to treat TR and improve their health status.

2.1 Introduction

The tricuspid valve is a one-way valve that controls blood flow from the right atrium into the right ventricle, which then pumps blood to the lungs. Oxygenated blood from the lung enters the left atrium and then through the mitral valve to the left ventricle, before exiting the heart through the aortic valve. During ventricular contraction, coaptation of the three leaflets of a normal tricuspid valve prevents backward regurgitation (**Figure 2-1**). The tricuspid valve is the largest valve in the heart and typically has three leaflets of unequal size (anterior, posterior, septal), with the number of leaflets varying even in healthy persons.

The valve leaflets are supported by complex chordal structure attached to papillary muscles. Given this complex chordal structure, the tricuspid valve is sensitive to changes in the position and function of the free wall of the right ventricle, as well as the interventricular septum.

The most common causes of TR are volume and pressure loading of the right ventricle. This condition is referred to as secondary (functional) TR and is commonly related to left-sided heart disease, pulmonary hypertension, and atrial arrhythmias. While the intrinsic structure of the leaflets appears normal, leaflet mal-coaptation leads to regurgitation into the right atrium during ventricular contraction (**Figure 2-2**).

Figure 2-1: The Tricuspid Valve

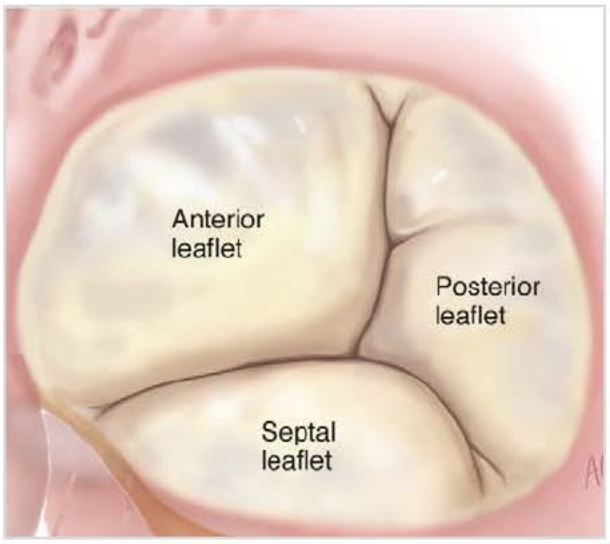
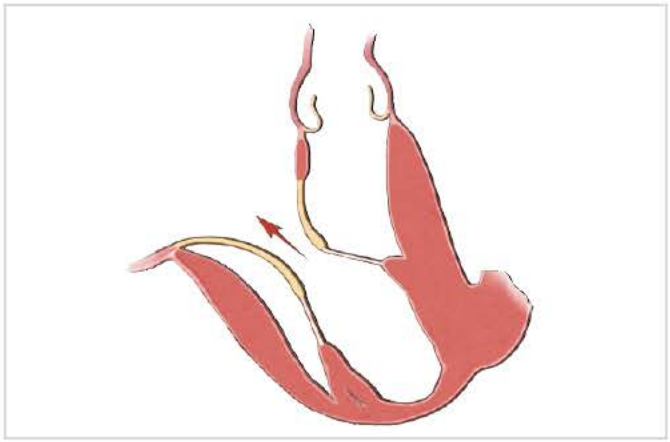


Figure 2-1: Functional Tricuspid Regurgitation



Source: Carpentier A, Adams DH, Filsoufi F. Carpentier's Reconstructive Valve Surgery. 2010 (1); Philadelphia, Saunders/Elsevier

Primary (degenerative) TR is a consequence of intrinsic disease of the valve and occurs because of congenital anomalies, blunt trauma, or degeneration of leaflets (**Table 2-1**). TR can also be associated with cardiac implantable electronic devices (CIED) as the device leads can interfere with any component of the tricuspid valve.

Table 2-1: Classification of TR Etiology (Adapted from Hahn et al. 2022)

Classification	Description	Etiologies	Mechanism
Secondary TR	Morphologically normal leaflets with annular dilatation and/or leaflet tethering	• Dilated tricuspid annulus and/or right atrium • Dilated right ventricle	Pulmonary hypertension, right ventricular dysfunction as a consequence of myocardial disease of the left heart, or atrial fibrillation
Primary TR	Structural abnormality of the tricuspid valve apparatus	• Prolapse • Flail • Leaflet clefts • Blunt trauma	Degenerative, congenital or acquired etiologies
CIED lead-induced TR	Caused by direct interaction of the lead with the valve leaflets		Impingement/tethering of leaflets directly caused by CIED lead

TR is an abnormal condition which has both short-term and long-term consequences. TR decreases forward cardiac output and raises right-sided systemic venous pressures. This physiology will often result in hepatorenal congestion and dysfunction. The

retrograde cardiac blood flow and volume loading from TR leads to further tricuspid dilatation exacerbating regurgitation over time. TR typically progresses and is an indolent process. Once severe, however, symptoms are often debilitating, impacting the health status of patients. Early symptoms include peripheral edema, fatigue, changes in appetite, and shortness of breath. While these symptoms are debilitating for a patient, if left untreated, TR can lead to organ failure, including liver and renal dysfunction, ascites, rhythm disorders, and right heart failure. Resolution of symptoms and reversing the sequalae of chronic severe TR are the primary consideration for intervention (Otto et al. 2021, Beckhoff et al. 2018, Fender et al. 2018, Hahn 2023).

2.2 Diagnosis and Disease Severity

Because TR is frequently diagnosed as an incidental finding in patients with coexisting conditions (such as mitral or aortic regurgitation or stenosis, atrial fibrillation, or pulmonary hypertension), many clinicians have, until recently, viewed it as an innocent bystander to the more consequential disease of the left heart or pulmonary vasculature. In the absence of left-sided disease, the clinical signs and symptoms of severe TR have historically been mistaken for normal signs and symptoms of aging, leaving many patients with TR untreated for long periods of time.

Severity of TR can be quite variable depending on right ventricular function, pulmonary hypertension and hydration status, and symptoms of TR are often not evident until the regurgitation is severe. TR is often detected too late and by the time of referral for treatment, some patients may be too high risk for cardiac surgery.

The 2017 American Society of Echocardiography guidelines categorize TR severity as trace/mild, moderate and severe based on an integrated evaluation of multiple quantitative, semi-quantitative and qualitative parameters (Zoghbi et al. 2017). With the recent development of transcatheter solutions, the traditional “severe” category has been stratified into severe (severe 3), massive (severe 4), and torrential (severe 5) to better assess changes in TR (Hahn and Zamorano 2017).

2.3 Prevalence

Published literature suggests that at least 3% of the population over 65 years old in the United States (~58 million people) have significant TR, resulting in an estimate of 1.7 million people (Singh et al. 1999, d’Arcy et al. 2016, Vieitez et al. 2021, Topilsky et al. 2019, Brennan et al. 2022, Offen et al. 2022, Rao et al. 2023). This estimate is consistent with the estimate of 1.6 million in a 2006 publication (Stuge and Liddicoat 2006). Based on a conservative assumption that a quarter of these patients have severe TR, 400,000 patients in the United States over 65 years old are estimated to have severe TR.

2.4 Tricuspid Regurgitation Treatment Options

As discussed below, neither medical therapy alone nor TV surgery adequately address the need for patients suffering from symptomatic severe TR, leaving these patients with limited options, and a population that is largely undertreated.

2.4.1 Medical Management

The ACC/AHA valvular guidelines (Otto et al. 2021) recommend a low-salt diet, support stockings, and diuretics in patients with signs and symptoms of right-sided heart failure attributable to severe TR. Medical therapy (diuretics) relieves systemic congestion and alleviates symptoms, but is often ineffective in reducing TR. The guidelines recommend addressing the primary causes of heart failure, such as pulmonary vasodilators for pre-capillary pulmonary hypertension, guideline-directed medical therapy (GDMT) for reduced left ventricular ejection fraction, and rhythm control for atrial fibrillation (**Table 2-2**).

Table 2-2: ACC/AHA Guidelines for Medical Therapy for TR

COR	LOE	Recommendations
2a	C-EO	**In patients with signs and symptoms of right-sided HF attributable to severe TR (Stages C and D), diuretics can be useful**
2a	C-EO	**In patients with signs and symptoms of right-sided HF attributable to severe secondary TR (Stages C and D), therapies to treat the primary causes of HF (e.g., pulmonary vasodilators to reduce elevated pulmonary artery pressures, GDMT for HF with reduced LVEF, or rhythm control of AF) can be useful (1,2)**

COR: Class of Recommendation (2a represents "moderate" strength of recommendation, i.e., is reasonable)
LOE: Level of Evidence (C-EO represents consensus of expert opinion based on clinical experience)

2.4.2 Surgery

The only Class 1 indication for the treatment of TR is in patients undergoing left-sided valve surgery (**Table 2-3**). All other indications are Class 2, reflecting the status of evidence for intervention in the setting of TR with no other valvular disease. The guidelines note “tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations”, but do not mention the potential impact on long-term mortality, as this evidence does not exist in the surgical literature.

Surgical treatment of TR is associated with high mortality and morbidity and isolated TV surgery is rarely offered or performed in the US. In-hospital mortality nears 10% in the largest studies with patients ranging in age from 55 to 65 years, with high rates of cardiogenic shock (6.2% – 19%), acute renal failure (5.3% – 26.5%) and the need for new permanent pacemaker implantation (10.8% – 26%) (Zack et al. 2017, Hamandi et al. 2019, Dreyfus et al. 2020, Chen et al. 2023).

Table 2-3: ACC/AHA Guidelines for Surgery for TR

COR	LOE	Recommendations
1	B-NR	In patients with severe TR (Stages C and D) undergoing left-sided valve surgery, tricuspid valve surgery is recommended (1-8).
2a	B-NR	In patients with progressive TR (Stage B) undergoing left-sided valve surgery, tricuspid valve surgery can be beneficial in the context of either 1) tricuspid annular dilation (tricuspid annulus end diastolic diameter >4.0 cm) or 2) prior signs and symptoms of right-sided HF (3-10).
2a	**B-NR**	**In patients with signs and symptoms of right-sided HF and severe primary TR (Stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations (11-14).**
2a	**B-NR**	**In patients with signs and symptoms of right-sided HF and severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease) who are poorly responsive to medical therapy (Stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations (11,12,15-19).**
2b	C-LD	In asymptomatic patients with severe primary TR (Stage C) and progressive RV dilation or systolic dysfunction, isolated tricuspid valve surgery may be considered (12,20).
2b	**B-NR**	**In patients with signs and symptoms of right-sided HF and severe TR (Stage D) who have undergone previous left-sided valve surgery, reoperation with isolated tricuspid valve surgery may be considered in the absence of severe pulmonary hypertension or severe RV systolic dysfunction (1,2,11,18).**

COR: Class of Recommendation (2b represents "moderate" strength of recommendation, i.e., may be reasonable)
LOE: Level of Evidence (B-NR represents moderate quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies)

2.4.3 Transcatheter Edge-to-Edge Repair (TEER) Therapy

As indicated in **Table 2-3**, the guidelines recommend that patients with severe primary TR, patients with severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease), who are poorly responsive to medical therapy, or patients who have previously undergone left-sided valve surgery, with signs and symptoms of right-sided heart failure, should undergo TV surgery (rows highlighted in yellow). Yet, TV surgery carries a high risk of mortality and complications. Symptomatic severe TR therefore remains challenging to treat.

While medical therapy has a role, medical therapy alone is often ineffective in reducing TR. TV surgery, being highly invasive with poor outcomes, is not a good option for many patients. Furthermore, as reported by Chen et al. 2023, hospitals in the US performed a median of only 2 cases annually and 93% of centers performed 5 or fewer of these procedures annually. This leaves TR patients with limited options and a population that is largely undertreated. These patients need a safe and effective option to treat TR and improve their health status. The European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines (Vahanian et al. 2022) recommend timely referral of patients with valvular heart disease before irreversible damage occurs and note that “tricuspid valve interventions are underused and often initiated too late.”

3 PRODUCT DESCRIPTION

SUMMARY

- The TriClip System is intended for reconstruction of an insufficient tricuspid valve through tissue approximation. It is designed to repair the tricuspid valve and reduce TR using a minimally invasive transcatheter approach to deliver a permanent implant.
- The TriClip System leverages the same clip-based technology as the well-established MitraClip System but has a differentiated delivery system and steerable guide designed specifically for ease of implant delivery to the tricuspid valve.

3.1 TriClip Builds on Well-Established MitraClip System

The TriClip System is a modification of the FDA approved MitraClip System, a transcatheter edge-to-edge repair system to treat severe mitral valve regurgitation by "coapting" the leaflets of the mitral valve. The MitraClip System received CE Mark in 2008 and FDA approval in 2013. The first report of MitraClip used to reduce TR was in 2015. The continued reports of off-label use with MitraClip to treat TR illustrated the unmet need to treat TR. TriClip leverages the same clip as the MitraClip device which has demonstrated safety and effectiveness with over 200,000 patients with mitral regurgitation treated worldwide. The TriClip System has a modified MitraClip delivery system, which includes a steerable guide catheter specifically designed to improve access to the tricuspid valve. There have been no changes to the implanted clip device. The TriClip G4 System is the current generation system for which Abbott is seeking approval. The TRILUMINATE Pivotal trial was initiated with a previous generation of the system.

3.2 Proposed Indication

The TriClip G4 System is indicated for the improvement of health status in patients with symptomatic severe tricuspid regurgitation despite being treated optimally with medical therapy, who are at intermediate or greater risk for surgery, and in whom tricuspid valve edge-to-edge repair is appropriate as determined by a heart team.

3.3 Device Overview

The TriClip G4 System (**Figure 3-2**) consists of the TriClip Delivery System and the TriClip Steerable Guide Catheter which acts as a conduit for introducing the TriClip Delivery System into the body via the femoral vein. The TriClip Delivery System includes the Delivery Catheter, the Steerable Sleeve and the implantable device (or clip), manufactured with metal alloys and polyester fabric that are commonly used in cardiovascular implants. The clip is mounted at the end of the TriClip Delivery System. This delivery system also includes controls that allow for the advancement and

manipulation of the clip, thereby facilitating proper positioning and placement of the implant on the tricuspid valve leaflets.

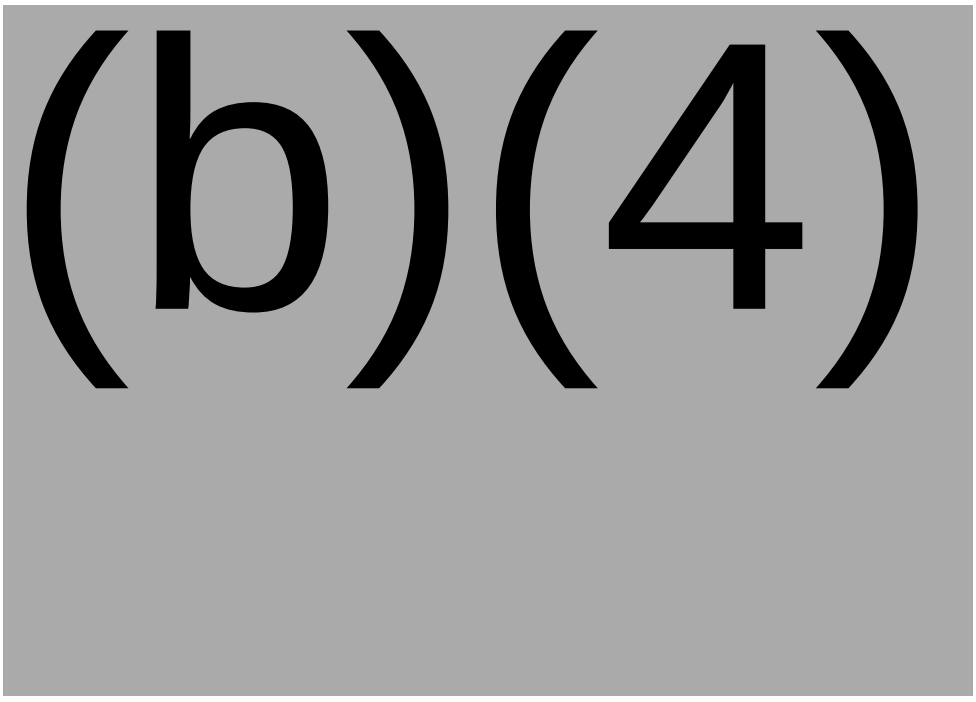
The clip is a mechanical implant that grasps and approximates the leaflet edges and results in leaflet coaptation throughout the cardiac cycle. It is implanted without the need for arresting the heart or cardiopulmonary bypass. The clip arms (**Figure 3-1**) can be adjusted to any position from opened, fully inverted, and fully closed. These positions are designed to allow the device to grasp and approximate the leaflets of the tricuspid valve using controls on the Delivery Catheter Handle. The clip can be locked, unlocked, and repeatedly opened and closed. The Grippers function to capture the leaflets in the device arms and can be raised or lowered repeatedly. The grippers can be operated either simultaneously or independently using levers in the TriClip G4 Delivery System.

The TriClip Steerable Guide Catheter is used to introduce the TriClip Delivery System into the right side of the heart, and aids in positioning and orienting the TriClip Delivery System and the device to an appropriate location above the tricuspid valve.

The TriClip G4 System comes in 4 different clip sizes (NT, NTW, XT, XTW - **Figure 3-2**), which are equivalent to the four clip sizes of the MitraClip G4 System. The TRILUMINATE Pivotal trial was initiated with a prior generation of the TriClip System with 2 clip sizes (NT and NTW).

Figure 3-1: TriClip Device

A) Clip Arms and Grippers



B) Clip Arm Positions

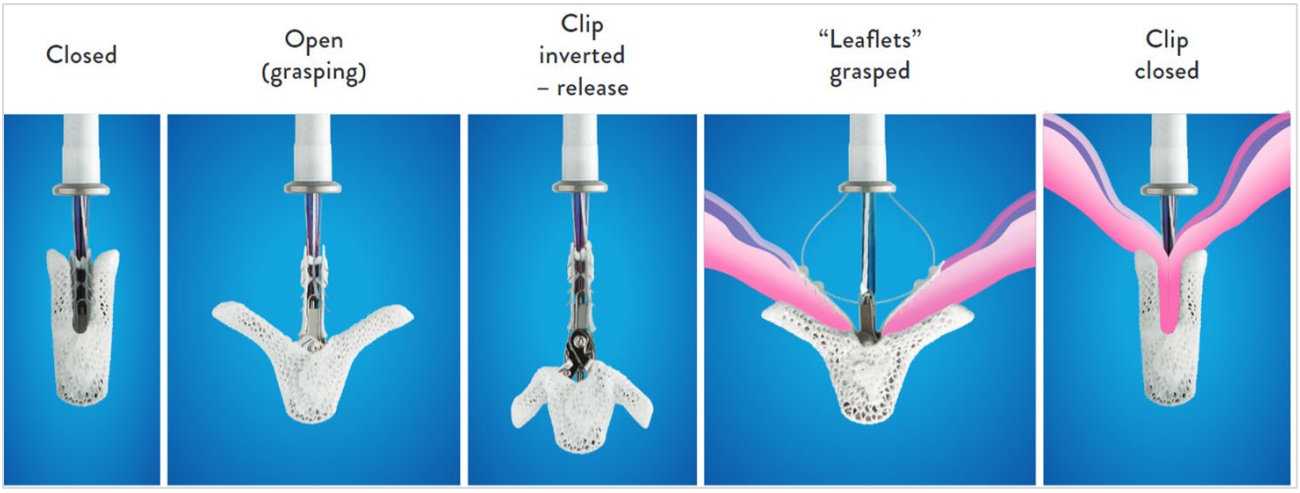
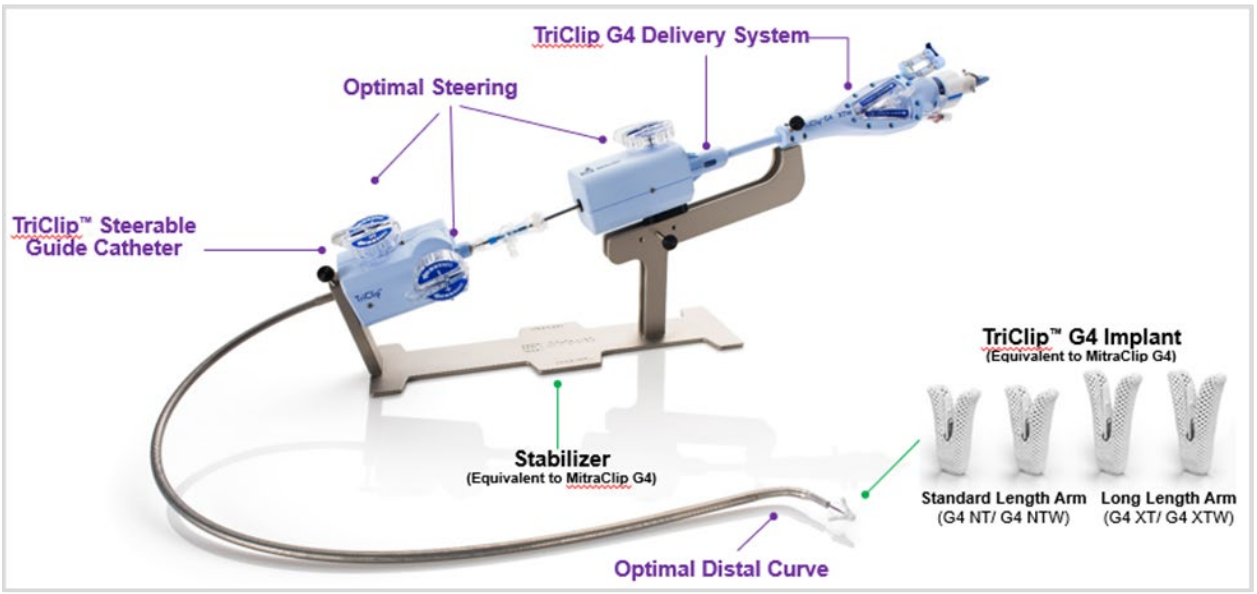


Figure 3-2: TriClip G4 System



4 REGULATORY MILESTONES

SUMMARY

- The TriClip G4 System is the current design iteration of the TriClip Family of Devices under FDA review.
- Abbott received US FDA approval to initiate the TRILUMINATE Pivotal trial in July 2019 for evaluation of the TriClip System, and subsequently the TriClip G4 System in March 2021.
- In November 2020 Abbott was granted Breakthrough Device Designation for the TriClip System.

The first iteration of the TriClip Family, the Tricuspid Valve Repair System (TVRS), was used in the TRILUMINATE CE study (approved by the FDA under an investigation device exemption (IDE) in June 2017), as part of a CE Mark study, with a single implant size (NT).

The TriClip System was the second iteration and included an additional clip size (XT) and minor modifications to the delivery system. This system received CE Mark in March 2020 supported by data from the TRILUMINATE CE study.

Based on the success of the TRILUMINATE CE study, Abbott filed and gained IDE approval in July 2019 to initiate the TRILUMINATE Pivotal trial.

The TriClip G4 System is the third iteration from the TriClip System: specifically, two additional clip sizes (NTW and XTW) and the Controlled Gripper Actuation mechanism are included.

The TriClip G4 System was introduced in the TRILUMINATE Pivotal trial through an IDE amendment in March 2021 and is the device under pre-market approval (PMA) review.

The TriClip G4 System received CE Mark in February 2021.

5 CLINICAL DEVELOPMENT PROGRAM

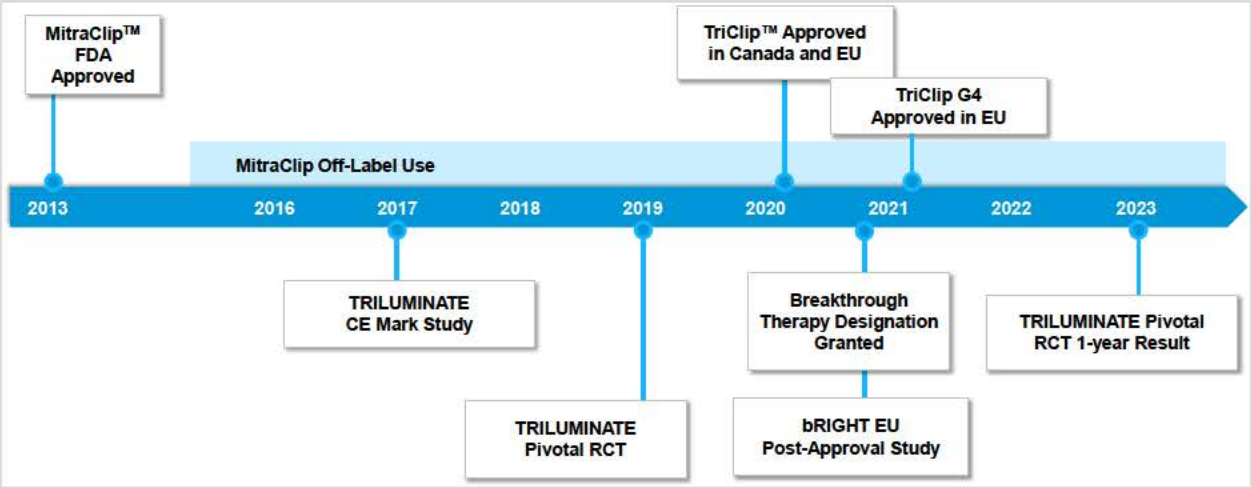
SUMMARY

- Early literature reports of off-label use of the MitraClip System demonstrated that transcatheter repair of the tricuspid valve is safe and reduces TR.
- Data from the TRILUMINATE CE study and the bRIGHT Post Market Clinical Follow-up study provide evidence that the TriClip System can be used to safely repair the tricuspid valve and reduce TR with excellent procedural success, leading to significant improvements in health status.

5.1 Overview of TriClip Clinical Program

Early off-label outcomes using the MitraClip System demonstrated that transcatheter tricuspid valve repair is feasible, safe, reduces TR, and is associated with improvements in heart failure symptoms and functional capacity (Nickenig et al. 2017, Besler et al. 2018a, Orban et al. 2018, Mehr et al. 2019). As a result of the continued interest in the treatment of TR using MitraClip, Abbott initiated product development to optimize the design of the delivery system for the tricuspid valve and sponsored a series of clinical studies to evaluate the safety and effectiveness of the TriClip System for the treatment of TR. An overview of the TriClip clinical program is shown in **Figure 5-1**.

Figure 5-1: Overview of TriClip Clinical Program



To date, over 10,000 patients have been treated with the TriClip System worldwide, among whom more than 1,300 were included in prospective clinical studies conducted by Abbott, with approximately 1,100 patients having completed at least 1-year follow-up, totaling follow-up of over 1,700 patient-years. The following sections provide study design and results from early TriClip studies.

5.1.1 TRILUMINATE CE Study

5.1.1.1 TRILUMINATE CE Study Design

The first clinical study of the TriClip System is the TRILUMINATE CE study initiated in 2017. The study is a prospective, single arm, multi-center study of the TriClip System (then labeled as TVRS) for treating patients with symptomatic moderate or greater TR who were deemed high risk for tricuspid valve surgery. The primary effectiveness endpoint was TR reduction of at least 1 grade at 30 days to be compared with a performance goal of 35%. The primary safety endpoint was major adverse event (MAE, a composite of cardiovascular mortality, myocardial infarction, stroke, new onset renal failure, endocarditis requiring surgery, and nonelective cardiovascular surgery for tricuspid valve repair system-related adverse events post procedure) rate at 6 months to be compared to a performance goal of 39%.

5.1.1.2 TRILUMINATE CE Study Results

The study was conducted in Europe (17 sites) and the United States (4 sites) and enrolled patients between 2017 and 2019. The primary study population (N=85) was on average 78 years old, and symptomatic (75% NYHA class III/IV) with comorbidities including atrial fibrillation (92%), hypertension (86%), renal impairment (46%) and diabetes (22%). TR etiology was functional in 84% of patients and TR grade was severe or greater in 94% of patients with 66% having massive/torrential TR (Nickenig et al 2019). Implant success, defined as successful delivery and deployment of at least one clip with leaflet approximation, was achieved in 100% of patients, with an average of 2.2 ± 0.8 clips implanted.

The primary effectiveness endpoint was met. At 30 days, 85.5% of patients had TR reduced by at least 1 grade, with 97.5% lower confidence limit of 77.3%, which is greater than the performance goal of 35% ($p < 0.0001$). Moderate or less TR was achieved in 57% of patients at 30 days.

The primary safety endpoint was also met. Through 6 months, the MAE rate was 6% (5 patients), with 97.5% upper confidence limit of 11.1%, which is lower than the performance goal of 39% ($p<0.0001$). The 5 MAEs were: 3 cardiovascular deaths (all > 30 days post-procedure, of which none were procedure- or device-related), 1 myocardial infarction (96 days post-procedure), and 1 new onset renal failure (6 days post-procedure). No patients experienced stroke or non-elective cardiovascular surgery for TriClip device related adverse events.

At 30 days, a significantly greater proportion of patients was categorized as NYHA class I or II compared to baseline (79.8% vs. 25.3%, $p<0.001$). Patients also experienced significant improvement in health status, with KCCQ-OS improving from baseline to 30 days by a mean of 14 ± 17 points ($p<0.001$).

One-year data from the study confirmed durability of the repair with 71% of patients having moderate or less TR at 1-year follow-up (Lurz et al. 2021). MAE and all-cause

mortality rates remained low at 1 year (both 7.1%). Symptoms and health status improvements were sustained through 1 year, with 83% of patients in NYHA class I/II ($p<0.0001$) and average improvement in KCCQ-OS of 20 points ($p<0.0001$). In addition, significant ($p < 0.05$) favorable reverse remodeling was observed (right ventricular end diastolic diameter decreased from 5.28 ± 0.07 cm to 4.79 ± 0.08 cm, right atrial volume decreased from 129 ± 5.84 mL to 116 ± 6.55 mL, and tricuspid annular diameter decreased from 4.34 ± 0.06 cm to 4.03 ± 0.07 cm).

At 2 years, the TR reduction to moderate or less was sustained in 75% of patients (von Bardeleben et al. 2023). All-cause mortality rate remained low at 2 years (18.7%). Symptoms and health status improvements were also sustained through 2 years, with 81% of patients in NYHA class I/II ($p<0.0001$) and average improvement in KCCQ-OS of 13 points ($p<0.0001$). In addition, significant ($p < 0.05$) favorable reverse remodeling was observed (right ventricular end diastolic diameter decreased from 5.28 ± 0.07 cm to 4.77 ± 0.10 cm).

5.1.2 bRIGHT Study

5.1.2.1 bRIGHT Design

A Post-Market Clinical Follow-up (PMCF) study of the TriClip and TriClip G4 Systems was initiated to prospectively collect and evaluate clinical data in a real-world setting (bRIGHT) to satisfy post-market clinical follow-up requirements of CE Mark in Europe. The bRIGHT study is a prospective, single-arm multi-center study conducted at 26 sites in Europe, with follow-up through 5 years.

The study enrolled 511 patients between August 2020 and September 2022. The primary endpoint was acute procedural success (APS) defined as successful implantation of the TriClip device with resulting TR reduction by at least 1 grade at discharge, with a performance goal of 75%. The secondary endpoint was all-cause mortality or tricuspid valve re-intervention/re-operation with a performance goal of 29%. The primary analysis population for the primary and secondary endpoints was the first 200 patients with an attempted implant. 30-day and 1-year results on these patients have been publicly presented (Lurz et al. London Valves 2021, Lurz et al. London Valves 2022).

5.1.2.2 bRIGHT Results

Patients were on average 78 years of age and symptomatic (81% NYHA class III/IV) with comorbidities including atrial fibrillation (84%), hypertension (85%), renal impairment (39%) and diabetes (21%). Nearly a quarter (23%) had a cardiac electronic implanted device. TR was severe or greater in 98% of patients with 92% having massive/torrential TR. Implant success was achieved in 98% of patients, with 2.0 ± 0.8 clips implanted on average.

The primary effectiveness endpoint was met. APS was achieved in 90% of patients, with 95% lower confidence limit of 82.7%, which was greater than the performance goal

of 75% ($p < 0.0001$). At 30 days, moderate or less TR was achieved in 66% of patients. The proportion of patients in NYHA class I/II improved from 19% at baseline to 76% at 30-day follow-up ($p<0.0001$). KCCQ-OS improved by 19 points on average through 30-day follow-up ($p<0.0001$). Through 30 days, major adverse events, defined as a composite of cardiovascular mortality, myocardial infarction, stroke, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip device-related adverse event, occurred in 1%, and all-cause mortality in 0.5%.

The secondary endpoint was also met. At 1 year, the Kaplan-Meier estimate of all-cause mortality or tricuspid valve re-intervention/re-operation was 17.6% (11% all-cause mortality, 3.5% re-intervention, 2% re-operation) with 95% upper confidence limit of 22.2%, which was lower than the performance goal of 29% ($p < 0.0001$). The benefits in health status and symptomatic improvement were maintained through 1 year, with an average KCCQ-OS improvement of 21 points ($p<0.0001$), and 77% of patients in NYHA functional class I/II. Site reported heart failure hospitalizations decreased by 44% ($p=0.0004$) in the year after TriClip intervention (0.32 events per patient-year) compared to the year prior (0.57 events per patient-year). At 1 year, there was significant reduction in tricuspid valve annular diameter (from 4.69 cm to 4.36 cm, $p=0.0027$) and right ventricle end diastolic dimension-base (from 4.62 to 4.22 cm, $p=0.0006$).

6 TRILUMINATE PIVOTAL TRIAL DESIGN

SUMMARY

- The TRILUMINATE Pivotal trial was designed to test the superiority of the TriClip device in addition to medical therapy over medical therapy alone to treat patients with symptomatic severe TR despite optimal medical therapy.
- The target population of the trial was symptomatic patients with severe TR despite optimal medical management and no concomitant untreated valvular disease or other significant comorbidities, who were at intermediate or greater surgical risk for mortality or morbidity.
- The trial included two cohorts: a Randomized cohort and a Single-arm cohort.
- The primary endpoint for the Randomized cohort was a hierarchical composite to be assessed at 12 months which included Time to all-cause death or TV surgery, Number of HFH and Improvement of ≥15 points in KCCQ-OS from baseline. Secondary endpoints included other relevant measures to be sequentially tested: Freedom from major adverse events at 30 days, Reduction of TR at 30 days, Change in KCCQ-OS at 12 months, and Change in 6MWD at 12 months.
- An adaptive design with an interim analysis for sample size re-estimation was planned for the Randomized cohort. The interim analysis indicated 350 randomized patients (Primary Analysis Population) with 12-month follow-up were adequate for the determination of superiority of treatment with TriClip over control. A total of 572 patients were ultimately randomized until the sample size re-estimation was completed.
- The primary endpoint for the Single-arm cohort was survival at 12 months with change in KCCQ-OS ≥10 points compared to baseline. A group sequential design was implemented, with one interim analysis with 100 patients and one final analysis with a goal to maintain the overall Type I error rate of 0.025. A total of 188 patients were enrolled and underwent implant with TriClip.

6.1 Design

The TRILUMINATE Pivotal trial is a prospective, multicenter, randomized, controlled, clinical trial to test the superiority of the TriClip device in addition to medical therapy over medical therapy alone to treat patients with symptomatic severe TR despite optimal medical therapy.

The trial consists of two cohorts: a Randomized cohort and a Single-arm cohort (**Figure 6-1**). ECL reviewed and assessed patients for TR severity for trial eligibility (≥severe TR) based on TTE. A Patient Management Eligibility Committee (ECPM) consisting of heart failure specialists reviewed right heart catheterization data and confirmed that patients were optimally treated with guideline-directed medical therapy. An Anatomic Eligibility Committee (ECA) consisting of echocardiographers and experienced

structural interventionalists assessed whether patients were appropriate for treatment with the TriClip device and assigned them to the Randomized or Single-arm cohort. Patients whose valve anatomic characteristics were deemed likely by the ECA to have TR reduction to moderate or less with TriClip were assigned to the Randomized cohort, and those deemed likely to have TR reduced by one grade with TriClip, but not likely to achieve moderate or less TR, were assigned to the Single-arm cohort. Patients in the Randomized cohort were randomized in a 1:1 ratio to receive the TriClip device in addition to medical therapy (Device group) or medical therapy alone (Control group). All patients in the Single-arm cohort were assigned to receive the TriClip device.

Prior to enrolling in the Randomized or Single-arm cohorts, up to 3 Roll-in patients were permitted per implanter without prior TriClip experience.

6.2 Cardiac Imaging Sub-Study

A Cardiac Imaging sub-study was conducted at a subset of participating sites which were selected based on cardiac MRI/CT imaging expertise, adequate imaging equipment and study enrollment. Cardiac MRI provides a more accurate measure of flow and cardiac CT provides a more accurate measure of cardiac chamber size than two-dimensional echocardiography and are considered “gold standard” for these measurements. Patients in the Roll-in, Single-arm and Randomized (both Device and Control groups) cohorts were allowed to participate in the sub-study. In addition to the TTE required for all patients, those participating in the imaging sub-study underwent Cardiac CT at baseline, 30-day and 12-month follow-up, and Cardiac MRI imaging at baseline and 30-day follow-up.

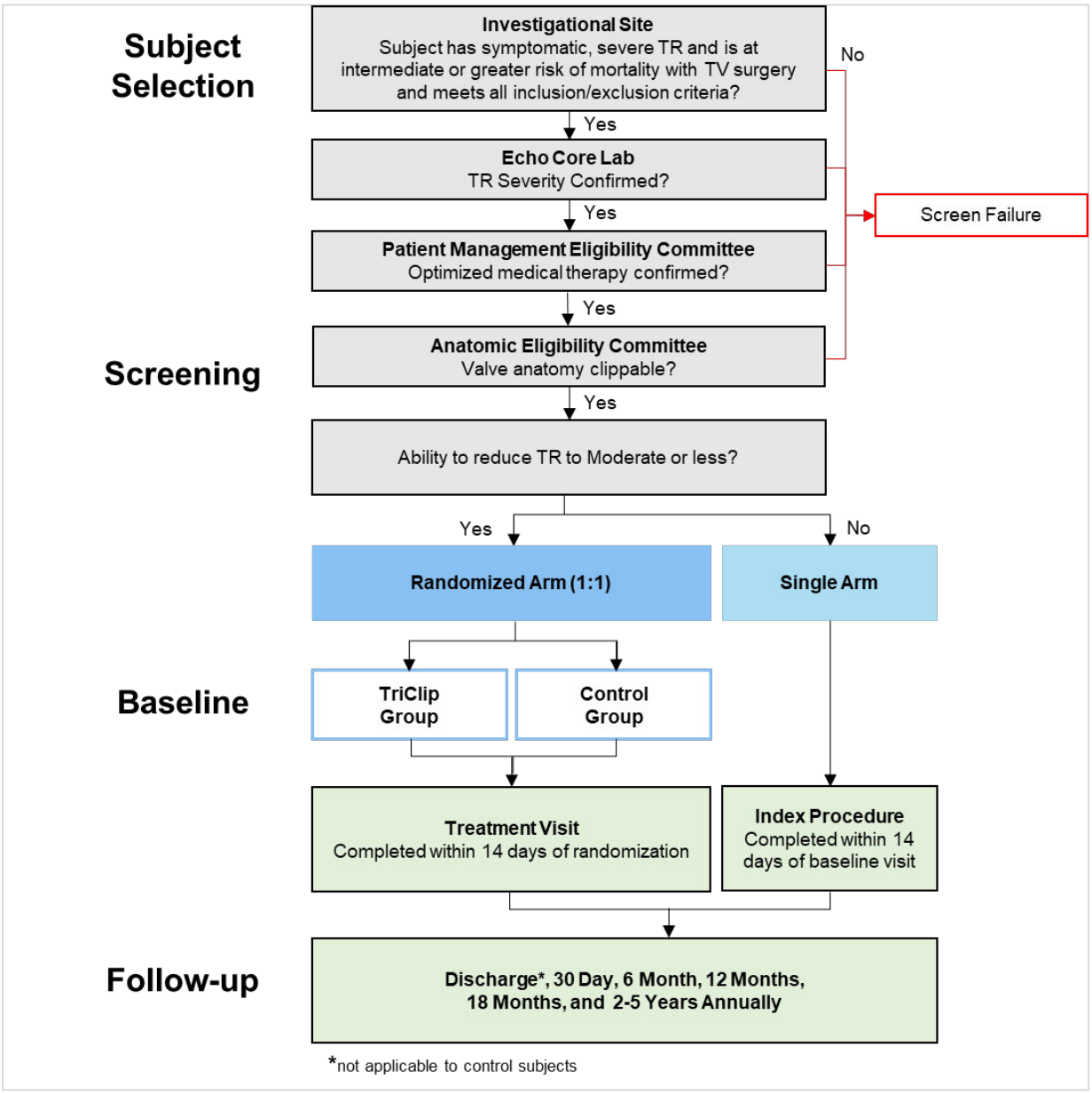
6.3 Study Assessments

At the baseline visit (prior to randomization), study personnel conducted the 6-Minute Walk Test (6MWT) and NYHA functional class assessments and administered the KCCQ, and the Short Form Survey Questionnaire (SF-36). Upon completion of baseline assessment, patients underwent randomization to the Device group or Control group. Both groups had a “Treatment visit” within 14 days of randomization. At this visit, Device patients underwent the TriClip procedure and Control patients were seen by the heart failure specialist, and underwent a physical exam, including vital signs, cardiac health status and evaluation of heart failure medications. Follow-up post-Treatment visit includes visits at Discharge (Device group only), 30-day, 6-month, 12-month, 18-month, 2-year, 3-year, 4-year, and 5-year, to capture TTE, adverse events and hospitalizations, as well as NYHA class, 6MWT, KCCQ and SF-36. Medications in both groups were to be continued, unless a change was deemed necessary per physician discretion. If TR remained severe (as assessed by the ECL) in a Control patient after completing the 12-month visit and the patient’s anatomy remained appropriate for TriClip therapy (as assessed by the Anatomic Eligibility Committee), crossover TriClip procedure was allowed.

6.4 Blinding

While patients were aware of the randomization and treatment, study personnel conducting the KCCQ, 6MWT, SF-36 and NYHA during the follow-up visits (30-day visit and afterwards) were blinded to treatment group and were not involved in day-to-day trial activities. Additionally, study personnel did not have access to the electronic case report forms. A standardized script was used when administering the assessments and the patient was reminded not to reveal their treatment history to the administrator. Site personnel did not have access to TR severity or other echocardiographic parameters measured by the ECL.

Figure 6-1: Trial Flow Chart



6.5 Inclusion and Exclusion Criteria

To evaluate the benefit of the device in patients whose symptoms were likely from TR, the trial included patients with symptomatic severe TR despite optimal medical management and excluded patients with concomitant untreated valvular disease or other significant comorbidities. Therefore, patients with severe left ventricular dysfunction (left ventricular ejection fraction, LVEF ≤ 20%), severe pulmonary hypertension (systolic pulmonary artery pressure sPAP > 70 mmHg) or pre-capillary pulmonary hypertension based on right heart catheterization, were excluded. The ECPM reviewed right heart catheterization data and confirmed that patients were optimally treated with guideline-directed medical therapy, indicating that TR was the likely source of the patient's symptoms. Key inclusion and exclusion criteria were:

6.5.1 Key Inclusion Criteria

- In the judgment of the site local heart team, patient has been adequately treated per applicable standards (including medical management) and stable for at least 30 days, confirmed by the Eligibility Committee, as follows:
    - Optimized medical therapy for treatment of TR (e.g. diuretics)
    - Medical and/or device therapy, for mitral regurgitation, atrial fibrillation, coronary artery disease and heart failure
- Patient has severe TR despite being optimally treated, as assessed by the ECL. The ECL confirms TR etiology via transesophageal echo (TEE)
- Cardiac surgeon of the site local heart team concurs that the patient is at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery
- Patient has NYHA functional class II, III or ambulatory class IV

6.5.2 Key Exclusion Criteria

- Systolic pulmonary artery pressure (sPAP) > 70 mmHg or fixed pre-capillary pulmonary hypertension as assessed by right heart catheterization
- Severe uncontrolled hypertension Systolic Blood Pressure ≥ 180 mmHg and/or Diastolic Blood Pressure ≥ 110 mm Hg
- Prior tricuspid valve procedure that would interfere with placement of the TriClip device
- Indication for other valve intervention. Patients with such an indication had to wait 60 days prior to being assessed for the trial
- Pacemaker or implantable cardioverter defibrillator (ICD) leads that would prevent appropriate placement of the TriClip
- Tricuspid valve stenosis defined as tricuspid valve orifice of ≤ 1.0 cm^2 and/or mean gradient ≥5 mmHg as measured by the ECL
- LVEF ≤20%
- Tricuspid valve leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets or sufficient reduction in TR

6.6 Endpoints

Primary and secondary endpoints for the Randomized cohort and the Single-arm cohort are presented in **Section 6.6.1** and **Section 6.6.2**, respectively. An independent Clinical Events Committee (CEC) adjudicated events including cause of death, hospitalizations, and components of major adverse events, along with relatedness to the procedure or device. Statistical details can be found in **Section 6.6.3**.

6.6.1 Randomized Cohort

The **Primary Endpoint** is a hierarchical composite as follows, to be assessed at 12 months:

1. Time to all-cause death or TV surgery
2. Number of HFH
3. Improvement of ≥15 points in KCCQ-OS from baseline

Death and TV surgery, being the most impactful clinical outcomes for a patient, were placed in the first level of hierarchy. Following this was the next most impactful clinical outcome, i.e., number of HFH, followed by health status improvement as the third component. This hierarchical approach also accounts for deaths, TV surgery and HFH which can be competing risks or confounders when evaluating an endpoint such as KCCQ-OS.

Hospitalization was defined as admission to inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay. HFH was defined as a hospitalization that met any of the following criteria:

- Hospitalization with the primary reason for admission as acute decompensated HF and administration of intravenous (IV) or mechanical heart failure therapies, especially IV administration of diuretic therapy
- An unscheduled or unplanned admission to the emergency department, hospital outpatient observation unit, or hospital inpatient unit, and IV administration of diuretic therapy. Overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, were included in the definition of hospitalization if related to a heart failure event.
- Patient arrives in emergency department with clinical presentation meeting the criteria of heart failure but dies in the emergency department before hospital admission.

Elective heart failure “tune-ups” that occurred following the TriClip procedure and prolonged the Index hospitalization did not count as a heart failure hospitalization.

Secondary Endpoints were to be assessed in the following sequence:

- **Secondary Endpoint #1:** Freedom from major adverse events (MAE) 30 days after procedure attempt (defined as femoral vein puncture) in the Device group. Components of MAE are:
    - Cardiovascular Mortality,
    - New Onset Renal Failure,
    - Endocarditis Requiring Surgery, and
    - Non-Elective Cardiovascular Surgery for TriClip device-related AE post-index procedure.
- **Secondary Endpoint #2:** Change in KCCQ-OS at 12 months from baseline
- **Secondary Endpoint #3:** TR Reduction to moderate or less at 30 days post procedure
- **Secondary Endpoint #4:** Change in 6MWD at 12 months from baseline

6.6.2 Single-Arm Cohort

The **Primary Endpoint** is survival at 12 months with change in KCCQ-OS ≥10 points compared to baseline.

6.6.3 Statistical Considerations

Hypotheses for the primary and secondary endpoints for the Randomized and Single-arm cohorts and statistical assumptions for sample size calculations are presented below.

6.6.3.1 Randomized Cohort

The null and alternative hypotheses for the **Primary Endpoint** are as follows:

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

Rejection of the null hypothesis at the two-sided 5% significance level would indicate the trial met its endpoint for the Randomized cohort, and that TriClip is superior to medical therapy.

Analysis of the hierarchical composite was performed on the ITT population using the FS method (Finkelstein and Schoenfeld 1999), a non-parametric method which compares every pair of patients based on the predetermined hierarchy of events described below:

- Whichever patient experienced death or TV surgery last would “win” in the comparison.
- If neither patient experienced death or TV surgery, the next component in the hierarchy, i.e., number of HFH, was compared and the patient with the lower number of HFH during the common follow-up time would “win”.
- If both patients experienced the same number of HFH, whichever patient experienced an improvement of ≥15 points in KCCQ-OS from baseline would

"win." If both patients (or neither) experienced a ≥ 15-point improvement in KCCQ-OS, the comparison would result in a tie.

- For patients who withdrew consent prior to 12 months, all data prior to withdrawal were included in the analysis (occurrence of death, TV surgery, HFH) and the common follow-up duration (i.e., the shorter of the follow-up durations in the comparison) was used to declare the "winner".
- Patients missing KCCQ-OS at either baseline or 12 months were included in the primary analysis but were counted as "ties" when there was no difference in the first two components of the endpoint.

The treatment effect was descriptively summarized by the win ratio defined as the ratio of the number of wins for the Device group to the number of wins for the Control group, along with 95% confidence intervals (Pocock et al. 2011).

Sample Size

The following assumptions were made for sample size calculations (see **Section 6.6.3.3** for details):

- All-cause mortality or TV surgery rate at 12 months: Control (20%), Device (15%)
- Annualized HFH rate: Control (0.5 events per patient-year), Device (0.35 events per patient-year)
- Proportion with KCCQ-OS improvement ≥15 points at 12 months compared to baseline: Control (20%), Device (45%)

A sample size of 350 patients would provide ~83% power at a two-sided significance level of 5% to demonstrate superiority of the Device group to the Control group. Sample size re-estimation was planned once the first 150 randomized patients completed 12-month follow-up, while the trial was still enrolling. The "promising zone" methodology of Mehta and Pocock (2011) was utilized to determine whether sample size increase would be required, by partitioning the sample space of the interim data (the data at the interim assessment) into 3 zones on the basis of estimated conditional power (CP), with a maximum of an additional 850 randomized patients (total 1000 randomized patients): unfavorable (CP<0.2), promising (0.2≤CP<0.8), and favorable (CP≥0.8). Type 1 error was controlled using the method by Cui, Hung and Wang (1999). The sample size for the primary endpoint analysis was re-estimated by an independent organization (Cytel) based on the interim results. Upon completion of the sample size re-estimation, Cytel informed Abbott about the sample re-estimation outcome, which indicated that 350 patients were sufficient to evaluate the trial's primary endpoint.

Upon the World Health Organization's declaration of the COVID-19 pandemic, in 2020, FDA issued a guidance titled "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency". Following the guidance, while remaining blinded to trial data, Abbott updated the primary endpoint analysis in the statistical analysis plan as follows: for patients who experienced death or any hospitalization adjudicated by the CEC as related to COVID-19, this event, and all subsequent data, were censored in the

primary endpoint analysis. FDA approved the updated statistical analysis plan in March 2021.

The following **subgroup analyses** were pre-specified for components of the primary endpoint via interaction tests at the 15% significance level:

- Sex (Male vs. Female)
- Baseline TR Grading (severe TR vs. > severe TR)
- Baseline NYHA Functional Class (I/II vs. III/IV)
- Baseline Etiology of TR (Primary TR vs. Secondary TR)

Sensitivity analyses were conducted for the As-Treated population, the Per-Protocol population, the ITT population using a four-component hierarchy with death and TV surgery separated out in two components, and an analysis of the ITT population including all available data and follow-up (i.e., no COVID-19 censoring).

Table 6-1 presents sensitivity analyses pre-specified for the primary endpoint.

Table 6-1: Study Populations and Primary Endpoint Analyses

Study Population	Definition	Analysis
Primary Analysis		
Intention-to-Treat (ITT)	All randomized patients in primary analysis Date of randomization is Day 0	COVID-19 related deaths and follow-up data post COVID-19 related hospitalization are censored
Sensitivity Analyses		
Intention-to-Treat (ITT)	All randomized patients in primary analysis Date of randomization is Day 0	Four-component hierarchy separating death and TV surgery in two layers (COVID-19 related deaths and follow-up data post COVID-19 related hospitalization are censored)
As-Treated (AT)	Randomized patients grouped by treatment received[a] Date of randomization is Day 0	COVID-19 related deaths and follow-up data post COVID-19 related hospitalization are censored
Per-Protocol (PP)	Randomized patients who followed all major study requirements Date of randomization is Day 0	COVID-19 related deaths and follow-up data post COVID-19 related hospitalization are censored
Intention-to-Treat (ITT)	All randomized patients Date of randomization is Day 0	Including all available data and follow-up (i.e., no COVID-19 censoring)

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

Secondary endpoints were specified in the following sequence and were each tested at either the two-sided 5% or one-sided 2.5% significance level, as applicable. Secondary endpoint #1 was assessed in Treated Device patients. The remaining secondary endpoints were assessed in the ITT population.

- **Secondary Endpoint #1:** Freedom from MAE occurring after procedure attempt (femoral vein puncture) at 30 days. The null and alternative hypotheses were as follows:

  H_0**:** $P_{30D}(MAE) \leq 90\%$
  H_1: $P_{30D}(MAE) > 90\ \%$

  where $P_{30D}(MAE)$ is the freedom from MAE at 30 days post procedure.

- **Secondary Endpoint #2:**
  Change in KCCQ-OS at 12 months: The null and alternative hypotheses were as follows:

  H_0: $\mu_{D,\,\Delta\mathrm{KCCQ-OS}} - \mu_{C,\,\Delta\mathrm{KCCQ-OS}} = 0$
  H_1: $\mu_{D,\,\Delta\mathrm{KCCQ-OS}} - \mu_{C,\,\Delta\mathrm{KCCQ-OS}} \neq 0$

  where $\mu_{D,\,\Delta\mathrm{KCCQ-OS}}$ and $\mu_{C,\,\Delta\mathrm{KCCQ-OS}}$ represent the mean change in KCCQ-OS between 12 months and baseline in the Device and Control groups, respectively. Analysis of covariance (ANCOVA), adjusting for baseline KCCQ-OS, was used to test the hypothesis. The analysis imputes KCCQ-OS of 0 at the 12-month visit for patients who experienced heart failure related death or underwent TV surgery prior to the 12-month visit. Other patients with missing KCCQ-OS score at either baseline or 12-month follow-up were to be excluded from the analysis.

- **Secondary Endpoint #3:**
  TR reduction to moderate or less at 30 days post procedure: The null and alternative hypotheses were as follows:

  H_0: $P_{D,TR\,\leq 2} - P_{C,TR\,\leq 2} = 0$
  H_1: $P_{D,TR\,\leq 2} - P_{C,TR\,\leq 2} \neq 0$

  where $P_{D,TR\,\leq 2}$ and $P_{C,TR\,\leq 2}$ represent the proportion of patients with TR reduced to moderate or less at 30-day visit in the Device and Control groups, respectively.

- **Secondary Endpoint #4:**
  Change in 6MWD at 12 months: The null and alternative hypotheses were as follows:

  H_0: $\mu_{D,\,\Delta 6\mathrm{MWD}} - \mu_{C,\,\Delta 6\mathrm{MWD}} = 0$
  H_1: $\mu_{D,\,\Delta 6\mathrm{MWD}} - \mu_{C,\,\Delta 6\mathrm{MWD}} \neq 0$

  where $\mu_{D,\,\Delta 6\mathrm{MWD}}$ and $\mu_{C,\,\Delta 6\mathrm{MWD}}$ represent the mean change in 6MWD between 12 months and baseline in the Device and Control groups respectively. ANCOVA, adjusting for baseline 6MWD, was used to test the hypothesis. The analysis

imputes 6MWD of 0 at the 12-month visit for patients who experienced heart failure related death or underwent TV surgery prior to the 12-month visit. Other patients with missing 6MWD at either baseline or 12-month follow-up were to be excluded from the analysis.

6.6.3.2 Single-arm Cohort

The **primary endpoint** null and alternative hypotheses were:

H_0: P ≤ 30%

H_1: P > 30%

where P represents the proportion of patients surviving at 12 months with KCCQ-OS improvement ≥10 points compared to baseline. The hypothesis is tested at the 2.5% significance level. The performance goal of 30% was based on the anticipated outcome for untreated patients (i.e., patients not treated with off-label MitraClip, TriClip or surgery) like those in the Single-arm cohort based on the following assumptions:

- Untreated patients like those in the Single-arm cohort would have higher mortality (25%) than the Control group of the Randomized cohort (20%).
- KCCQ-OS change at 12 months from baseline in untreated patients like those in the Single-arm cohort is normally distributed with mean ± SD improvement of 1 ± 20 points. Based on this distribution, the probability of a ≥10-point improvement at 12 months is calculated as ~42%.

With the assumed 12-month mortality rate of 25%, 31.5% (=0.42 x (1-0.25)) of untreated patients like those in the Single-arm cohort were expected to meet the endpoint. Therefore, the performance goal was set at 30%.

Patients who withdrew or were lost to follow-up prior to 12 months, or experienced hospitalizations or death within 12 months related to COVID-19 (as adjudicated by the CEC) or were missing paired KCCQ-OS were to be excluded.

Sample Size

The proportion of surviving patients in the Single-arm cohort (i.e., patients treated with TriClip) with at least a 10-point improvement in KCCQ-OS at 12 months is assumed to be 50% based on the following assumptions:

- In the TRILUMINATE CE study, among patients with a baseline torrential TR grade, the mean change in KCCQ-OS at 6 months was 16 $\pm$ 16 points. It was assumed that a majority of Single-arm patients would have torrential TR. Therefore, the change in KCCQ-OS at 12 months for the Single-arm cohort was assumed to be normally distributed with mean of 16 points and a slightly larger SD of 18 points. The chance of at least 10-point improvement in KCCQ-OS at 12 months assuming a normal distribution is approximately 63%.
- The mortality rate at 12 months was assumed to be 20% (absolute mortality difference of 5% from untreated patients). Therefore, the proportion of surviving patients at 12 months was estimated as 80%.

Total attrition was assumed to be 15% at 12 months. Based on these assumptions, 200 patients would provide >90% power to reject the null hypothesis at the 2.5% significance level. A group sequential design was implemented, with one interim analysis when 100 patients completed 12 months and one final analysis after all patients completed 12 months. At the first interim analysis, the primary endpoint would be assessed, and the p-value would be compared to the one-sided 0.0125 level of significance. If the primary endpoint was not met at the interim analysis, the hypothesis would be tested when all enrolled patients completed 12 months at the one-sided 0.0168 level of significance to maintain the overall Type I error rate of 0.025.

6.6.3.3 Trial Design Rationale and Statistical Assumptions

The Randomized cohort was designed to assess the effect of reduction of TR to moderate or less, therefore only patients in whom TR was expected to be reduced to moderate or less with high certainty were included in this cohort. In the TRILUMINATE CE study it was noted that patients with complex tricuspid valve anatomy, such as larger coaptation gaps (> 7 mm), had a lower likelihood of TR reduction to moderate or less. The objective of the Single-arm cohort was to show that *any* reduction in TR grade would provide health status benefit. The Single-arm cohort may be considered analogous to trials wherein more complex or higher risk patients are studied in single-arm registries embedded within randomized trials (clinicaltrial.gov IDs: NCT00209274, NCT03706833, NCT01240902).

Assumptions for each component of the primary endpoint of the Randomized cohort are discussed below. As described below, given the significant uncertainty in statistical assumptions, an adaptive design was implemented.

- Mortality Rate
  Given the paucity of literature on patients with severe TR with no untreated left-sided heart disease, mortality and morbidity rates for medical management of patients with severe TR with no concomitant left heart disease are difficult to estimate. Published 1-year mortality rates in severe TR patients likely with concomitant valve disease and/or left ventricular dysfunction ranged between 7% and 52% (see **Table 6-2**) and all referenced publications indicated strong association between TR severity and mortality. Excluding the publication by Topilsky et al. in 2014 TR patients without significant comorbidities, structural valve disease, significant pulmonary artery systolic pressure elevation by Doppler, or overt cardiac cause, the 1-year mortality rate ranged between 34% and 52%. Given these variable background rates and the very low rate anticipated for TV surgery, the 1-year mortality/TV surgery rate in the Control group was assumed to be 20%. Contemporary literature suggests the range is between 7% and 28% (Topilsky et al. 2019, Santoro et al. 2019, Wang et al. 2022, Nishiura et al. 2023).

- HFH Rate
  Patients with TR present with edema and fluid overload requiring treatment with (oral or IV) diuretics. It was expected that TR patients would routinely be hospitalized for IV diuretics treatment, and that reducing TR would result in lowering the rate of HFH. At the time of trial design in 2018, published HFH rates on untreated severe TR ranged between 30% and 50%, with a high proportion of patients having concomitant left-sided valve disease and/or left ventricular dysfunction. The COAPT trial of moderate-to-severe or severe secondary mitral regurgitation patients with left ventricular dysfunction, reported an event rate of 0.68 HFH/patient-year in the control group. Based on the available data/literature on TR (see **Table 6-2**) the Control group event rate was conservatively assumed to be 0.5 HFH/patient-year. A relative risk reduction of 30% was assumed in the Device group (i.e., 0.35 HFH/patient-year).
- KCCQ
  The KCCQ is a 23-item questionnaire across multiple domains, targeted to understand symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy (the patient's understanding of how to manage their heart failure). The KCCQ-OS ranges from 0 to 100, with higher scores indicating better health-related health status (Spertus et al. 2020). Scores are categorized in 25-point ranges as summarized in **Table 6-3**. Standardized cut-offs for clinically meaningful changes are not well established, and interpretation of these changes may depend on the population in which KCCQ is assessed. The trial design specified a high threshold for KCCQ-OS improvement to define success (≥15 points, which is well above the 10-point improvement defined as "moderate improvement" by Spertus et al 2020 and by Stone et al 2015 in the Mitral Valve Academic Research Consortium consensus document), so as to pick up impactful differences between the Device and Control group.

  As noted in Spertus et al. 2020, "a change of 5 points is considered to be a small but clinically important change, whereas changes of 10 and 20 points are considered moderate-to-large". The trial design specified a high threshold for KCCQ-OS improvement to define success (≥15 points, which is well above the "moderate" 10-point improvement defined by Spertus et al. 2020) to pick up impactful differences between the Device and Control group.

  The statistical assumptions for KCCQ-OS were primarily derived from the TRILUMINATE CE study which showed an improvement of 14 points, and somewhat aligned with the COAPT trial which showed an improvement of 17 points in the device group and only 5 points in the control group. The proportion with KCCQ-OS improvement ≥15 points was derived assuming a normal distribution for KCCQ-OS change with Mean ± SD of 15 ± 25 in the Device group and 0 ± 25 in the Control group, which yielded estimates of 50% and 27%, respectively. The trial

assumed slightly lower proportions of the Device and Control group would experience KCCQ-OS improvement of ≥15 points of 45% and 20%, respectively.

Table 6-2: Assumptions for Primary Endpoint Components at 12 Months

Source	Mortality		HF Hospitalizations		Change in KCCQ-OS	
	Assumption for Control[d] Rate	Assumption for Device Rate	Assumption for Control[d] Rate	Assumption for Device Rate	Assumption for Control[d] Rate	Assumption for Device Rate
TRILUMINATE CE Study	N/A	7% Rate per patient calculated from clinical study report on file at Abbott (6 deaths reported in 85 patients through1 y)	N/A	14% Rate per patient calculated from clinical study report on file at Abbott (12 HFH in 85 patients through 6m)	N/A	Mean ± SD: 14.2 ± 16.7 points
Besler et al. 2018a[a]	52% (estimated from Fig 1B for pts with unsuccessful TTVr)	22% (estimated from Fig 1B for pts with successful TTVr)	50% (KM estimate for pts with unsuccessful TTVr)	11% (KM estimate for pts with successful TTVr)	N/A	N/A
Besler et al. 2018b[b]	N/A	N/A	~30% (estimated from Fig 4 showing freedom from HFH for pts with TMVr only)	0% (estimated from Fig 4 showing freedom from HFH for pts with TMVr & TTVr)	N/A	N/A
Nath et al. 2004	42% & 28% (for severe & moderate TR per Table 2)	10-13% (for none/mild TR per Table 2)	N/A	N/A	N/A	N/A
Kalbacher et al. 2017	34.0% (reported in text for severe TR)	14.6% & 21.0% (reported in text for no/mild & moderate TR)	N/A	N/A	N/A	N/A
Topilsky et al. 2014 ("isolated TR")	7%	N/A	N/A	N/A	N/A	N/A
Stone et al. 2018[c] Arnold et al. 2019	N/A	N/A	0.68 per patient-year	N/A	Mean (95% CI): 5.1 (1.5, 8.6) points	Mean (95% CI): 17.0 (13.6, 20.3) points
Assumed rate in Randomized Cohort	Mortality/TV surgery at 1 year: 20% Mortality at 1 year: 17%-20%	Mortality/TV surgery: 15%	HFH rate: 0.5 per patient-year	HFH rate: 0.35 per patient-year	Mean ± SD: 15 ± 25 Proportion with KCCQ-OS improvement≥15 points: 20%	Mean ± SD: 0 ± 25 Proportion with KCCQ-OS improvement≥15 points: 45%
Assumed rate in Single-arm Cohort	25%	20%	N/A	N/A	1 ± 20 points	16 ± 18 points

KM: Kaplan-Meier; TMVr: Transcatheter mitral valve repair; TTVr: Transcatheter tricuspid valve repair

[a] 33% of patients in this publication had LVEF<40%

[b] 39% of patients in this publication had LVEF<45%

[c] 82% of patients in this publication had LVEF<40%

[d] For Single-arm Cohort, "Control" reflects untreated patients (i.e., patients not treated with off-label MitraClip, TriClip or surgery)

Table 6-3: Clinically Meaningful Thresholds for KCCQ-OS (Spertus et al. 2020)

KCCQ-OS	Health status
0-24	Very poor to poor
25-49	Poor to fair
50-74	Fair to good
75-100	Good to very good
Change in KCCQ-OS	**Change in health status**
≤ -5	Decline
-5 to 5	Stable, no change
5-10	Small change
10-20	Moderate change
≥20	Large change

6.7 Patient Disposition and Analysis Cohorts

Trial enrollment began on 21 August 2019 and was completed on 29 June 2022. A total of 2170 patients consented for the trial, of whom 761 (35%) were excluded prior to ECL or Eligibility Committee review primarily due to not meeting trial eligibility criteria (**Figure 6-2**).

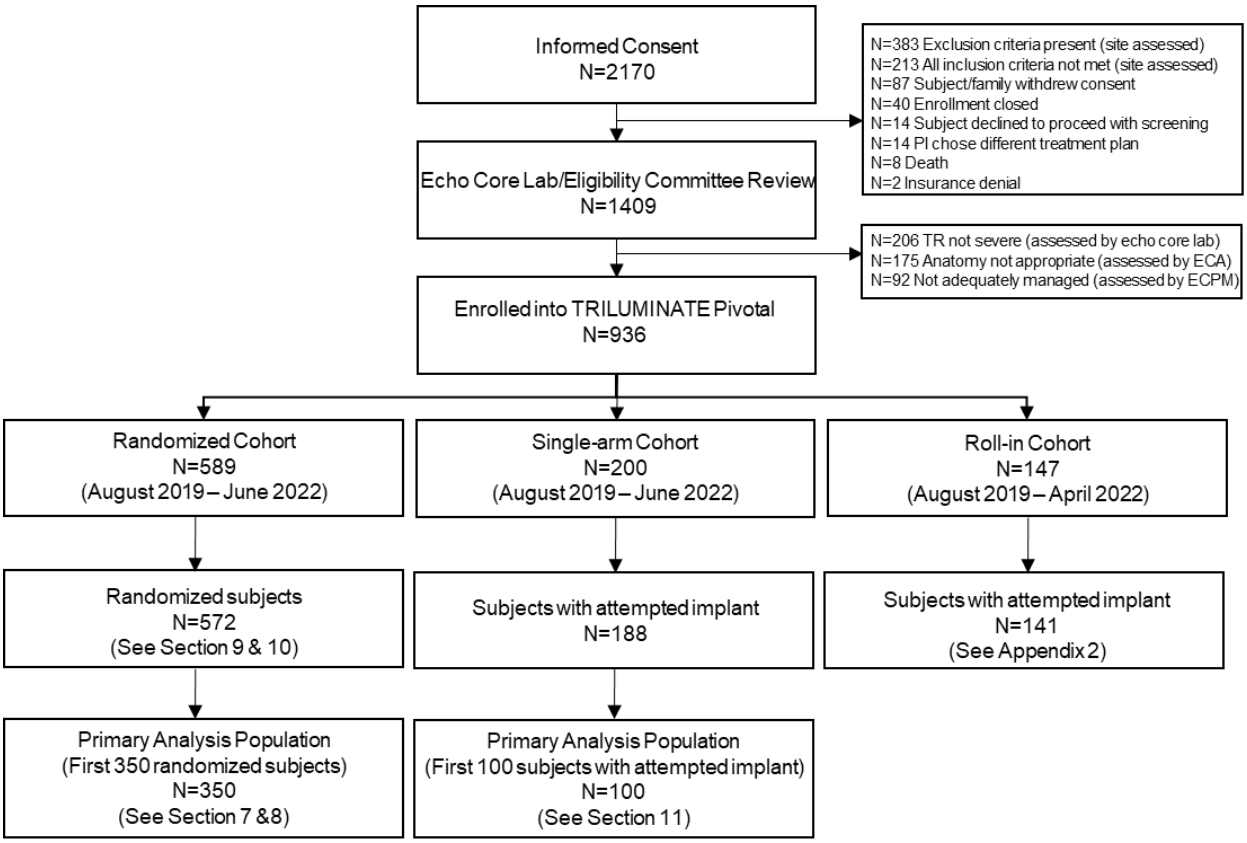
Among the 1409 patients who were presented to the ECL or Eligibility Committee, 473 (22% of total consented) were deemed not to meet Eligibility Committee or ECL requirements. Of these, 175 (8% of total consented) were denied due to anatomy being unsuitable for TriClip. The remaining 936 (43% of total consented) patients were approved for trial enrollment (589 Randomized, 200 Single-arm, 147 Roll-in):

- Of 589 patients assigned to the Randomized cohort, 572 were randomized.
- Of 200 patients assigned to the Single-arm cohort, 188 patients were treated.
- Of 147 patients assigned as Roll-in, 141 patients were treated.

Based on the results of the sample size re-estimation for the Randomized cohort, the Primary Analysis Population consists of the first 350 randomized patients. Trial cohort definitions are provided below and **Figure 6-2** shows the analysis cohorts across the trial:

- **Randomized Cohort:** First 350 randomized patients (also referred to as **Primary Analysis Population**, **Sections 7** and **8**)
- **Full Randomized Cohort:** All patients randomized in the trial (N=572) (**Section 9**)
- **Single-arm Cohort:** Patients treated in the Single-arm (N=100) (**Section 10**)
- **Cardiac CT/MRI Imaging Sub-Study** (**Section 11**)
- **Summary of Full Randomized Cohort through 2 years** (**Section 13**)
- **Roll-in Cohort:** Patients treated as roll-ins (N=141) (**Appendix 2**)

Figure 6-2: Screening, Enrollment and Analysis Cohorts



Upon PMA approval, patients with symptomatic severe TR despite optimization of treatment for other cardiac conditions and use of diuretics for right heart disease, as determined by the site heart team, would be considered for TriClip. Of the 1111 patients[4] who met trial eligibility criteria with severe TR confirmed by the ECL and deemed adequately managed on medical therapy by the Eligibility Committee, 84% were assessed as having appropriate anatomy for the TriClip device. It is therefore estimated that 84% of patients with symptomatic severe TR in the real world would have anatomy eligible for TriClip.

[4] 1111 patients is calculated as follows: 1409 patients reviewed by ECL or Eligibility Committee minus 206 patients assessed by ECL as not having severe TR minus 92 patients assessed by Eligibility Committee as not adequately managed on medical therapy.

7 CLINICAL EFFECTIVENESS (RANDOMIZED COHORT PRIMARY ANALYSIS POPULATION)

SUMMARY

- TriClip in conjunction with medical therapy demonstrated superiority to medical therapy alone. The results confirm the effectiveness of TriClip in treating patients with severe symptomatic TR and improving their health status.
- The primary endpoint was met (p=0.0311) and showed superiority of the TriClip device over medical therapy alone, driven by changes in health status (KCCQ-OS) favoring TriClip over medical therapy, with a win ratio of 1.44.
- The first and second components of the primary endpoint (all-cause mortality/TV surgery and HFH) occurred at low rates in both treatment groups. While the HFH rate was numerically higher in the Device group, this trend was not noted in the Full Randomized Cohort (see **Section 9**), confirming no difference between treatment groups. At 12 months, the average improvement in KCCQ-OS with TriClip was greater than that in the Control group by more than 10 points.
- The secondary endpoint of change in KCCQ-OS at 12 months was met. On average, KCCQ-OS increased from baseline by 12.3 points in the Device group and only by 0.6 points in the Control group (between-group difference = 11.7 points, p<0.0001, imputed analysis).
- The TriClip device was designed to reduce TR and the trial demonstrated that the device achieved this purpose: at 30 days, TR reduction to moderate or less was achieved in 87.0% of the Device group, vs. only 5.4% of the Control group (p<0.0001). The secondary endpoint of TR reduction at 30 days was met.
- The secondary endpoint of change in 6MWD, while favoring TriClip, did not achieve statistical significance (between-group difference = 17.1 meters, p=0.2482, imputed analysis). However, as discussed in **Section 9**, the between-group difference was larger (24.8 meters) in the Full Randomized Cohort (N=572), favoring the Device group, with 95% confidence interval that does not overlap 0.
- **Section 12** presents additional analyses and rationale to substantiate that the health status improvement is a true treatment benefit.

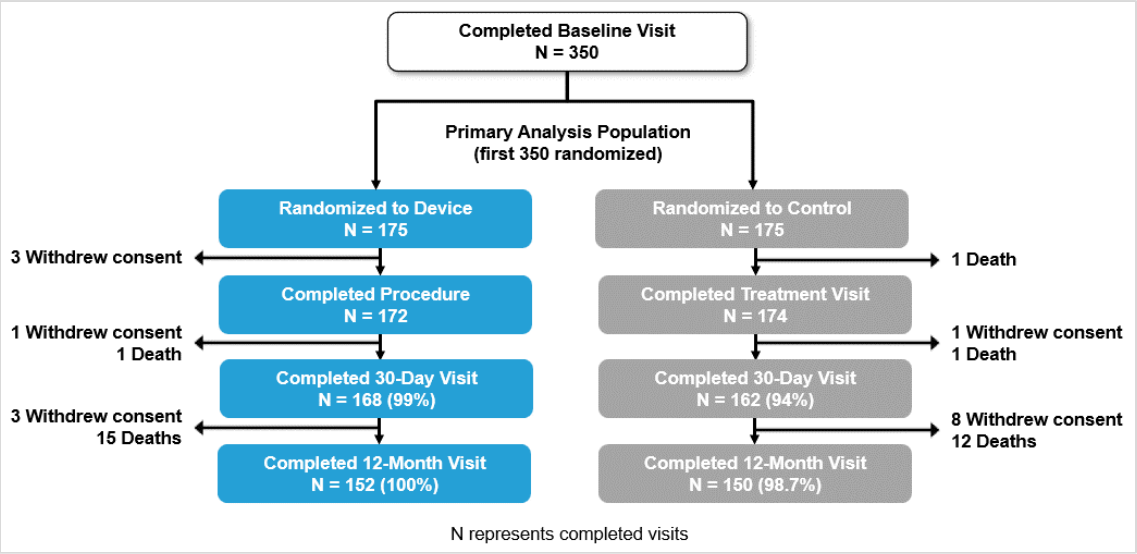
7.1 Patient Enrollment

The Primary Analysis Population consists of the first 350 randomized patients enrolled at 65 sites. Most patients were enrolled in the US (296 patients, 85%), followed by Canada (38 patients, 11%) and Europe (16 patients, 4%).

7.2 Disposition and Discontinuation of Patients

Figure 7-1 shows the disposition of the Randomized cohort (175 Device, 175 Control) for protocol-required study visits through 12 months. A total of 4 patients (3 Device, 1 Control) were randomized but did not complete the Treatment visit due to withdrawal (n=3) or death (n=1). Overall, 30 patients died (8.6%) and 16 patients withdrew (4.6%) prior to 12-month follow-up: 16 deaths and 7 withdrawals occurred in the Device group, and 14 deaths and 9 withdrawals occurred in the Control group.

Figure 7-1: **Disposition of Patients**



Note: Figure includes withdrawals prior to completion of the 12-month follow-up visit which could occur after 365 days (12-month follow-up visit window extends to 393 days from Treatment visit),

Please note that the results presented in this briefing document are slightly different from those reported in Sorajja et al. 2023 which used an earlier data cut-off.

7.3 Baseline Characteristics

Key demographics, baseline characteristics and medical history are summarized in **Table 7-1**. Patients were on average 78 years of age, with significant atrial fibrillation (90.3%), hypertension (80.9%) and renal disease (35.4%). Nearly 40% had prior mitral or aortic intervention. More than half of the cohort (57.4%) were in NYHA class III or IV, and the average KCCQ-OS score was on the lower end of the “Fair to Good” range (50-74). Only a quarter had experienced HFH in the previous year and the annualized rate in the prior year (0.32 per patient-year) was well below the assumed rate of 0.5 per patient-year.

Table 7-1: Key Baseline Characteristics (Primary Analysis Cohort, N=350)

Characteristic	Device (N=175)	Control (N=175)	Total (N=350)
Age			
Mean ± SD	78.0 ± 7.4	77.8 ± 7.2	77.9 ± 7.3
≥ 75 years	73.7%	76.6%	75.1%
Female	56.0%	53.7%	54.9%
Caucasian[a]	85.1%	81.7%	83.4%
Renal disease	35.4%	35.4%	35.4%
Liver disease	6.3%	9.1%	7.7%
Stroke/TIA	13.1%	17.7%	15.4%
Hypertension	81.1%	80.6%	80.9%
Atrial fibrillation	87.4%	93.1%	90.3%
COPD	10.9%	13.7%	12.3%
HFH			
HFH in prior year, %patients	25.1%	25.1%	25.1%
HFH rate in prior year, per patient-year	0.32	0.33	0.32
CRT/ICD/Pacemaker	16.0%	13.7%	14.9%
Prior mitral/aortic intervention	38.9%	34.9%	36.9%
NYHA III/IV	59.4%	55.4%	57.4%
KCCQ-OS, Mean ± SD	56.0 ± 23.4	54.1 ± 24.2	55.1 ± 23.8
6MWD (m), Mean ± SD	240.5 ± 117.1	253.6 ± 129.1	247.1 ± 123.3 meters

COPD: Chronic Obstructive Pulmonary Disease
CRT: Cardiac Resynchronization Therapy
ICD: Implantable Cardioverter Defibrillator
TIA: Transient Ischemic Attack
[a] Among patients who disclosed race (26 patients did not disclose race due to local regulation)

Key echocardiography parameters are shown in **Table 7-2**. Torrential TR was present in 50.9% of patients and TR etiology was secondary in 93.9% patients. Patients had enlarged right atrium (148.1 mL), dilated tricuspid valve annulus (4.4 cm), and dilated right ventricle end diastolic diameter (RVEDD-base 5.1 cm, RVEDD-mid 3.7 cm). However, right ventricular function was normal with right ventricular (RV) tricuspid annular plane systolic excursion (TAPSE) of 1.6 cm, as was left ventricular function with an ejection fraction of 59%.

Table 7-2: Key Baseline Echocardiography Parameters

Characteristic	Device (N=175)	Control (N=175)	Randomized Cohort (N=350)
TR Severity			
Moderate[a]	2.3%	1.2%	1.8%
Severe	25.4%	29.7%	27.5%
Massive	21.4%	18.2%	19.8%
Torrential	50.9%	50.9%	50.9%
Secondary Etiology	94.8%	92.9%	93.9%
Coaptation gap, mm	5.5 ± 1.8	5.2 ± 1.7	5.4 ± 1.8
Heart size/function (Mean ± SD)			
Tricuspid annulus diameter, cm	4.3 ± 0.7	4.5 ± 0.8	4.4 ± 0.7
RVEDD-base, cm	5.0 ± 0.8	5.2 ± 0.8	5.1 ± 0.8
RVEDD-mid, cm	3.7 ± 0.7	3.7 ± 0.7	3.7 ± 0.7
Right atrial volume, mL	143.2 ± 85.4	153.2 ± 83.2	148.1 ± 84.3
Right ventricular TAPSE, cm	1.7 ± 0.4	1.6 ± 0.4	1.6 ± 0.4
Cardiac output, L/min	4.1 ± 1.2	4.2 ± 1.1	4.2 ± 1.2
LVEF (Mean ± SD)	***59.3 ± 9.3***	***58.7 ± 10.5***	***59.0 ± 9.9***
LVEF ≤ 40%	4.3%	7.1%	5.6%
LVEF ≤ 50%	14.0%	14.2%	14.1%

RVEDD: Right Ventricular End Diastolic Diameter
TAPSE: Tricuspid Annular Plane Systolic Excursion
[a] Patients with moderate TR qualified for the trial with ≥severe TR based on the screening echocardiogram

For each patient, the ECPM ensured appropriate administration of medical and/or device therapy for conditions such as mitral valve regurgitation, atrial fibrillation, coronary artery disease and heart failure. For TR, the committee assessed whether patients were on appropriate diuretic therapy. As shown in **Table 7-3**, diuretics were used in 98% of patients. The only other drug with high usage was Beta Blockers (72.9%). Since most patients had normal LVEF, angiotensin-converting enzyme (ACE)-Inhibitors or angiotensin receptor blockers (ARB) and vasodilators were used in lower proportions of patients (43.7% and 11.4%, respectively).

Table 7-3: Baseline Cardiac Medications

Medication Category	%Patients
Beta Blockers	72.9%
ACE-Inhibitors or ARB (including ARNI)	43.7%
Vasodilators	11.4%
Diuretics	98.0%

ACE: Angiotensin-Converting Enzyme
ARB: Angiotensin Receptor Blocker
ARNI: Angiotensin Receptor/Neprilysin Inhibitor

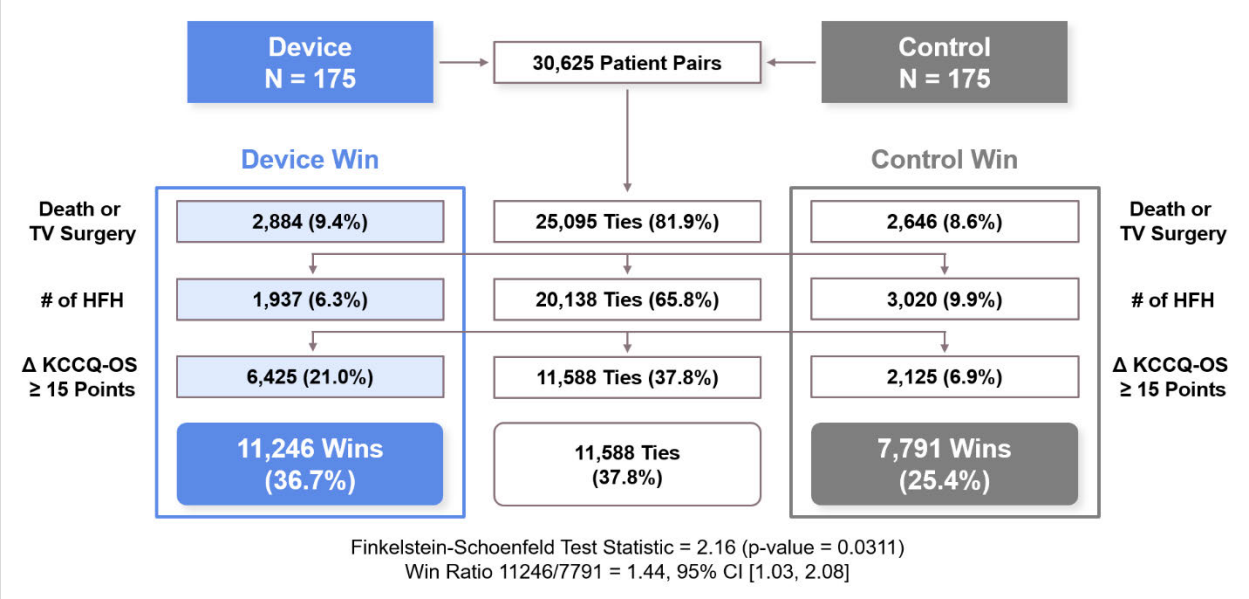
Biomarkers are biological molecules found in the body that can indicate physiologic responses to various conditions or diseases and are commonly assessed through blood tests. Patients had elevated levels of GGT and MELD score indicating impaired liver function, elevated levels of BNP and NT-proBNP indicating moderate heart failure, and

low eGFR and elevated BUN suggesting impaired kidney function (**Table A-1** in **Appendix 1**).

7.4 Primary Endpoint Results

The primary endpoint was met with FS p=0.0311, which is less than the 0.05 significance level, demonstrating that the TriClip device in addition to medical therapy is superior to medical therapy alone. The win ratio analysis showed there were 11246 "wins" for the Device group, 7791 "wins" for the Control group and 11588 "ties" between Device and Control, and a win ratio estimate of 1.44 with 95% confidence interval [1.03, 2.08] (**Figure 7-2**).

Figure 7-2: Primary Endpoint (Intention-to-Treat, Primary Analysis Population, N=350)



Two patients (both in the Device group) who experienced hospitalization related to COVID-19 had their follow-up information after the COVID-19 related hospitalization excluded.

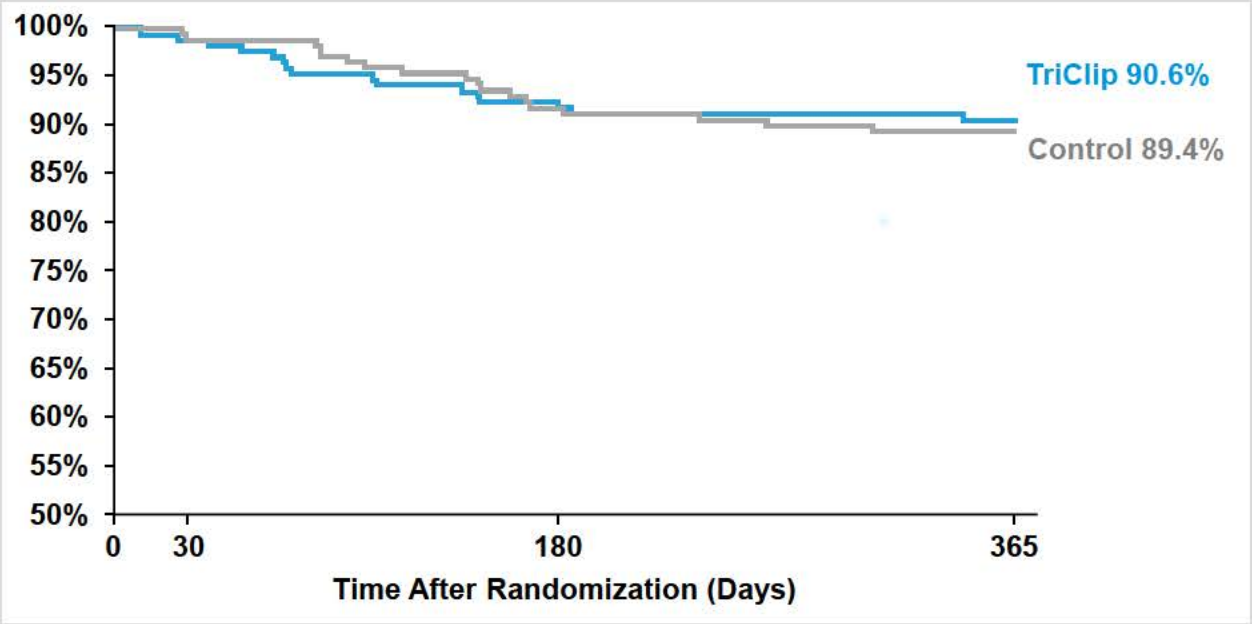
Primary Endpoint Components

Each component of the primary endpoint is examined below:

- Kaplan-Meier (KM) rates of all-cause mortality or TV surgery through 12 months were 9.4% and 10.6% in the Device and Control groups, respectively (**Figure 7-3**). The difference in rates was -1.2% with 95% confidence interval: [-7.6%, 5.2%] (data not presented in table).
- Annualized HFH rates through 12 months were comparable between Device (0.22 per patient-year) and Control (0.17 per patient-year) groups. The difference in rates was 0.05 HFH per patient-year with 95% confidence interval: [-0.05, 0.14] (**Table 7-4**).

- The KCCQ-OS component showed a substantial treatment benefit, with 50% of Device patients and 26% of Control patients achieving a ≥15-point improvement in KCCQ-OS (**Figure 7-4**). The difference in proportions between Device and Control groups is 23.3% with 95% confidence interval: [12.3%, 33.6%] (data not presented in table).

Figure 7-3: Freedom from All-Cause Mortality or TV Surgery through 12 Months (Primary Analysis Population, N=350)

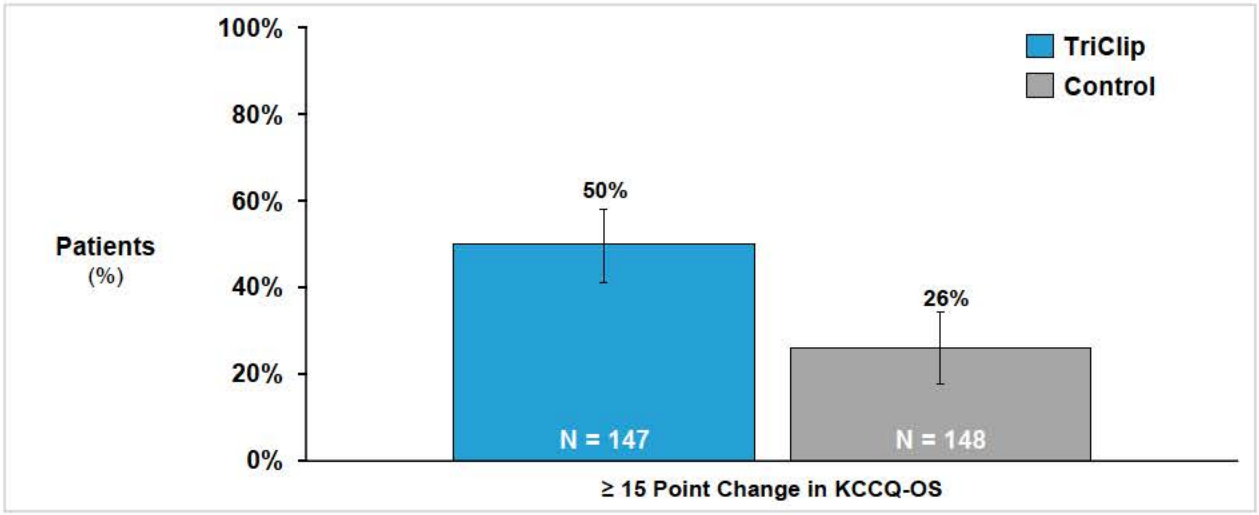


		Time After Randomization (Days)			
Group	**Data Category**	**0**	**30**	**180**	**365**
Device	# At Risk	175	170	158	152
	# Events	0	2	14	16
	Event Rate (%)	0.0%	1.2%	8.2%	9.4%
	95% CI	[100%, 100%]	[95.5%, 99.7%]	[86.6%, 95.1%]	[85.2%, 94.2%]
Control	# At Risk	175	173	154	149
	# Events	0	2	14	18
	Event Rate (%)	0.0%	1.1%	8.2%	10.6%
	95% CI	[100%, 100%]	[95.5%, 99.7%]	[86.6%, 95.1%]	[83.8%, 93.2%]

Table 7-4: HFH Rate Through 12 Months (Primary Analysis Population, N=350)

	Device (N=175)	Control (N=175)
Patients with HFH, n (%)	26 (14.9%)	20 (11.4%)
Number of HFH Events	35	28
Total Follow-up (Patient-years)	160.0	161.5
Annualized Rate [95% CI]	0.22 [0.16, 0.30]	0.17 [0.12, 0.25]
Difference [95% CI]	0.05 [-0.05, 0.14]	

Figure 7-4: Proportion of Patients with ≥15 Point KCCQ-OS Improvement at 12 Months (Paired Analysis, Primary Analysis Population, N=350)



Error bars represent 95% CI.

Sensitivity Analyses

Results of prespecified sensitivity analyses are shown in **Table 7-5**. The endpoint was met in the four-component hierarchical structure (where death and TV surgery are separated into their own tiers) (win ratio = 1.44, p=0.0362). The primary endpoint was also met in the AT population (win ratio = 1.55, p = 0.0126). The PP analysis excluded 25 patients who had the following protocol deviations: 3 Device patients who did not undergo the TriClip procedure, 21 Device patients who had Treatment visit beyond 14 days post randomization, and 1 Control patient who did not have a Treatment visit. While the win ratio estimate (1.39) in the PP analysis favored the Device group, the endpoint was not met (p=0.0652). The last sensitivity analysis, i.e., ITT analysis without COVID-19 censoring includes the follow-up data following two COVID-19 related hospitalizations, both of which occurred in the Device group. In this analysis, the win ratio (1.39) favored the Device group, but the endpoint was not met (p=0.0574).

Table 7-5: Prespecified Primary Endpoint Sensitivity Analyses Results (Primary Analysis Population, N=350)

Sensitivity Analysis	Sample Size	Win Ratio (95% Confidence Interval)	Two-sided p-value of F-S Test	Result
Four-component hierarchy (ITT)	Device: 175 Control: 175	1.44 [1.03, 2.08]	0.0362	**ENDPOINT MET**
As-Treated (AT)	Device: 171 Control: 179	1.55 [1.10, 2.24]	0.0126	**ENDPOINT MET**
Per-Protocol (PP)	Device: 151 Control: 174	1.39 [0.97, 2.05]	0.0652	**ENDPOINT NOT MET**
No COVID-19 censoring (ITT)	Device: 175 Control: 175	1.39 [0.99, 2.00]	0.0574	**ENDPOINT NOT MET**

Additional post hoc sensitivity analyses were conducted using the win odds method to incorporate ties in the primary endpoint analysis (Brunner et al. 2021). Win odds is an adaptation of the win ratio, calculated by adding half the number of ties to the numerator and half to the denominator of the win ratio. The win odds can be interpreted as the ratio of wins to losses in the treatment group with ties counted as half a win and half a loss. As shown in the first row of **Table 7-6**, the win odds estimate is 1.25, with 95% confidence interval [1.02, 1.56], which does not overlap 1, supporting the conclusion that the statistically significant primary analysis result is robust. Post hoc sensitivity analysis was also performed using the last observation carried forward (LOCF) if the 12-month KCCQ-OS was missing. Both the win ratio and win odds analyses based on LOCF support the conclusion that the statistically significant primary analysis result is robust (second row of **Table 7-6**).

Table 7-6: Post hoc Primary Endpoint Sensitivity Analyses Results (Primary Analysis Population, N=350)

Study Population	N	Analysis	Result
ITT	350	Win odds	Win odds [95% CI]: 1.25 [1.02,1.56]
ITT	350	Use last observation carried forward (LOCF) for missing 12-month KCCQ-OS Win ratio and Win odds	Win ratio [95% CI]: 1.54 [1.10, 2.20] Win odds [95% CI]: 1.33 [1.07, 1.66]

7.5 Secondary Effectiveness Endpoints

This section contains the results for secondary endpoints #2, #3, and #4 (see **Section 8.1** for secondary endpoint #1 results).

7.5.1 Change in KCCQ-OS at 12 Months (Secondary Endpoint #2)

The secondary endpoint of KCCQ-OS change at 12 months from baseline was significantly greater in Device patients compared to Control. The endpoint was met demonstrating that reduction in TR with TriClip results in improvement in health status. On average, KCCQ-OS increased from baseline by 12.0 ± 25.8 points in the Device group and 1.0 ± 21.0 points in the Control group (**Table 7-7**). Adjusting for the baseline KCCQ-OS value, the analysis of covariance (ANCOVA) model also showed a significantly greater improvement in the Device group compared to the Control group (12.34 vs. 0.61, p<0.0001). These results were based on imputing KCCQ-OS of 0 at the 12-month visit for patients who experienced heart failure related death or underwent TV surgery prior to the 12-month visit. Complete-case analysis of paired data (i.e., without imputations) indicates similarly large improvements in the Device group compared to the Control group (15.2 versus 4.8 points).

Table 7-7: Secondary Endpoint #2 – Change in KCCQ-OS (Primary Analysis Population, N=350)

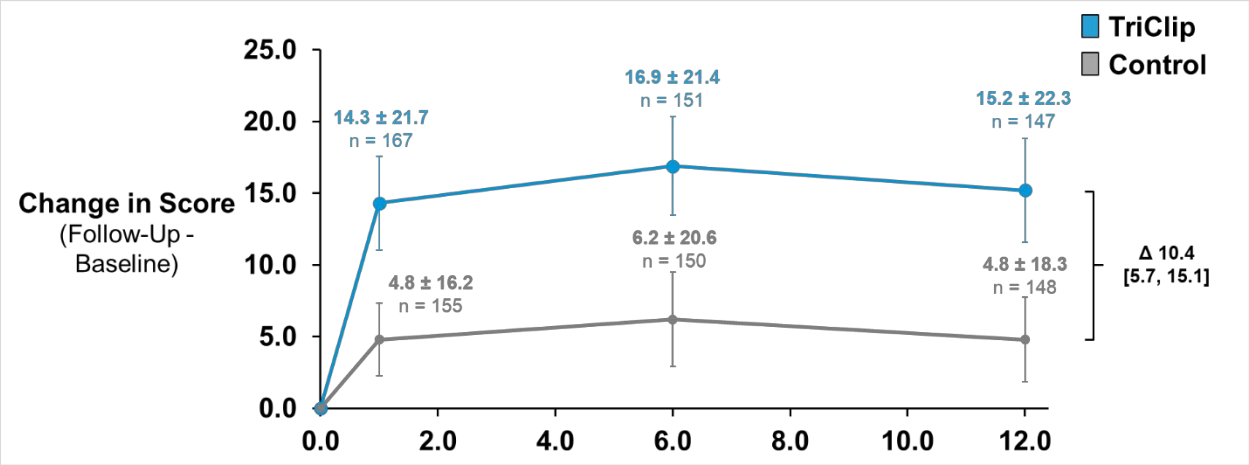
Visit/ KCCQ-OS	Device (N=175)	Control (N=175)	Difference [95% CI][a]	p-value[a]
Baseline				
Mean ± SD (n)	57.1 ± 23.7 (155)	55.2 ± 24.2 (155)	2.0	
Median (Q1, Q3)	58.6 (37.5, 76.8)	55.5 (35.7, 76.6)	[-3.4, 7.3]	
12 Month				
Mean ± SD (n)	69.1 ± 26.9 (155)	56.1 ± 26.2 (155)	13.0	
Median (Q1, Q3)	75.5 (58.6, 89.8)	57.8 (37.5, 76.6)	[7.0, 18.9]	
Change from Baseline to 12 Month (Imputed)[b]				
Mean ± SD (n)	12.0 ± 25.8 (155)	1.0 ± 21.0 (155)	Δ11.0	
Median (Q1, Q3)	12.8 (0.0, 28.6)	1.0 (-9.6, 13.0)	[5.8, 16.3]	
ANCOVA Model (Imputed)[b,c]				
Least Square Means (SE)	12.34 (1.75)	0.61 (1.75)	Δ11.73	< 0.0001
[95% CI]	[8.89, 15.79]	[-2.84, 4.06]	[6.85, 16.61]	
RESULT	**ENDPOINT MET**			
Change from Baseline to 12-Month (Complete-Case Paired)[d]				
Mean ± SD (n)	15.2 ± 22.3 (147)	4.8 ± 18.3 (148)	Δ10.4	
Median (Q1, Q3)	14.9 (1.8, 30.0)	3.1 (-7.3, 15.2)	[5.7, 15.1]	

[a] By normal approximation.
[b] Patients who experienced HF related death or had TV surgery prior to 12-month visit were assigned 12-month KCCQ-OS of 0.
[c] ANCOVA with baseline KCCQ-OS and treatment effect as covariates. Least squares means and 95% confidence interval are calculated.
[d] For patients who experienced hospitalization related to COVID-19, their follow-up information after the COVID-19 related hospitalization was excluded.

Change in KCCQ-OS at Follow-up

Despite the variability in the data (represented by the standard deviations shown in the figure), the KCCQ-OS improvement from baseline was evident at 30 days in the Device group with an approximately 10-point difference from the Control group, that was sustained through 6 and 12 months (**Figure 7-5**). The 95% confidence interval for the difference in change from baseline to 12 months between groups is [5.7, 15.1], which do not overlap 0.

Figure 7-5: KCCQ-OS Change Over Time (Complete-Case Paired Analysis, Primary Analysis Population, N=350)

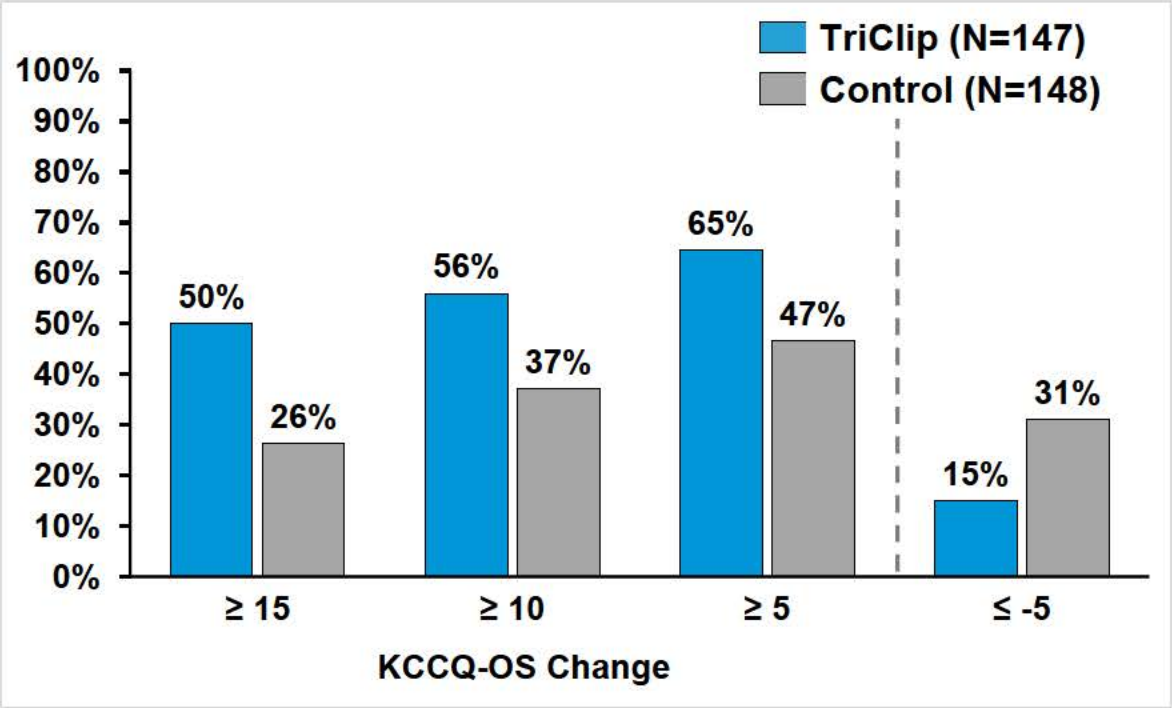


Numbers shown are Mean ± SD (n); Error bars represent 95% CI (not adjusted for multiple testing). Numbers in square brackets represent 95% CI for the between-group difference in change from baseline to 12 months.

Proportion of Patients with Improved KCCQ-OS at 12 Months over Baseline

Figure 7-6 shows the proportion of Device and Control patients with KCCQ-OS change at 12 months of ≥15 points, ≥10 points, ≥5 points and ≤-5 points. Regardless of the cutoff used to define KCCQ-OS improvement, a higher proportion of Device patients than Control patients experienced improvement. Additionally, a lower proportion of Device patients had worsening of KCCQ-OS by at least 5 points than Control patients (15% vs. 31%).

Figure 7-6: Proportion of Patients with Change in KCCQ-OS at 12 Months (Paired Analysis, Primary Analysis Population, N=350)



Dotted line represents cutoff for positive KCCQ-OS change threshold (left) versus negative KCCQ-OS change threshold (right)

KCCQ Domains

Given the day-to-day variability in heart failure symptoms, to ensure reproducibility, the KCCQ has 23 items that map to multiple domains, targeted to understand symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy (the patient's understanding of how to manage their heart failure). All domains of the KCCQ had an average improvement well above 10 points in the Device group, except the Physical Limitation domain, which had a nearly 10-point change (9.2 points, **Table 7-8**). On the other hand, the Control group had smaller average changes across domains, typically less than 5 points. The consistency of benefit observed in the domains of the KCCQ extends to a separate health status questionnaire (SF-36): the between-group difference in change in SF-36 Physical and Mental Component Summary (PCS and MCS) scores from baseline to 12 months were Δ5.7 points and Δ2.2 points, respectively, favoring the Device group.

Table 7-8: KCCQ Domains and SF-36 Components – Change from Baseline to 12 Months (Paired Analysis, Primary Analysis Population, N=350)

Change from Baseline to 12 Months Mean ± SD (n)	Device (N=175)	Control (N=175)	Difference [95% CI]
KCCQ			
Overall Summary Score	15.2 ± 22.5 (145)	4.0 ± 17.7 (144)	Δ11.2 [6.5, 15.9]
Physical Limitation Domain Score	9.2 ± 22.9 (141)	1.6 ± 21.6 (142)	Δ7.6 [2.4, 12.8]
Total Symptom Domain Score	12.0 ± 23.2 (145)	4.2 ± 20.9 (144)	Δ7.8 [2.7, 12.9]
Quality of Life Domain Score	21.4 ± 26.3 (145)	6.4 ± 20.8 (144)	Δ15.0 [9.5, 20.4]
Social Limitation Domain Score	19.1 ± 28.4 (125)	3.6 ± 28.1 (136)	Δ15.5 [8.6, 22.3]
SF-36			
Physical Component Score	4.2 ± 9.7 (144)	-1.5 ± 8.2 (144)	Δ5.7 [3.7, 7.8]
Mental Component Score	3.5 ± 11.3 (144)	1.3 ± 10.5 (144)	Δ2.2 [-0.3, 4.8]

Note: Excludes patients who had TV surgery prior to 12 months

Missing Data Analysis

The prespecified analysis for this endpoint imputed KCCQ-OS of 0 at the 12-month visit for patients who experienced heart failure related death or underwent TV surgery prior to the 12-month visit (this resulted in 21 patients having a score of 0 imputed at 12 months). Other patients with missing KCCQ-OS at either baseline or 12-month follow-up were excluded from the analysis (there were 40 such patients, 20 in each group). Reasons for missing data are shown in **Table 7-9**.

Table 7-9: Reasons for missing KCCQ-OS paired differences (Primary Analysis Population, N=350)

Reason	Device	Control
Missing at baseline	**0**	**1**
Missing at 12 months	**20**	**19**
Non-HF related death	8	8
Withdrew	6	8
Declined/missed visit	6	3

As shown in **Table 7-8**, non-imputed paired changes in KCCQ-OS (i.e., complete-case paired analysis) in the Device and Control groups at 12 months from baseline demonstrated a between-group difference of Δ10.4 points and 95% confidence interval [5.7, 15.1] favoring the Device group. Post hoc sensitivity analysis using 0 values for patients who died regardless of cause of death and LOCF for other patients with missing data showed nearly identical results, demonstrating that the paired complete-

case results are robust to missing data (between-group difference: Δ10.5 points, 95% confidence interval [5.4,15.6] – data not presented in table).

7.5.2 TR Reduction to Moderate or Less at 30 Days (Secondary Endpoint #3)

The proportion of patients with moderate or less TR at 30-day follow-up was significantly greater in the Device group (87%) compared to the Control group (5.4%) (p<0.0001), therefore this secondary endpoint was met (**Table 7-10**). These results demonstrate that the clinical objective of TriClip to reduce TR to moderate or less was met.

Missing Data Analysis

Forty-one (13 Device, 28 Control) of 350 patients, or 12%, were not included in the analysis of this endpoint as ECL-assessed TR at 30 days was not available. Sensitivity analysis was performed to assess the impact of missing TR severity data on the results. In this analysis, any patient with missing TR severity at 30 days was imputed with the first available TR severity from 6 months, 1 year, discharge or baseline (in that order). This analysis showed results consistent with the primary analysis, with a significantly higher proportion of patients having TR reduced to moderate or less TR at 30 days in the Device group (84.6%, 148/175) compared to the Control group (4.6%, 8/173), a difference which remained statistically significant (p<0.0001) – data not presented in table.

Table 7-10: Secondary Endpoint #3 – TR Severity at 30-Day Follow-up (Primary Analysis Population, N=350)

	Device (N=175)	Control (N=175)
TR Severity		
Trace	10.5% (17/162)	0.7% (1/147)
Mild	39.5% (64/162)	0.7% (1/147)
Moderate	37.0% (60/162)	4.1% (6/147)
Severe	11.1% (18/162)	22.4% (33/147)
Massive	0.6% (1/162)	21.8% (32/147)
Torrential	1.2% (2/162)	50.3% (74/147)
≤ Moderate [95% CI][a]	**87.0% (141/162) [80.9%, 91.8%]**	**5.4% (8/147) [2.4%, 10.4%]**
p-value[b]	<0.0001	
RESULT	**ENDPOINT MET**	
Reason for missing TR severity		
Died	1	2
Withdrawal/Loss to follow-up/missed visit	6	11
Echo not done	4	8
ECL unable to assess TR	2	7

[a] By Clopper-Pearson exact confidence interval.

[b] From Chi-square test.

7.5.3 Change in 6MWD at 12 Months (Secondary Endpoint #4)

The change in 6MWD from baseline to 12 months is shown in **Table 7-11**. The prespecified analysis imputed a 6MWD of 0 meters at 12 months for patients who experienced heart failure related death or underwent TV surgery prior to the 12-month visit. Patients who were unable to exercise due to cardiac reasons were also assigned a 6MWD of 0 meters at 12-month follow-up. This resulted in 21 patients having 0 meters imputed at 12 months. On average, 6MWD changed by -5.1 ± 131.4 meters for the Device group and by -28.1 ± 122.3 meters for the Control group. Adjusting for the baseline 6MWD, the ANCOVA model did not show a significant difference between Device and Control groups (-8.12 vs. -25.17, p=0.2482), therefore this secondary endpoint was not met. Complete-case analysis of paired data indicates larger improvement in the Device group (11.5 meters), whereas the Control group experienced a reduction (-8.7 meters). As shown in **Section 9**, the difference was larger in the Full Randomized Cohort (Δ27 meters), with 95% confidence interval that does not overlap 0.

Table 7-11: Secondary Endpoint #4 – Change in 6MWD (Primary Analysis Population, N=350)

Visit/ 6MWD (meters)	Device (N=175)	Control (N=175)	Difference [95% CI][a]	p-value
Baseline Mean ± SD (n) Median (Q1, Q3)	256.6 ± 116.7 (131) 250.0 (178.0, 331.3)	273.7 ± 125.7 (136) 271.0 (173.7, 369.9)	-17.1 [-46.3, 12.1]	
12-Month Mean ± SD (n) Median (Q1, Q3)	251.5 ± 145.0 (131) 245.0 (148.0, 336.0)	245.7 ± 142.9 (136) 241.9 (157.5, 352.3)	5.8 [-28.9, 40.5]	
Change from Baseline at 12-Month (Imputed)[b] Mean ± SD (n) Median (Q1, Q3)	-5.1 ± 131.4 (131) -1.3 (-51.0, 56.4)	-28.1 ± 122.3 (136) -15.1 (-77.0, 30.2)	Δ22.9 [-7.7, 53.6]	
ANCOVA Model (Imputed)[b,c] Least Square Means (SE) [95% CI]	-8.12 (10.50) [-28.80, 12.57]	-25.17 (10.31) [-45.47, -4.87]	Δ 17.06 [-11.96, 46.07]	0.2482
RESULT	**ENDPOINT NOT MET**			
Change from Baseline to 12-Month (Complete-Case Paired)[d] Mean ± SD (n) Median (Q1, Q3)	11.5 ± 111.4 (124) 0.0 (-37.3, 60.0)	-8.7 ± 109.7 (128) -6.0 (-51.9, 35.2)	Δ20.3 [-7.2, 47.7]	

[a] By normal approximation.
[b] Patients who experienced HF-related death or had TV surgery prior to 12-month visit were assigned 12-month 6MWD of 0. Patients who were unable to exercise due to cardiac reasons were also assigned a 6MWD of 0 meters at 12-month follow-up.
[c] ANCOVA model with baseline 6MWD and treatment effect as covariates. Least squares means and 95% confidence interval are calculated.
[d] For patients who experienced hospitalization related to COVID-19, their follow-up information following the COVID-19 related hospitalization was excluded.

7.6 Responder Analyses

Each component of the primary endpoint was examined for the following pre-specified subgroups by assessing treatment by subgroup interaction effects at the 0.15 significance level: sex, TR severity, NYHA class and TR etiology (**Table A-2** in **Appendix 1**). Given the lack of significant differences in the rate of the first two components, subgroup analyses for these components are considered exploratory. The table shows there is heterogeneity in all-cause mortality/TV surgery and HFH event rates across the two levels of some subgroups. For example, patients with > Severe TR at baseline have higher rate of all-cause mortality/TV surgery and HFH than patients with Severe TR at baseline. Similarly, patients with Secondary TR etiology have higher rates of all-cause mortality/TV surgery and HFH than patients with Primary TR. However, across both levels of all subgroups, the Device group had a higher proportion of patients with KCCQ-OS improvement ≥ 15 points at 12 months than the Control group.

Since patients with low baseline KCCQ-OS have the largest potential for improvement (and vice versa), exploratory analysis was conducted to characterize which patients may best benefit from TriClip. **Table 7-12** summarizes the baseline KCCQ-OS for different patient groupings based on various cut points (≥ 15, ≥ 10, ≥ 5 and ≤ -5 points) for change in KCCQ-OS at 12 months (∆ KCCQ-OS) in Device patients. The table shows that patients who experienced the largest improvement in KCCQ-OS (≥ 15 points) had the lowest baseline KCCQ-OS (46.8 points) and there is an increasing trend as the cut point changes from 15 points to 10 points (49.1 points) and 5 points (50.6 points), with patients who experienced a reduction in KCCQ-OS of more than 5 points having the highest baseline KCCQ-OS (76.6 points). These data reinforce the importance of baseline KCCQ-OS in identifying responders to TriClip.

Table 7-12: KCCQ-OS at Baseline for Randomized Device Group for Different Cut Points for Change in KCCQ-OS at 12 Months (N=147, Paired Data)

	Change in KCCQ-OS ≥ 15 points (N=73, 50%)	Change in KCCQ-OS ≥ 10 points (N=83, 56%)	Change in KCCQ-OS ≥ 5 points (N=95, 65%)	Change in KCCQ-OS ≤ -5 points (N=22, 15%)
Baseline KCCQ-OS Mean ± SD	46.8 ± 17.7	49.1 ± 18.8	50.6 ± 19.9	76.6 ± 13.0

7.7 Key Descriptive Endpoints

Key descriptive endpoints are summarized in **Appendix 1**.

The data show the TriClip device was successfully implanted in 98.8% of attempts with an average of 2.2 ± 0.7 clips used per patient and procedure duration averaged 151 minutes. Procedural success was achieved in 87.0% of patients. Length of stay in the hospital averaged 1.6 days and there were no in-hospital deaths. Approximately 98% of patients were discharged home (**Table A-6**, **Table A-7**, **Table A-8**).

The proportion of patients categorized as NYHA functional class I/II improved from 46% at baseline to 84% at 12 months for the Device group versus 47% to 59% for the Control group, indicating significant symptomatic benefit from the device (**Figure A-1**). Edema requiring hospitalization and ascites occurred at a lower rate in the Device group compared to the Control group (0.02 versus 0.11 per patient-year for edema and 0.02 versus 0.07 per patient-year for ascites, **Table A-9**). IV diuretic use was comparable between treatment groups. At 12 months, TR reduction with TriClip was durable, with 89% of Device patients having moderate or less TR, compared to 8% of the Control group (**Figure A-2**). Echocardiography showed substantial reduction in TR parameters (effective orifice area, regurgitant volume and vena contracta width) at 12 months in the Device group, but not in the Control group. There was a small decrease in right ventricle and annulus size and a small increase in right atrial volume in the Device group as measured by 2D echocardiography. See **Section 11** for high-resolution three-dimensional measurements from the Cardiac Imaging sub-study which showed substantial reductions in right ventricle and right atrial volume in the Device group. The 95% confidence intervals for the change from baseline within the Device and Control groups overlapped 0 for all parameters except TV diastolic mean gradient, which had a modest increase in the Device group from the TriClip implant (see also **Section 8.9)**.

7.8 Discussion of Clinical Effectiveness

The primary endpoint was met, indicating superiority of TriClip in combination with medical therapy over medical therapy alone. TriClip was successful in reducing TR: at 30 days, reduction of TR to moderate or less was achieved in 87% of the Device group, whereas only 5.4% of the Control group experienced such a reduction ($p<0.0001$). TR reduction with TriClip was durable through 12 months, with 89% of Device patients having moderate or less TR, compared to only 8% of Control patients.

The primary endpoint was met with two-sided FS $p=0.0311$. The win ratio estimate was 1.44 with 95% confidence interval [1.03, 2.08]. The first and second components of the primary endpoint (all-cause mortality/TV surgery and HFH) at 12 months occurred at low rates and comparable between Device and Control groups. In interpreting the results, the following considerations are important:

- Compared to assumed rates, the mortality/TV surgery rate at 12 months in the Control group (10.6%) was lower than the assumed rates of 17-20% derived from patients primarily with concomitant left-sided disease, but consistent with that reported by Topilsky et al 2014 (7%). The 12-month mortality/TV surgery rates were comparable between Device and Control groups (Difference: -1.2%, 95% confidence interval [-7.6%, 5.2%]).
- The HFH rate in the 12 months before entry into the trial (0.32 HFH/patient-year) was lower than assumed (0.5 HFH/patient-year) and even lower in the 12-months post randomization (0.17 and 0.22 HFH/patient-year in the Control group and Device groups, respectively). The difference in event rates was 0.05

HFH/patient-year, 95% confidence interval [-0.05, 0.14]. While the HFH rate was numerically higher in the Device group, this trend was not noted in the Full Randomized Cohort (see **Section 9**), confirming no difference between treatment groups. Unlike the data on which trial assumptions were based, most trial patients did not have concomitant left-sided heart disease or severe left ventricular dysfunction (more than 1/3rd of patients in the literature articles had low LVEF, whereas less than 6% in the trial had LVEF <40%). However, the HFH rates in the trial are within the range of rates reported in other transcatheter device trials for TR (Kitamura et al. 2021[1], Kodali et al. 2023[2]).

- The trial was almost entirely conducted during the COVID-19 pandemic. Other trials that enrolled and followed patients during the pandemic also reported low HFH rates. This is attributed to improved patient compliance during the pandemic, particularly related to diuretics (Zile et al. 2022, Lindenfeld et al. 2021, Ponikowski et al. 2021). The impact of the pandemic on trial outcomes is difficult to assess because almost the entire trial enrolled during the pandemic (August 2019 to June 2022) and it is possible that the pandemic suppressed the HFH rate in the trial.
- The trial was designed with the expectation that a small proportion of Control patients would experience an improvement of 15 points in KCCQ-OS due to random variation, and that Device patients would experience improvement over and above the Control group due to reduction in TR. Accordingly, the trial assumed 20% of Control patients and 45% of Device patients would experience KCCQ-OS improvement of ≥15 points, a difference of 25 percentage points (ppts). The trial results were consistent with these assumptions, with 26% of Control patients and 50% of Device patients having experienced this level of improvement, a difference of 24 ppts. A cutoff of 10 points for KCCQ-OS improvement similarly showed a large between-group difference (57% vs. 37% for Device vs. Control, a difference of 20 ppts). Importantly, KCCQ-OS worsened by at least 5 points in over 31% of Control patients compared to only 15% of Device patients (a difference of 16 ppts).
- The trial met the primary composite endpoint driven by the KCCQ-OS component. The KCCQ-OS increase of 15.2 points in the Device group (complete-case paired analysis) is a substantial improvement from baseline, higher than that observed in the Control group (4.8 points).

The secondary endpoints of change in KCCQ-OS at 12 months, and TR reduction to moderate or less at 30 days were also met. At 12 months, 6MWD increased in the Device group (11.5 meters) and decreased in the Control group (-8.7 meters) based on complete-case paired analysis, resulting in a between-group difference of Δ20 meters, however, this endpoint was not met. As shown in **Section 9**, the difference was larger in the Full Randomized Cohort (Δ27 meters), with 95% confidence interval that does not overlap 0.

Preliminary results shown in **Section 9** on the Full Randomized Cohort (N=572) reinforce the conclusions of the Randomized cohort (N=350). **Section 12** presents additional analyses and rationale to substantiate that the health status improvement is a true treatment benefit and cannot be attributed solely to a “placebo effect.”

In summary, the TriClip System demonstrated significant reduction in TR severity, with associated improvement in health status and reduction in heart failure symptoms. These results confirm the effectiveness of TriClip in treating patients with symptomatic, severe TR and improving their health status.

8 CLINICAL SAFETY (RANDOMIZED COHORT PRIMARY ANALYSIS POPULATION)

SUMMARY

- The TriClip System demonstrated a favorable safety profile with no significant risks identified acutely or during 12-month follow-up:
  - The trial met secondary endpoint #1 with 98.3% of patients being free of MAE at 30 days, no procedural mortality, and very low rates of cardiovascular mortality and renal failure. The MAEs included 1 cardiovascular death and 2 new onset renal failure events. There were no non-elective cardiovascular surgeries for device-related adverse event or endocarditis requiring surgery.
  - Mortality (both all-cause and cardiovascular) rates at 12 months were low and comparable between Device and Control groups (all-cause: 8.8% and 7.7%, cardiovascular: 6.5% and 4.7%, respectively).
  - Hospitalization rates at 12 months also were comparable between groups (37.1% and 35.4%, respectively), with most hospitalizations being non-cardiovascular (23.1% and 22.3%, respectively).
  - Major bleeding rate at 30 days was higher in the Device group than the Control group (5.2% and 1.7%), which were attributed to access-site complications.
  - Rates for all other events such as stroke, TV surgery/intervention at 12 months were low and comparable between groups.
- Through 12 months, there was no device embolization and no device thrombosis. The need for new permanent pacemaker implantation was low and comparable between Device and Control groups through 30 days (0.7% in the Device group and 1.3% in the Control group) and through 12 months (3.6% and 3.4% in Device and Control groups, respectively), indicating no increased risk of conduction disturbances with TriClip therapy.
- Site-reported serious adverse event rates were comparable between Device and Control groups.

AEs were defined in the study protocol as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the medical device under investigation. An adverse event was reported and classified by the investigator at each site as serious if it met any of the criteria below:

- Led to a death
- Led to a serious deterioration in health of the patient, that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient hospitalization or prolongation of existing hospitalization, or

    - Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
    - Chronic disease
- Fetal distress, fetal death or a congenital abnormality or birth defect

The investigator also assessed the relationship of each event to the device or the procedure.

The CEC adjudicated the following events:

- New onset renal failure (defined as new need for dialysis or a creatinine increasing to 3.5 mg/dL or greater) through 30 days
- Endocarditis requiring surgery through 30 days
- Myocardial infarction through 30 days
- Major bleeding (BARC Type 3 or greater, Mehran et al. 2011) through 30 days
- Non-elective cardiovascular surgery for device related adverse event post index procedure through 30 days
- Death (cardiovascular vs. non-cardiovascular, based on VARC-II)
- Tricuspid valve surgery
- Tricuspid valve intervention
- Hospitalization (heart failure, other cardiovascular, non-cardiovascular)
- Stroke (VARC II definition)
- Transient Ischemic Attack (TIA)
- Cardiogenic shock
- Device/procedure relatedness for all events
- COVID-19 relatedness for all hospitalization and death event types with a start date or death date on or after 01-Jan-2020
- COVID-19 relatedness for all new events, other than hospitalization or death, beginning 03-Jun-2020

The ECL assessed device thrombosis and single leaflet device attachment (SLDA), defined as unilateral clip detachment from one leaflet based on follow-up echocardiography images.

8.1 Freedom from Major Adverse Events (MAE) at 30-Days Post-Procedure (Secondary Endpoint #1)

The secondary endpoint of freedom from MAE through 30-days post-procedure was assessed in patients who underwent an attempted procedure (Treated Device patients, N=172). Three MAEs occurred within 30-days post-procedure. Freedom from MAEs through 30-days post-procedure was 98.3% with the lower limit for the 95% confidence interval of 96.3%, which was greater than the performance goal of 90% ($p<0.0001$, **Table 8-1**). Therefore, this secondary endpoint was met.

Table 8-2 provides a breakdown of MAEs. The 3 MAEs included 1 cardiovascular death and 2 new onset renal failure events. There was no non-elective cardiovascular surgery

for device-related adverse event or endocarditis requiring surgery. The cardiovascular death was adjudicated as not procedure- or device-related. One of the two renal failure events was adjudicated as procedure-related and neither event was adjudicated as device-related.

Table 8-1: Secondary Endpoint #1 – Freedom from MAE through 30-Days Post-Procedure (Treated Device Patients, N=172)

	Estimate (SE)	Lower Limit for 95% CI	Performance Goal	p-value[a]
Kaplan-Meier Estimate (SE)	98.3% (1.0%)	96.3%	90.0%	< 0.0001
Result				**ENDPOINT MET**

[a] p-value calculated from Z test using Kaplan Meier survival estimate together with Greenwood method estimated variance at a one-sided 2.5% level of significance.
Follow-up duration is calculated from the procedure date (i.e., Treatment visit).

Table 8-2: MAE Component Event Rates at 30-Days Post-Procedure (Treated Device Patients, N=172)

MAE Component	n (%)
Any MAE	**3 (1.7%)**
Cardiovascular death[a]	1 (0.6%)
New onset renal failure[b]	2 (1.2%)
Endocarditis requiring surgery	0 (0%)
Non-elective cardiovascular surgery for TriClip device-related AE post-index procedure	0 (0%)

[a] Adjudicated by CEC as not procedure- or device-related
[b] One event was adjudicated by CEC as procedure-related and neither event as device-related

8.2 Adjudicated Adverse Events Post Treatment Visit through 30 Days

To assess the impact of the TriClip procedure, **Table 8-3** summarizes CEC adjudicated deaths, hospitalizations, and adverse events from the Treatment visit through 30 days post Treatment visit. The table shows comparable rates between the Device and Control groups for almost all events except hospitalization and major bleeding events, which occurred more frequently in the Device group than the Control group. As discussed below, the higher rate of hospitalization in the Device group is driven primarily by higher non-cardiovascular hospitalizations (mostly due to major bleeding events) and the higher rate of major bleeding events is attributed to access-site bleeding.

Table 8-3: Adjudicated Adverse Events (Treatment Visit through 30 Days, Primary Analysis Population, N=350)

Event	Device (N=172[a])					Control (N=174[a])		
	#Events	#Patients (Event Rate[b])	#Device Related Events	#Proc Related Events	#COVID-19 Related Events	#Events	#Patients (Event Rate[b])	#COVID-19 Related Events
Death (All-Cause)	**1**	**1 (0.6%)**	**0**	**0**	**0**	**1**	**1 (0.6%)**	**0**
Cardiovascular	***1***	***1 (0.6%)***	***0***	***0***	***0***	***1***	***1 (0.6%)***	***0***
Heart Failure-Related	1	1 (0.6%)	0	0	0	1	1 (0.6%)	0
Non-Heart Failure-Related	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
Non-Cardiovascular	***0***	***0 (0.0%)***	***0***	***0***	***0***	***0***	***0 (0.0%)***	***0***
Hospitalization	**24**	**22 (12.8%)**	**0**	**5**	**0**	**8**	**8 (4.6%)**	**0**
Heart Failure Hospitalization	6	6 (3.5%)	0	1	0	3	3 (1.7%)	0
Other Cardiovascular Hospitalization	7	6 (3.5%)	0	4	0	3	3 (1.7%)	0
Non-Cardiovascular Hospitalization	11	11 (6.4%)	0	0	0	2	2 (1.1%)	0
Other Adjudicated Adverse Events								
New Onset Renal Failure	2	2 (1.2%)	0	1	0	1	1 (0.6%)	0
Endocarditis Requiring Surgery	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
Non-Elective Cardiovascular Surgery for TriClip Related AE	0	0 (0.0%)	0	0	0	-	-	-
Major Bleeding (≥BARC 3)	9	9 (5.2%)	0	3	0	3	3 (1.7%)	0
Stroke	1	1 (0.6%)	0	0	0	1	1 (0.6%)	0
TIA	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
Myocardial Infarction	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
TV Surgery[c]	1	1 (0.6%)	1	1	0	1	1 (0.6%)	0
TV Intervention[d]	3	3 (1.7%)	2	3	0	0	0 (0.0%)	0
Cardiogenic Shock	0	0 (0.0%)	0	0	0	1	1 (0.6%)	0

[a] 3 Device patients and 1 Control patient did not complete a Treatment visit

[b] Calculated as percentage of patients who completed Treatment visit (172 for Device and 174 for Control)

[c] One additional Control patient underwent TV surgery 84 days post-randomization with a non-study surgeon due to continued symptoms and deteriorating kidney function (not included in this table because the patient did not complete a Treatment visit). The patient died 3 days post-surgery.

[d] Two of the 3 Device patients underwent a second TriClip procedure after an unsuccessful index procedure, the third patient had an additional TriClip procedure due to an SLDA.

Details on each event from Treatment visit through 30-days post Treatment visit are provided below:

Deaths

One death occurred in each of the two groups (both heart failure related). These are discussed below:

> ***Device group, POD 20 (20 days post procedure)*** (74-year-old male with ECL assessed functional, massive TR and NYHA Class III, comorbidities included recurrent pleural effusions requiring thoracentesis, ascites requiring paracentesis, severe and oxygen-dependent COPD, pulmonary HTN, CKD (IIIB)

and chronic CAD): The patient underwent the TriClip procedure at the Treatment visit. Due to atypical venous anatomy on the right (caput medusa), the left femoral vein was used for access. A total of 3 clips were placed with reduction of TR to severe noted on ECL adjudicated echocardiogram on POD 1. The post-procedure course was complicated by the discovery of a pulsatile right groin mass which was determined to be due to worsening heart failure on the existing atypical venous anatomy. It was determined to be unrelated to the TriClip procedure and was treated with a catheter-based procedure (Amplatzer device and chemical embolization). During and after this procedure, there was difficulty oxygenating the patient due to moderate pleural effusion, therefore the patient underwent ultrasound-guided thoracentesis with removal of 2000 mL of serous fluid. Despite this, the patient developed hypoxia unresponsive to IV diuretic therapy and required mechanical ventilation. He also developed hypotension requiring both inotropic and vasopressor support. Renal function worsened with creatinine rising to 2.2 mg/dL. CT showed pleural effusion as well as ascites. Echocardiogram revealed “wide-open” TR in the leaflets that were not clipped; the patient’s overall condition continued to decline despite aggressive medical management. As he was not considered a candidate for advanced heart failure therapies or surgery, palliative care was pursued after consultation with the family. The patient expired on POD 20. The death was adjudicated as not procedure- or device-related.

Control group, Day 21 (21 days post Treatment visit) (80-year-old male patient with ECL assessed severe TR and NYHA Class III, comorbidities included hypertension, liver disease, CAD and aortic valve stenosis, s/p CABG and aortic valve replacement): The patient was randomized to the Control group and completed the Treatment visit 8 days post randomization. On Day 19 (19 days post Treatment visit), he was noted to have progressively worse heart failure despite the addition of oral torsemide 2 days earlier with a 16 lbs. weight gain, BNP of 4,507 pg/mL and hypotension. He was hospitalized and evaluation confirmed worsening heart failure with BNP rising to over 8000 pg/mL in addition to cardiogenic shock with a lactic acid level of 7.0 mmol/L. Echocardiogram showed both severe MR and TR. He was now anuric and hypoxic. Despite aggressive IV support with inotropes and vasopressors, mechanical ventilation and CRRT, the patient’s clinical status continued to decline. The family elected to pursue comfort care measures and the patient expired on Day 21.

Hospitalizations

There were 24 hospitalizations in the Device group and 8 in the Control group, with most hospitalizations in the Device group being non-cardiovascular. Details are below:

HFH: 6 Device patients had HFH with admit dates ranging from POD 3 to POD 18. One event was adjudicated as procedure-related (patient had received

several liters of fluid during and after index procedure and was volume overloaded on POD 8) and none were device-related. 3 Control patients had HFH with admit dates ranging from Day 1 to Day 19.

Other cardiovascular hospitalization: 6 Device patients had 7 events. Four of these events were adjudicated as procedure-related but not device-related (1 event was due to thrombus noted during index procedure with the patient requiring an additional hospitalization for a second procedure attempt, and 3 events in 2 patients were for access-site related complication). 3 Control patients had events with admit dates ranging from Day 14 to Day 27.

Non-cardiovascular hospitalization: 11 Device patients had 11 events. None were adjudicated as procedure- or device-related. Reasons for these hospitalizations were infection (n=2), pneumonia (n=1), major bleeding (n=7, see also “Major Bleeding” below) and abdominal pain (n=1). Two Control patients experienced events for fall (n=1) and major bleeding (n=1).

New Onset Renal Failure

New onset renal failure occurred in 2 Device patients (POD 2 and POD 28) and 1 Control patient.

Both Device events were in patients with a history of renal disease. The first patient presented to Emergency Department (ED) one day post discharge from TriClip procedure with complaint of elevated blood sugar. Lab values revealed creatinine increased from 2.0 mg/dL at baseline to 3.8 mg/dL. The patient was hospitalized and diuresed with IV furosemide. The patient was discharged 8 days later with stable creatinine level of 3.0 mg/dL. The event was adjudicated as procedure-related but not device-related. The second event was adjudicated as not procedure- or device-related. The Control event occurred in the patient who died on Day 21 (described earlier).

Major Bleeding

Major bleeding occurred in 9 Device patients and 3 Control patients.

Three of the 9 Device events were adjudicated as procedure-related and none as device-related. None of these events were adjudicated as BARC 4 (i.e., cardiovascular surgery related bleeding) or BARC 5 (i.e., fatal bleeding). All 3 procedure-related major bleeding events occurred at the access site (2 were on POD 1 and 1 was on POD 13):

- The first patient presented to ED on POD 1 due to left femoral access site bleeding. While in ED, the patient developed hypotension and tachycardia secondary to acute blood loss. The event was resolved by a FemoStop device and manual pressure, and blood transfusion for hypotension.
- The second patient developed left groin hematoma on POD 1 while in hospital for the TriClip procedure, which resolved with manual pressure.

- The third patient presented on POD 13 with left groin discomfort and difficulty walking due to pain and weakness and was noted to have a hematoma at the access site. Ultrasound indicated a pseudoaneurysm. The patient had a thrombin injection.

All 3 events resolved without long-term sequelae.

The 6 non-procedure related events included intracranial hemorrhage following loss of consciousness (POD 21), hematuria (POD 15) and 4 GI bleeds (POD 7, 9, 15 and 17).

All 9 patients who experienced major bleeding events were on intensive anticoagulation therapy pre-procedure, and none of the bleeding events were associated with an escalation of antithrombotic therapy post-procedure.

The 3 major bleeding events in the Control group were GI bleed (Day 4), pseudo-aneurysm/hematoma (Day 14) and hemorrhage in brain (Day 18).

Stroke

Stroke occurred in one patient in each group. The Device patient experienced an ischemic stroke on POD 5, which was adjudicated as not procedure- or device-related. The Control patient experienced a hemorrhagic stroke on Day 18.

TV Surgery

One Device patient who experienced severe TR as a result of SLDA post-procedure underwent surgical TV replacement (non-urgent), mitral valve repair and left atrial appendage excision on POD 2 during index hospitalization. The patient was discharged home 6 days later. One Control patient experienced progressive shortness of breath for several weeks post Treatment visit and underwent TV replacement, mitral valve ring annuloplasty and ligation of the left atrial appendage on Day 21. The patient was discharged home 10 days later.

TV Intervention

Three Device patients underwent TV intervention. The first patient had an unsuccessful index procedure after 4 hours of unsuccessful leaflet grasping. The patient was then treated with IV diuretics for fluid overload and had a successful TriClip procedure on POD 7 with 4 clips implanted and residual moderate TR. The second patient had an aborted index procedure due to mobile thrombus found attached to the right atrial pacemaker lead. Post procedure heparin administration continued. TEE performed 3 days later revealed resolution of the thrombus and the patient was readmitted and underwent a successful TriClip procedure on POD 8 with resulting mild TR. The third patient underwent a successful index procedure with 2 clips implanted but POD 1 echo showed severe TR. The patient underwent a second TriClip procedure on POD 5, receiving 2 clips with residual moderate TR.

Other Events

Cardiogenic shock occurred in one Control patient on Day 19. There were no endocarditis requiring surgery, non-elective cardiovascular surgery for TriClip-related adverse event, TIA or myocardial infarction through 30-days post-Treatment visit in either group.

8.3 Adjudicated Adverse Events from Randomization through 12 Months

Table 8-4 summarizes CEC-adjudicated deaths, hospitalizations, and adverse events from randomization through 12 months. Mortality (both all-cause and cardiovascular) rates at 12 months were low and comparable between the Device and Control groups (all-cause: 8.8% and 7.7%, cardiovascular: 6.5% and 4.7%, respectively). Despite the higher rate of hospitalization 30-days post Treatment visit in the Device group, the rates at 12 months from randomization were comparable between groups (37.1% and 35.4%, respectively), with the majority in both groups being non-cardiovascular (23.1% and 22.3%, respectively).

Table 8-4: Adjudicated Adverse Events (Randomization through 12 Months (Primary Analysis Population, N=350)

Event	Device (N=175)					Control (N=175)		
	#Events	#Patients (Event Rate[a])	#Device Related Events	#Proc Related Events	#COVID-19 Related Events	#Events	#Patients (Event Rate[a])	#COVID-19 Related Events
Death (All-Cause)	**15**	**15 (8.6%)**	**0**	**0**	**1**	**13**	**13 (7.4%)**	**0**
Cardiovascular	***11***	***11 (6.3%)***	***0***	***0***	***0***	***8***	***8 (4.6%)***	***0***
Heart Failure-Related	7	7 (4.0%)	0	0	0	5	5 (2.9%)	0
Non-Heart Failure-Related	4	4 (2.3%)	0	0	0	3	3 (1.7%)	0
Non-Cardiovascular	***4***	***4 (2.3%)***	***0***	***0***	***1***	***5***	***5 (2.9%)***	***0***
Hospitalization	**111**	**63 (36.0%)**	**2**	**7**	**2**	**100**	**60 (34.3%)**	**0**
Heart Failure Hospitalization	35	26 (14.9%)	1	2	0	28	20 (11.4%)	0
Other Cardiovascular Hospitalization	17	16 (9.1%)	1	5	0	21	16 (9.1%)	0
Non-Cardiovascular Hospitalization	59	38 (21.7%)	0	0	2[b]	51	37 (21.1%)	0
Other Adjudicated Adverse Events								
Stroke	3	3 (1.7%)	0	0	0	4	3 (1.7%)	0
TIA	1	1 (0.6%)	0	0	0	0	0 (0.0%)	0
TV Surgery	3	3 (1.7%)	2	2	0	6	6 (3.4%)	0
TV Intervention	4	4 (2.3%)	3	4	0	3[c]	3 (1.7%)	0
Cardiogenic Shock	0	0 (0.0%)	0	0	0	1	1 (0.6%)	0

[a] Calculated as percentage of patients randomized (175 each for Device and Control)
[b] One patient died after a lengthy hospitalization (36 days) and is counted in COVID-19-related death. The second patient subsequently died within 12 months, which was not COVID-19-related.
[c] 2 of the 3 TV interventions with TriClip occurred after completion of 12-month visit but within 365 days of randomization and the remaining TV intervention with a competitive device occurred 116 days post randomization in a patient enrolled at a European site.

8.4 ECL-Confirmed SLDAs

SLDAs confirmed by the ECL occurred in 12 (7.0%) Device patients: 3 were intraprocedural, 4 were noted post-procedure but prior to discharge, and 5 were noted between discharge and 30-day follow-up. All 3 intra-procedural SLDAs occurred with the first Clip deployed, following which additional clip(s) were implanted. Despite SLDA, TR reduction was achieved in 10 of the 12 cases. Two patients had additional interventions (1 non-urgent surgery, 1 additional clip implant) and no patient experienced a MAE through 12 months.

8.5 Site-Reported Serious Adverse Events (SAE)

Table 8-5 summarizes site-reported SAEs from Treatment visit through 12 months post randomization. The table shows that overall, SAE rates post Treatment visit are comparable between Device (42.9%) and Control (41.1%) groups, with 95% confidence interval [-8.5%, 11.9%]. Procedure/device related SAEs post Treatment visit occurred in 3.5% of Device patients and are summarized in **Table 8-6**. As noted in the table, 5 of the 6 SAEs were already included in **Table 8-3**, and the remaining SAE was an access site complication that did not meet the definition of major bleeding event (BARC Type 2).

Table 8-5: Summary of Site-Reported SAEs (From Treatment Visit[a] through 12 Months Post Randomization, Primary Analysis Population, N=350)

	Device (N=172) n (%)	**Control (N=174)** n (%)	**Difference** [95% Conf Int]
Serious Adverse Events	**74 (43.0%)**	**71 (40.8%)**	**2.2%**
Procedure/device related[b]	6 (3.5%)	N/A	[-8.1%, 12.5%]

[a] Post discharge for Device group and post Treatment visit for Control group

Table 8-6: Listing of Procedure/Device Related SAEs in Device Group (From Treatment Visit[a] through 12 Months Post Randomization, Primary Analysis Population, N=350)

Patient	Description (POD)	CEC Adjudicated Event[b]
1	Access site bleeding (POD 1)	Bleeding Type 3a
	Hypotension with tachycardia secondary to acute blood loss (POD 1)	
2	Access site complication (POD 4)	Bleeding Type 2
3	Access site complication – thrombin injection for pseudoaneurysm (POD 13)	Bleeding Type 3b
	Access site complication – surgical repair of pseudoaneurysm (POD 29)	
4	TV surgery due to unsuccessful TriClip procedure (POD 56)	TV surgery
5	Re-intervention due to SLDA (POD 65)	Additional TriClip procedure
6	Heart failure due to volume overload (POD 123)	HFH (not procedure- or device-related)

[a] Post discharge for Device group and post Treatment visit for Control group
[b] All events, except row #6, are included in **Table 8-3**.

8.6 New Permanent Pacemaker Implantation

No Device patient underwent a pacemaker implant during the index hospitalization. One patient in the Device group and 2 patients in the Control group underwent permanent pacemaker implant within 30 days of Treatment visit, resulting in a new permanent pacemaker implant rate of 0.6% and 1.1%, respectively (KM estimates). Through 12 months post randomization, 5 patients in each group underwent a pacemaker implant, resulting in KM estimates of 3.4% and 3.3%, in the Device and Control groups respectively (**Table 8-7**).

Table 8-7: Site-Reported New Permanent Pacemaker Implantation (Primary Analysis Population, N=350)

	Device % (#Patients / # at risk[a])	Control % (#Patients / # at risk[a])
Treatment visit through 30-days post Treatment visit	0.7% (1/145)	1.3% (2/151)
Randomization through 12-months post randomization	3.4% (5/147)	3.3% (5/151)

[a] Patients with pre-existing pacemaker at baseline are excluded from the calculation.

8.7 Device Embolization

There were no occurrences of device embolization.

8.8 Device Thrombosis

There were no occurrences of device thrombosis.

8.9 Tricuspid Valve Pressure Gradient

On average, the Device group had approximately 1 mmHg higher tricuspid valve gradient than the Control group through 12-month follow-up. Ten patients (9 Device, 1 Control) had mean tricuspid gradient ≥ 5 mmHg at 30-day follow-up (data not shown in table). Five (5) of the 9 Device patients continued to have mean tricuspid gradient ≥ 5 mmHg at 6 months and 4 patients continued to have mean tricuspid gradient ≥ 5 mmHg 12 months. However, there were no related clinical symptoms, and no further intervention was required in any of the 9 Device patients. Only 1 of these patients had a HFH within 12 months.

8.10 Summary of Clinical Safety

The trial met the secondary endpoint for safety, with 98.3% of Device patients being free of MAE at 30 days, no procedural mortality, no urgent or emergent need for surgery due to TriClip-related AE, and very low rates of cardiovascular mortality and new onset renal failure. All-cause mortality and hospitalization rates at 12 months were low and comparable between Device and Control groups. Through 12 months, there was no device embolization and no device thrombosis. The higher major bleeding rate in the Device group than the Control group at 30 days is attributed to access-site complications which is as expected as only Device patients underwent a large-bore access procedure. The need for new permanent pacemaker implantation was low and comparable between Device and Control groups (~3.5% at 12 months in each group), indicating no increased risk of conduction disturbances with TriClip therapy. Other adverse events such as stroke, TIA, and myocardial infarction, were either absent or occurred at low and comparable rates between treatment groups. Common site-reported serious adverse event rates are comparable between Device and Control groups. Overall, the device has a favorable safety profile.

9 FULL RANDOMIZED COHORT

SUMMARY

- The Randomized cohort utilized an adaptive design with an interim analysis for sample size re-estimation. Sample size re-estimation indicated 350 patients was sufficient to evaluate the trial's primary endpoint. The trial continued to randomize patients until the interim analysis was completed, and a total of 572 patients were ultimately randomized (Full Randomized Cohort).
- The safety and effectiveness of TriClip demonstrated in the Primary Analysis Population is strengthened by the results in the Full Randomized Cohort:
    - The FS test yielded a p-value of 0.0042. The win ratio was 1.53 with 95% confidence interval [1.14, 2.06] - p-value and confidence interval not adjusted for multiple testing.
    - Through 12 months, all-cause mortality or TV surgery rates in the Full Randomized Cohort remained low (Device: 9.9%, Control: 9.7%) and consistent with those in the Primary Analysis Population (Device: 9.4%, Control: 10.6%).
    - Annualized HFH rates in the Full Randomized Cohort continued to indicate no between-group difference (Device: 0.17, Control: 0.19 HFH/patient-year).
    - Consistent with the Primary Analysis Population, the proportion of patients with improvement in KCCQ-OS of ≥15 points showed a substantial treatment benefit, with ~50% of Device patients and only ~26% of Control patients achieving such an improvement.
- Secondary effectiveness endpoints in the Full Randomized Cohort also remained consistent with the Primary Analysis Population. The between-group difference in 6MWD favoring Device patients was larger in the Full Randomized cohort than in the Primary Analysis Population (Δ24.8 vs. Δ17.1 meters with imputation; Δ27.2 vs. Δ20.3 meters without imputation), with 95% confidence interval for the between-group difference that does not overlap 0 (confidence interval not adjusted for multiple testing).
- Safety results in the Full Randomized Cohort were consistent with the Primary Analysis Population.
- The Full Randomized Cohort reinforces the safety and effectiveness results in the Primary Analysis Population.

9.1 Introduction

As highlighted in **Section 6**, 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 patients completed 12-month follow-up, while the trial was still enrolling. Timing of endpoint analysis for the Randomized cohort was determined by the sample size re-estimation outcome, which indicated that 350 patients was sufficient to evaluate the trial's primary endpoint. The trial continued to randomize patients until the sample size re-estimation analysis was completed, by which point a total of 572 patients were randomized at 68 sites (Full Randomized Cohort). This section summarizes and descriptively compares the preliminary results from the Full Randomized Cohort (N=572) with those from the Primary Analysis Population (N=350). At this time of data cutoff, 56 patients (29 Device, 26 Control) were pending 12-month follow-up visits.

9.2 Baseline Characteristics

Baseline characteristics, echocardiography parameters, baseline medications and biomarkers of the Full Randomized Cohort were nearly identical to the Primary Analysis Population (**Table 9-1** and **Table A-1** in **Appendix 1**).

Table 9-1: Baseline Characteristics, Echocardiography Parameters and Cardiac Medication (Primary Analysis Population, N=350 and Full Randomized Cohort, N=572)

Characteristic	Primary Analysis Population (N=350)	Full Randomized Cohort (N=572)
Baseline Characteristic		
Age		
Mean ± SD	77.9 ± 7.3	78.1 ± 7.8
≥ 75 years	75.1%	74.8%
Female	54.9%	58.9%
Caucasian[a]	83.4%	83.6%
Renal disease	35.4%	33.4%
Liver disease	7.7%	7.2%
Stroke/TIA	15.4%	12.9%
Hypertension	80.9%	81.3%
Atrial fibrillation	90.3%	87.8%
COPD	12.3%	14.3%
HFH		
HFH in prior year, %patients	25.1%	23.8%
HFH rate in prior year, per patient-year	0.32	0.31
CRT/ICD/Pacemaker	14.9%	16.4%
Prior mitral/aortic intervention	36.9%	36.2%
NYHA III/IV	57.4%	55.1%
KCCQ-OS, Mean ± SD	55.1 ± 23.8	55.1 ± 23.3
6MWD (m), Mean ± SD	247.1 ± 123.3	245.1 ± 121.0
Key Echocardiography Parameters		
TR Severity		
Moderate[b]	1.8%	1.8%
Severe	27.5%	26.8%
Massive	19.8%	21.3%
Torrential	50.9%	50.1%
Secondary Etiology	93.9%	94.8%
Coaptation gap, mm	5.4 ± 1.8	5.3 ± 1.8
Heart size/function (Mean ± SD)		
Tricuspid annulus diameter, cm	4.4 ± 0.7	4.3 ± 0.8
RVEDD-base, cm	5.1 ± 0.8	5.0 ± 0.8
RVEDD-mid, cm	3.7 ± 0.7	3.7 ± 0.7
Right atrial volume, mL	148.1 ± 84.3	143.8 ± 79.6
Right ventricular TAPSE, cm	1.6 ± 0.4	1.7 ± 0.4
Cardiac output, L/min	4.2 ± 1.2	4.2 ± 1.2
LVEF (Mean ± SD)	59.0 ± 9.9	59.6 ± 9.1
LVEF ≤ 40%	5.6%	4.2%
LVEF ≤ 50%	14.1%	10.8%
Medication Category		
Beta Blockers	72.9%	71.0%
ACE-Inhibitors or ARB (including ARNI)	43.7%	42.7%
Vasodilators	11.4%	9.3%
Diuretics	98.0%	97.2%

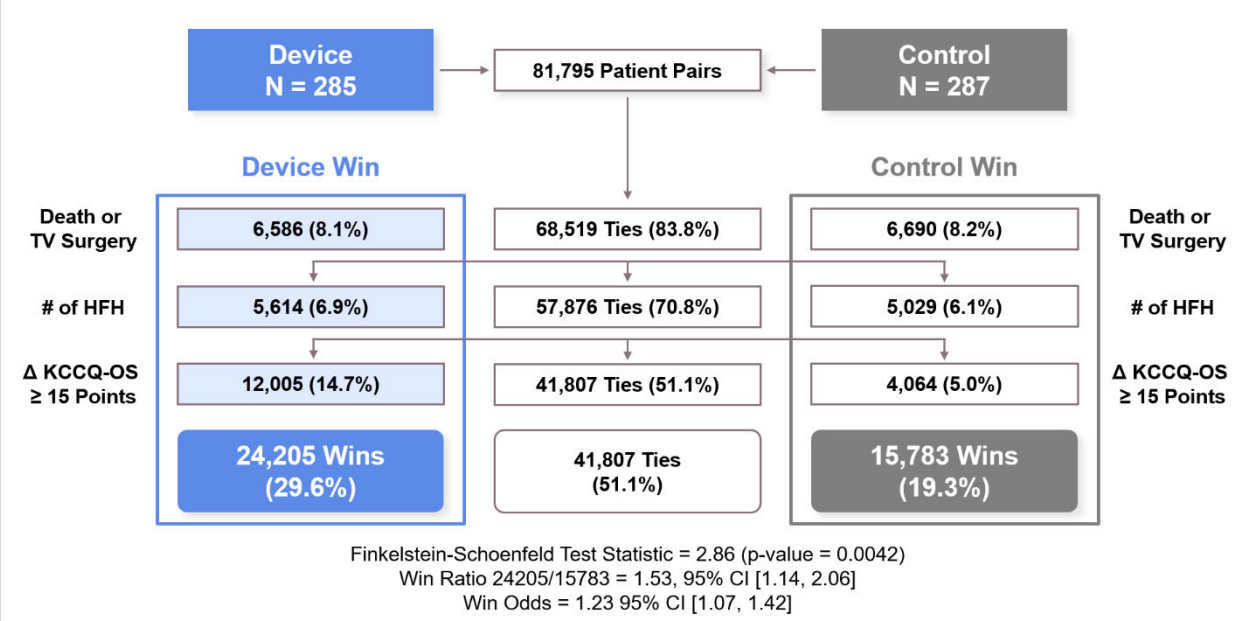
[a] Among patients who disclosed race (37 patients did not disclose race due to local regulation)

[b] Patients with moderate TR qualified for the trial with ≥severe TR based on the screening echocardiogram

9.3 Primary Endpoint

The primary endpoint for the Full Randomized Cohort is summarized using FS test, and the win ratio and win odds estimates, along with 95% confidence interval (**Figure 9-1**). The FS test yielded a nominal p-value of 0.0042 (p-value not adjusted for multiple testing), indicating a more robust result than the Primary Analysis Population. The win ratio estimate was 1.53, with 95% confidence interval [1.14, 2.06], and the win odds estimate was 1.23 with 95% confidence interval [1.07, 1.42]. These results are consistent with those from the Primary Analysis Population. These analyses censored follow-up after a COVID-19 related hospitalization and COVID-19 related death. Without censoring COVID-19 events, the results remained robust with p-value is 0.0092 (p-value not adjusted for multiple testing).

Figure 9-1: Win Ratio and Win Odds for Primary Endpoint (Full Randomized Cohort, N=572)



Eight patients (all in the Device group) who experienced hospitalization related to COVID-19 had their follow-up information following the COVID-19 related hospitalization excluded. One COVID-19 related death in the Device group was censored.
p-value not adjusted for multiple testing

Components of the primary endpoint are shown in **Table 9-2**. All-cause mortality or TV surgery rates (Device: 9.9%, Control: 9.7%) in the Full Randomized Cohort are consistent with those in the Primary Analysis Population (Device: 9.4%, Control: 10.6%). Annualized HFH rates in the Full Randomized Cohort continue to indicate no between-group difference (Device: 0.17, Control: 0.19 HFH/patient-year). The proportion of patients with improvement in KCCQ-OS ≥15 points in the Full Randomized Cohort was identical to those in the Primary Analysis Population, with 50% of Device patients and only 26% of Control patients achieving such an improvement. These

results strengthen the conclusions of the primary endpoint analysis and confirm the safety and effectiveness of TriClip.

Table 9-2: Primary Endpoint Components (Full Randomized Cohort, N=572)

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 (%)	9.4%	10.6%	9.9%	9.7%
Difference [95% CI]	-1.2% [-7.6%, 5.2%]		0.1% [-5.0%, 5.2%]	
Annualized HFH Rate, per patient-year	0.22	0.17	0.17	0.19
Difference [95% CI]	0.05 [-0.05, 0.14]		-0.02 [-0.09, 0.06]	
Proportion with KCCQ-OS improvement ≥15 points at 12 months	50%	26%	50%	26%
Difference [95% CI]	23% [12%, 34%]		24% [14%, 33%]	

Subgroup analyses for the Full Randomized Cohort are shown in **Table A-3** in **Appendix 1**. Consistent with the Primary Analysis Population, across both levels of all subgroups, the Device group had a higher proportion of patients with KCCQ-OS improvement ≥ 15 points at 12 months than the Control group.

9.4 Secondary Endpoints

Secondary endpoints are presented in **Table 9-3**.

- Freedom from MAE at 30 days in the Full Randomized Cohort was comparable to that in the Primary Analysis Population (98.9% vs. 98.3%).
- Consistent with the results in the Primary Analysis Population, TR reduction to moderate or less at 30 days was achieved in 88.9% of Device patients compared to 5.3% of Control patients in the Full Randomized Cohort.
- The between-group difference in change in KCCQ-OS from baseline in the Full Randomized Cohort is consistent with that observed in the Primary Analysis Population (Δ11.9 vs. Δ11.7 points with imputation; Δ11.0 vs. Δ10.4 in complete-case paired analysis).
- Device patients experienced a larger improvement in 6MWD than Control patients in the Full Randomized Cohort than in the Primary Analysis Population (Δ24.8 vs. Δ17.1 meters with imputation; Δ27.2 vs. Δ20.3 meters in complete-case paired analysis), with 95% confidence interval that does not overlap 0.

Table 9-3: Secondary Endpoints (Primary Analysis Population, N=350 and Full Randomized Cohort, N=572)

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*, 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]	Δ11.7 [6.9, 16.6]		Δ11.9 [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]	Δ10.4 [5.7, 15.1]		Δ11.0 [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]	Δ17.1 [-12.0, 46.1]		Δ24.8 [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]	Δ20.3 [-7.2, 47.7]		Δ27.2 [5.5, 48.9]	

[a] Patients who experienced HF-related death or had TV surgery prior to 12-month visit were assigned 12-month KCCQ-OS or 6MWD of 0. Patients who were unable to exercise due to cardiac reasons were also assigned a 6MWD of 0 meters at 12-month follow-up.
Patients who experienced hospitalization related to COVID-19 had their follow-up information following the COVID-19 related hospitalization excluded.

9.5 Safety

Freedom from MAE at 30 days in the Full Randomized Cohort was 98.9%. There were no MAEs in the additional 109 treated Device patients (**Table 9-4**).

Table 9-4: MAE Component Event Rates at 30-Days Post-Procedure (Treated Device Patients, N=281)

MAE Component	n (%)
Any MAE	**3 (1.1%)**
Cardiovascular death[a]	1 (0.4%)
New onset renal failure[b]	2 (0.7%)
Endocarditis requiring surgery	0 (0.0%)
Non-elective cardiovascular surgery for TriClip device-related AE post-index procedure	0 (0.0%)

[a] Adjudicated by CEC as not procedure- or device-related
[b] One event was adjudicated by CEC as procedure-related and neither event as device-related

Table 9-5 summarizes CEC adjudicated deaths, hospitalizations and adverse events from the Treatment visit through 30 days post Treatment visit. Only one death occurred in each group within 30 days of Treatment visit. HFH rates were low and comparable between groups (2.5% and 2.1%, respectively). Major bleeding rate in the Device group of this cohort was lower than in the Primary Analysis Population (3.2% vs. 5.2%). Through 30 days, non-cardiovascular hospitalizations occurred at the same rate in the Device group of this cohort as in the Primary Analysis Population (6.8% vs. 6.4%).

Other events, except TV intervention, remained low and comparable between groups.

Table 9-5: Adjudicated Adverse Events (Treatment Visit through 30 Days, Full Randomized Cohort, N=572)

Event	Device (N=281)					Control (N=286)		
	#Events	Patients (Event Rate[b])	#Device Related Events	#Proc Related Events	#COVID-19 Related Events	#Events	Patients (Event Rate[b])	#COVID-19 Related Events
Death (All-Cause)	**1**	**1 (0.4%)**	**0**	**0**	**0**	**1**	**1 (0.3%)**	**0**
Cardiovascular	***1***	***1 (0.4%)***	***0***	***0***	***0***	***1***	***1 (0.3%)***	***0***
Heart Failure-Related	1	1 (0.4%)	0	0	0	1	1 (0.3)	0
Non-Heart Failure-Related	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
Non-Cardiovascular	***0***	***0 (0.0%)***	***0***	***0***	***0***	***0***	***0 (0.0%)***	***0***
Hospitalization	**33**	**30 (10.7%)**	**0**	**5**	**2**	**16**	**15 (5.2%)**	**0**
Heart Failure Hospitalization	7	7 (2.5%)	0	1	0	6	6 (2.1%)	0
Other Cardiovascular Hospitalization	7	6 (2.1%)	0	4	0	4	4 (1.4%)	0
Non-Cardiovascular Hospitalization	19	19 (6.8%)	0	0	2	6	6 (2.1%)	0
Other Adjudicated Adverse Events								
Major Bleeding (≥BARC 3)	9	9 (3.2%)	0	3	0	5	5 (1.7%)	0
New Onset Renal Failure	2	2 (0.7%)	0	1	0	1	1 (0.3%)	0
Endocarditis Requiring Surgery	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
Non-Elective Cardiovascular Surgery for TriClip Related AE	0	0 (0.0%)	0	0	0	-	-	-
Stroke	1	1 (0.4%)	0	0	0	1	1 (0.3%)	0
TIA	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
Myocardial Infarction	0	0 (0.0%)	0	0	0	0	0 (0.0%)	0
TV Surgery[c]	1	1 (0.4%)	1	1	0	1	1 (0.3%)	0
TV Intervention[d]	3	3 (1.1%)	2	3	0	0	0 (0.0%)	0
Cardiogenic Shock	0	0 (0.0%)	0	0	0	1	1 (0.3%)	0

[a] 4 Device patients and 1 Control patient did not complete a Treatment visit

[b] Calculated as percentage of patients who completed Treatment visit (281 for Device and 286 for Control)

[c] One additional Control patient underwent TV surgery 84 days post-randomization with a non-study surgeon due to continued symptoms and deteriorating kidney function (not included in this table because the patient did not complete a Treatment visit). The patient died 3 days post-surgery.

[d] Two of the 3 Device patients underwent a second TriClip procedure after an unsuccessful index procedure, the third patient had an additional TriClip procedure due to an SLDA.

Table 9-6 summarizes CEC adjudicated deaths, hospitalizations, and adverse events from randomization through 12 months in the two treatment groups. Mortality (both all-

cause and cardiovascular) rates at 12 months were comparable between groups (all-cause: 8.8% and 7.6%, cardiovascular: 5.6% and 4.1%, respectively), although there were 9 hospitalizations adjudicated as COVID-19 related in the Device group and none in the Control group. Hospitalization rates through 12 months remained comparable between groups (35.7% and 33.8%, respectively), with the majority still being non-cardiovascular (24.6% and 21.8%, respectively).

Table 9-6: Adjudicated Adverse Events (Randomization through 12 Months, Full Randomized Cohort, N=572)

Event	Device (N=285)					Control (N=287)		
	#Events	#Patients (Event Rate[a])	#Device Related Events	#Proc Related Events	#COVID-19 Related Events	#Events	#Patients (Event Rate[a])	#COVID-19 Related Events
Death (All-Cause)	**23**	**23 (8.1%)**	**0**	**0**	**1**	**20**	**20 (7.0%)**	**0**
Cardiovascular	***15***	***15 (5.3%)***	***0***	***0***	***0***	***11***	***11 (3.8%)***	***0***
Heart Failure-Related	11	11 (3.9%)	0	0	0	8	8 (2.8%)	0
Non-Heart Failure-Related	4	4 (1.4%)	0	0	0	3	3 (1.0%)	0
Non-Cardiovascular	***8***	***8 (2.8%)***	***0***	***0***	***1***	***9***	***9 (3.1%)***	***0***
Hospitalization	**161**	**96 (33.7%)**	**2**	**7**	**9**	**155**	**89 (31.0%)**	**0**
Heart Failure Hospitalization	44	32 (11.2%)	1	2	0	48	34 (11.8%)	0
Other Cardiovascular Hospitalization	23	22 (7.7%)	1	5	0	25	20 (7.0%)	0
Non-Cardiovascular Hospitalization	94	65 (22.8%)	0	0	9	82	56 (19.5%)	0
Other Adjudicated Adverse Events								
Stroke	3	3 (1.1%)	0	0	0	4	3 (1.0%)	0
TIA	1	1 (0.4%)	0	0	0	0	0 (0.0%)	0
TV Surgery	5	5 (1.8%)	2	2	0	7	7 (2.4%)	0
TV Intervention	7	7 (2.5%)	5	7	0	3[b]	3 (1.0%)	0
Cardiogenic Shock	0	0 (0.0%)	0	0	0	1	1 (0.3%)	0

[a] Calculated as percentage of patients randomized (285 for Device and 287 for Control)

[b] 2 of the 3 TV interventions with TriClip occurred after completion of 12-month visit but within 365 days of randomization and the remaining TV intervention with a competitive device occurred 116 days post randomization in a patient enrolled at a European site.

ECL-Confirmed SLDAs

The SLDA rate was 5.3%. All SLDAs were noted at or prior to 30-day follow-up and none required urgent or emergent re-intervention.

Site-Reported SAEs

Table 9-7 summarizes site-reported SAEs from Treatment visit through 12 months post randomization. The table shows that overall, SAE rates post Treatment visit are comparable between Device (41.1%) and Control (37.6%) groups, with 95% confidence interval [-4.6%, 11.3%]. In addition to SAEs already described in **Section 8.5**, there was one new procedure- or device-related SAE in this cohort (TV surgery due to inability to reduce TR with TriClip – **Table 9-8**).

Table 9-7: Summary of Site-Reported Adverse Events (From Treatment Visit[a] through 12 Months Post Randomization, Full Randomized Cohort, N=572)

	Device (N=281) n (%)	Control (N=286) n (%)	Difference [95% Conf Int]
Serious Adverse Events	**116 (41.3%)**	**107 (37.4%)**	**3.9%**
Procedure/device related[b]	7 (2.5%)	N/A	[-4.2%, 11.8%]

[a] Post discharge for Device group and post Treatment visit for Control group

Table 9-8: Listing of Procedure/Device Related SAEs in Device Group (From Treatment Visit[a] through 12 Months Post Randomization, Full Randomized Cohort, N=572)

Patient	Description (POD)	CEC Adjudicated Event[b]
1	Access site bleeding (POD 1)	Bleeding Type 3a
	Hypotension with tachycardia secondary to acute blood loss (POD 1)	
2	Access site complication (POD 4)	Bleeding Type 2
3	Access site complication – thrombin injection for pseudoaneurysm (POD 13)	Bleeding Type 3b
	Access site complication – surgical repair of pseudoaneurysm (POD 29)	
4	TV surgery due to unsuccessful TriClip procedure (POD 56)	TV surgery
5	Re-intervention due to SLDA (POD 65)	Additional TriClip procedure
6	Heart failure due to volume overload (POD 123)	HFH (not procedure- or device-related)
7	TV surgery due to inability to sufficient reduce TR with TriClip (POD 32)	TV surgery

[a] Post discharge for Device group and post Treatment visit for Control group
[b] All events, except row #6, are included in **Table 9-5**.

New Permanent Pacemaker Implantation

New permanent pacemaker implant rate within 30-days post Treatment visit were 0.8% and 0.8% in Device and Control group respectively (KM estimates). Through 12 months post randomization, new permanent pacemaker was implanted in 3.4% of Device patients and 2.1% of Control patients (**Table 9-9**).

Table 9-9: Site-Reported New Permanent Pacemaker Implantation (Full Randomized Cohort, N=572)

	Device % (# Patients / # at risk [a])	Control % (#Patients / # at risk [a])
Treatment visit through 30-days post Treatment visit	0.9% (2/235)	0.8% (2/240)
Randomization through 12-months post randomization	3.4% (8/238)	2.1% (5/240)

[a] Patients with pre-existing pacemaker at baseline are excluded from the calculation.

9.6 Summary

These preliminary results on the Full Randomized Cohort reinforce the safety and effectiveness conclusions in the Primary Analysis Population of 350 Randomized patients. The FS p-value for the Full Randomized Cohort is 0.0042 (p-value not adjusted for multiple testing) and the win ratio estimate is higher than in the Primary Analysis Population, with tighter confidence interval. These results also support an improvement in exercise capacity measured by the 6-Minute Walk Test with TriClip over the Control group.

10 SINGLE-ARM COHORT

SUMMARY

- The objective of the Single-arm cohort was to demonstrate that any reduction in TR would provide health status benefit to these patients despite being anatomically more complex than the Randomized cohort.
- In terms of baseline characteristics, Single-arm cohort patients had more torrential TR, larger coaptation gaps and were more likely to have a CRT/ ICD/pacemaker than Randomized patients. While these differences are as anticipated, Single-arm cohort patients were older with more co-morbidities (COPD, prior mitral/aortic intervention), and had larger right ventricles and larger right atria, suggesting more advanced disease than Randomized patients.
- The results in the Single-arm cohort confirm the safety and effectiveness of the TriClip System in more technically complex patients with advanced disease:
    - The primary endpoint of survival at 12 months with ≥ 10-point improvement in KCCQ-OS was met, with 46.2% of patients meeting the the performance goal of 30% (p=0.0008).
    - At 12 months, Single-arm patients had nearly identical KCCQ-OS improvement as the Randomized cohort (14.5 points versus 15.2 points).
    - The procedure was extremely safe, with no procedure- or device-related deaths, no device thrombosis, and no device embolization through 12 months. Consistent with the Randomized cohort, new permanent pacemaker implantation occurred at a very low rate (1.6% at 12 months).
    - Despite being more technically challenging, TR was reduced to moderate or less in 80% of patients at 30 days and was sustained in 79% of patients through 12 months.
    - Mortality and HFH rates at 30 days in the Single-arm cohort (mortality: 0.0%, HFH: 3.0%) were low and comparable with the Randomized cohort (mortality: 0.6%, HFH: 3.5%) and there were no procedure- or device-related deaths. Mortality rate at 12 months in the Single-arm cohort was 15%, which is within the range of rates anticipated for this population (7% to 28%, based on contemporary literature). HFH rate in the Single-arm cohort was 0.36 per patient-year. These higher rates for mortality and HFH at 12 months in the Single-arm cohort than the Randomized cohort are likely due to the age and other baseline characteristics of the enrolled population.
- TriClip was shown to be safe and effective in the Single-arm cohort.

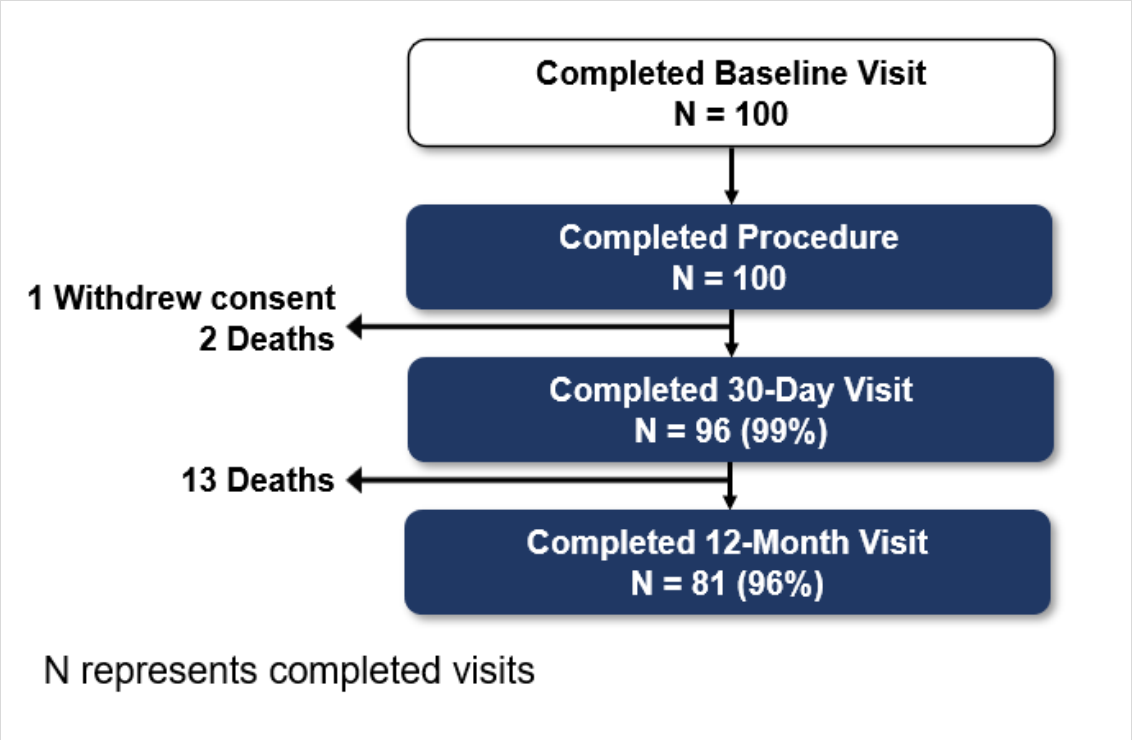
10.1 Patient Enrollment

A total of 188 patients were treated in the Single-arm cohort. The statistical analysis plan specified a group sequential interim analysis with 100 patients. This section summarizes the results on the first 100 Single-arm patients who enrolled and underwent a TriClip implant across 44 sites, with a majority enrolled in the US (n=85), followed by Canada (n=13) and Europe (n=2).

10.2 Disposition and Discontinuation of Patients

Figure 10-1 shows the disposition of patients with respect to completion of protocol-required study visits through 12 months. One patient withdrew consent and 15 patients died prior to 12-month follow-up.

Figure 10-1: **Disposition of Patients**



10.3 Baseline Characteristics

Table 10-1 shows key baseline characteristics and co-morbidities of the Single-arm cohort in comparison to the Randomized cohort.

Single-arm cohort patients were on average slightly older than Randomized patients (80.4 vs. 77.9 years), had more COPD (22% vs. 12.3%), and more prior mitral/aortic intervention (44% vs. 36.9%). Single-arm patients also had more torrential TR (74.0% vs. 50.9%), larger coaptation gap (7.4 ± 2.7 mm vs. 5.4 ± 1.8 mm) and were more likely to have a history of CRT/ICD/pacemaker (35% vs. 14.9%) than Randomized patients. While these differences are as anticipated, Single-arm patients also had larger right

ventricles (RVEDD base, 5.4 ± 0.9 cm vs. 5.1 ± 0.8 cm, RVEDD mid, 4.0 ± 0.8 cm vs. 3.7 ± 0.7 cm) and larger right atria (181.7 ± 103.7 mL vs. 148.1 ± 84.3 mL), suggesting more advanced disease than Randomized patients. Baseline biomarkers (**Table A-1** in **Appendix 1**) for the Single-arm cohort were consistent with the Randomized cohort.

Table 10-1: Baseline Characteristics, Echocardiography Parameters and Cardiac Medication (Randomized Cohort, N=350 and Single-Arm Cohort, N=100)

Characteristic	Randomized Cohort (N=350)	Single-arm Cohort (N=100)
Baseline Characteristic		
Age		
Mean ± SD	77.9 ± 7.3	80.4 ± 6.2
≥ 75 years	75.1%	85.0%
Female	54.9%	53.0%
Caucasian[a]	83.4%	87.0%
Renal disease	35.4%	36.0%
Liver disease	7.7%	3.0%
Stroke/TIA	15.4%	18.0%
Hypertension	80.9%	83.0%
Atrial fibrillation	90.3%	93.0%
COPD	12.3%	22.0%
Heart Failure Hospitalizations (HFH)		
HFH in prior year, %patients	25.1%	22.0%
HFH rate in prior year, per patient-year	0.32	0.33
CRT/ICD/Pacemaker	14.9%	35.0%
Prior mitral/aortic intervention	36.9%	44.0%
NYHA III/IV	57.4%	59.0%
KCCQ-OS, Mean ± SD	55.1 ± 23.8	54.5 ± 22.6
6MWD (m), Mean ± SD	247.1 ± 123.3	237.7 ± 120.4
Echocardiography Parameters		
TR Severity		
Moderate	1.8%	0.0%
Severe	27.5%	9.4%
Massive	19.8%	16.7%
Torrential	50.9%	74.0%
Secondary (Functional) Etiology	93.9%	85.9%
Coaptation gap, mm	5.4 ± 1.8	7.4 ± 2.7
Heart size/function (Mean ± SD)		
Tricuspid annulus diameter, cm	4.4 ± 0.7	4.6 ± 0.8
RVEDD-base, cm	5.1 ± 0.8	5.4 ± 0.9
RVEDD-mid, cm	3.7 ± 0.7	4.0 ± 0.8
Right atrial volume, mL	148.1 ± 84.3	181.7 ± 103.7
Right ventricular TAPSE, cm	1.6 ± 0.4	1.6 ± 0.4
Cardiac output, L/min	4.2 ± 1.2	4.3 ± 1.3
LVEF (Mean ± SD)	59.0 ± 9.9	58.9 ± 9.5
LVEF ≤ 40%	5.6%	6.3%
LVEF ≤ 50%	14.1%	13.5%
Medication Category		
Beta Blockers	72.9%	74.0%
ACE-Inhibitors or ARB	43.7%	41.0%
Vasodilators	11.4%	12.0%
Diuretics	98.0%	98.0%

[a] Among patients who disclosed race (3 patients did not disclose race due to local regulation)

10.4 Primary Endpoint Results

The primary endpoint of the Single-arm cohort is survival through 12 months with KCCQ-OS improvement ≥10 points compared to baseline. The endpoint was evaluated in 91 patients, which included 15 patients who died prior to 12 months and 76 patients

who survived through 12 months and had KCCQ-OS score available at both baseline and 12-month follow-up. Nine (9) patients were excluded from the analysis due to: missed 12-month visit (n=3), patient declined to complete KCCQ-OS at 12-month visit (n=2), patient did not complete a 12-month visit due to COVID-19 (n=1), patient experienced COVID-19 related hospitalization prior to 12 months (n=2) and is therefore censored from analysis, and patient withdrew prior to 12-month visit (n=1).

Table 10-2 shows 42 patients with paired baseline and 12-month KCCQ-OS achieved KCCQ-OS improvement ≥10 points, therefore, the primary endpoint rate is 46.2% (42/91), with 98.75% lower confidence limit of 34.3%, which exceeds the performance goal of 30% (p=0.0008).

Table 10-2: Primary Endpoint Results (Single-Arm Cohort, N=100)

	Estimate	98.75% Lower Confidence Limit	Performance Goal	p-value[a]
Survival at 12 Months with at least 10-point improvement in KCCQ-OS at 12 Months from Baseline	46.2% (42/91)	34.3%	30%	0.0008
Result				**ENDPOINT MET**

[a] p-value calculated from the exact test for binomial proportion.

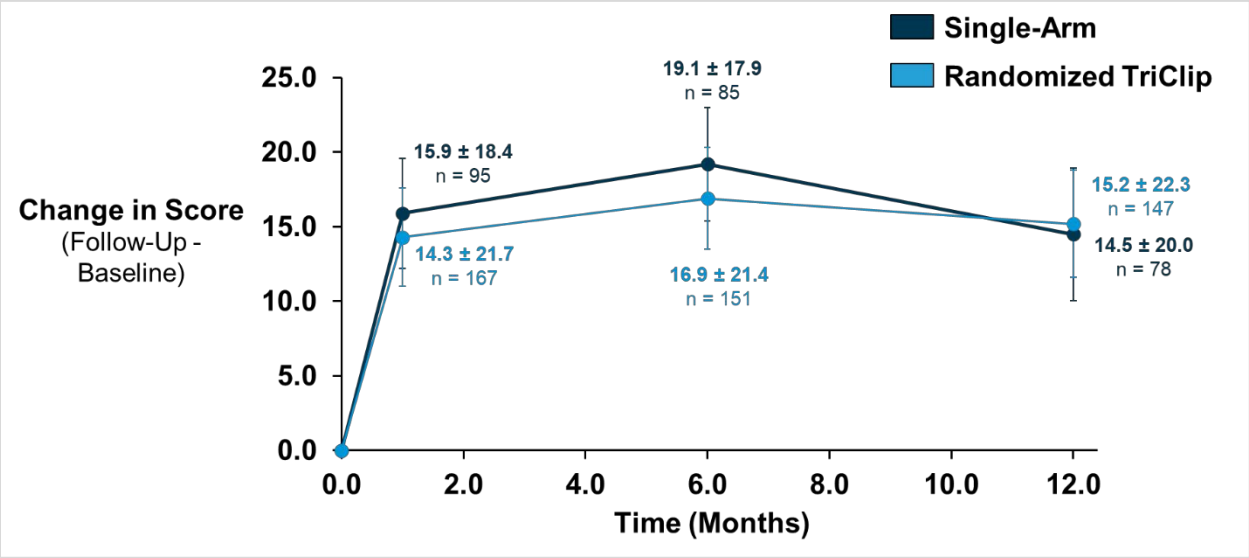
Sensitivity Analysis

Sensitivity analysis was performed to evaluate the effect of COVID-19 events on the primary endpoint, in which events that occurred after a COVID-19 related event are included in the analysis (these events were censored in the primary analysis). Of the 2 patients who were excluded in the primary analysis due to COVID-19 related events, 1 patient died following a COVID-19 related hospitalization and is included in the sensitivity analysis. The second patient did not complete a 12-month visit and is therefore not included in the sensitivity analysis. The primary endpoint was met in this sensitivity analysis (estimate: 45.7%, 98.75% lower confidence limit: 33.9%, p=0.0011 – data not presented in table).

Magnitude of Health Status Benefit

Through 12 months, Single-arm patients experienced the same magnitude of health status benefit as the Device group of the Randomized cohort (**Figure 10-2**).

Figure 10-2: KCCQ-OS Change in the Single-arm Cohort (N=100) and Randomized Cohort Device Group (N=175)



Error bars represent 95% CI (not adjusted for multiple testing).

Subgroup Analysis

Subgroup analysis results are included in **Table A-4** in **Appendix 1.** The only notable subgroup is sex: more females than males experienced KCCQ-OS improvement ≥ 10 points (71.4% vs. 34.3%, p=0.0011). This is as anticipated as females had lower baseline KCCQ-OS than males (46.5 ± 21.6 vs. 63.7 ± 20.4 – data not presented in table).

10.5 Clinical Results

Table 10-3 summarizes the safety and effectiveness results in the Single-arm cohort with a comparison to the Device group of the Randomized cohort (N=350).

Safety

There were no deaths through 30 days in the Single-arm cohort. HFH rate at 30 days in the Single-arm cohort is 3.0%, which is similar to the Randomized Device group (3.5%) There were no strokes, no device thrombosis, and no device embolization through 12 months, and none of the deaths through 12 months were adjudicated as related to the procedure or device. At 30 days, major bleeding rate was 4%, and at 12 months, new pacemaker implantation and TV surgery each occurred at a very low rate of 1.6% and 2.2%, respectively. These rates are all comparable to those in the Randomized Device group. The 12-month mortality rate of 15.2% was within the range of rates anticipated for this population (7% to 28% based on contemporary literature, see **Section 6.6.3.3**).

Effectiveness

Despite the Eligibility Committee's determination that Single-arm patients were unlikely to achieve moderate or less TR, 80% achieved TR reduction to moderate or less at 30

days, which was sustained in 79% of patients through 12 months. Single-arm patients also had nearly identical KCCQ-OS improvement as the Randomized cohort (14.5 points versus 15.2 points). NYHA class improved to Class I or II in nearly the same proportion of patients in the Single-arm cohort as the Randomized Device group (80% vs. 84%), and 6MWD improved by approximately the same amount in both the Single-arm cohort and the Randomized Device group (13.7 meters versus 11.5 meters).

The higher rates of all-cause mortality and HFH at 12 months in the Single-arm cohort than the Randomized cohort likely reflect the higher risk characteristics (older, more COPD, more stroke, more prior mitral/aortic intervention) and more advanced disease of the Single-arm cohort than the Randomized cohort.

Table 10-3: Safety and Effectiveness Results from Single-arm Cohort and Randomized Device Patients

	Randomized TriClip[a]	Single-arm (N=100)
Safety		
30-Day Outcomes (%)[a]		
All-Cause Death	***0.6%***	***0.0%***
Procedure- or Device-Related	0.0%	0.0%
Cardiovascular	0.6%	0.0%
Endocarditis Requiring Surgery	0.0%	0.0%
Non-Elective Cardiovascular Surgery for TriClip Related AE	0.0%	0.0%
HFH	***3.5%***	***3.0%***
Procedure- or Device-Related	0.6%	0.0%
Major Bleeding (≥ BARC 3)	5.2%	4.0%
New Onset Renal Failure	1.2%	0.0%
Stroke	0.6%	0.0%
TIA	0.0%	0.0%
Myocardial Infarction	0.0%	0.0%
Cardiogenic Shock	0.0%	1.0%
SLDA	3.5%	5.0%
New Permanent Pacemaker Implantation	0.7%	0.0%
12-Month Outcomes (%)[a]		
All-Cause Death	***8.6%***	***15.0%***
Procedure- or Device-Related	0.0%	0.0%
Cardiovascular	6.3%	11.0%
HFH	***14.9%***	***24.0%***
Annualized rate, per patient-year	0.22	0.36
Procedure- or Device-Related	1.1%	1.0%
Stroke	1.7%	0.0%
TIA	0.6%	1.0%
TV Surgery	1.7%	2.0%
Cardiogenic Shock	0.0%	1.0%
Device Embolization	0.0%	0.0%
Device Thrombosis	0.0%	0.0%
New Permanent Pacemaker Implantation	3.4%	1.5%
ECL-Confirmed SLDA	7.0%	7.0%
Effectiveness		
TR grade		
TR ≤ moderate at 30 days (%)	87%	80%
TR ≤ moderate at 12 months (%)	88%	79%
KCCQ-OS change from baseline to 12 months (Mean ± SD)	15.2 ± 22.3	14.5 ± 20.0
NYHA class I/II	84%	80%
6MWD change from baseline to 12 months (Mean ± SD), meters	11.5 ± 111.4	13.7 ± 92.7

[a] 30-day rates are reported for Device patients who underwent the TriClip procedure (N=172) and 12-month rates are reported for patients randomized to the Device group (N=175)

10.6 Summary of Single-arm Effectiveness and Safety

The Single-arm cohort was strategically included in the trial to demonstrate that *any* reduction in TR grade in these anatomically more complex patients would provide health status benefit. The primary endpoint of survival at 12 months with ≥ 10-point improvement in KCCQ-OS was met, demonstrating that these patients experienced meaningful health status improvement. Despite being more technically challenging, TR reduction to moderate or less was achieved in 80% of patients at 30 days. Although Single-arm patients were older and had more comorbidities and more advanced disease than the Randomized cohort, the safety profile of TriClip in this cohort was comparable to that in the Device group of the Randomized cohort. There were no procedure- or device-related deaths, no device thrombosis, no device embolization and very low rate of new permanent pacemaker implant (1.6%) through 12 months. The higher rates of all-cause mortality and HFH at 12 months in the Single-arm cohort than the Randomized cohort likely reflect the higher risk characteristics and more advanced disease of the Single-arm cohort than the Randomized cohort.

Given the favorable safety profile of the TriClip procedure and the significant symptomatic improvement and health status benefit, the benefit/risk profile of TriClip is favorable in the Single-arm cohort.

11 CARDIAC IMAGING SUB-STUDY RESULTS

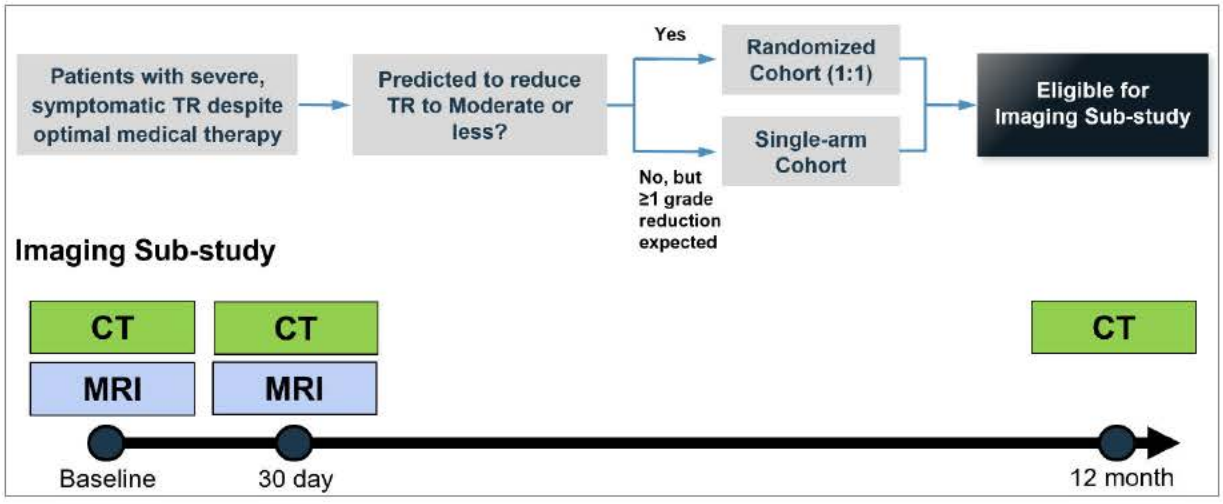
SUMMARY

- A Cardiac Imaging sub-study was conducted to provide insights into TR reduction and cardiac reverse remodeling using serial Cardiac MRI and Cardiac CT imaging at baseline and follow-up. MRI was used specifically to assess change in TR severity and blood flow measurements and CT was primarily used to assess changes in cardiac size.
- Preliminary sub-study results:
  - Confirm significant reduction of TR with TriClip relative to the Control group and confirm TR severity assessment via TTE
  - Demonstrate improved RV function with TriClip relative to the Control group
  - Demonstrate right heart reverse remodeling with TriClip which is sustained through 12 months.

A Cardiac Imaging sub-study was initiated to provide insights into cardiac reverse remodeling and quantitative "gold standard" measurements to assess which echocardiographic measurements most accurately quantify TR severity, RV size and RV function. The sub-study includes a subset of patients in the TRILUMINATE Pivotal trial who consented for the sub-study at participating sites. Cardiac CT and cardiac MRI were both required at baseline and 30-day follow-up, and CT was required at 12-month follow-up (**Figure 11-1**).

MRI was used specifically to assess change in TR severity and is also considered the "gold standard" for blood flow measurements, while CT was primarily used to assess changes in cardiac size. The sub-study is ongoing and preliminary results from the Randomized cohort are summarized in this section.

Figure 11-1: Cardiac Imaging Sub-study



11.1 Cardiac MRI Results

Table 11-1 provides quantification of changes in TR severity and right heart size at 30-day follow-up assessed by Cardiac MRI in the Randomized cohort.

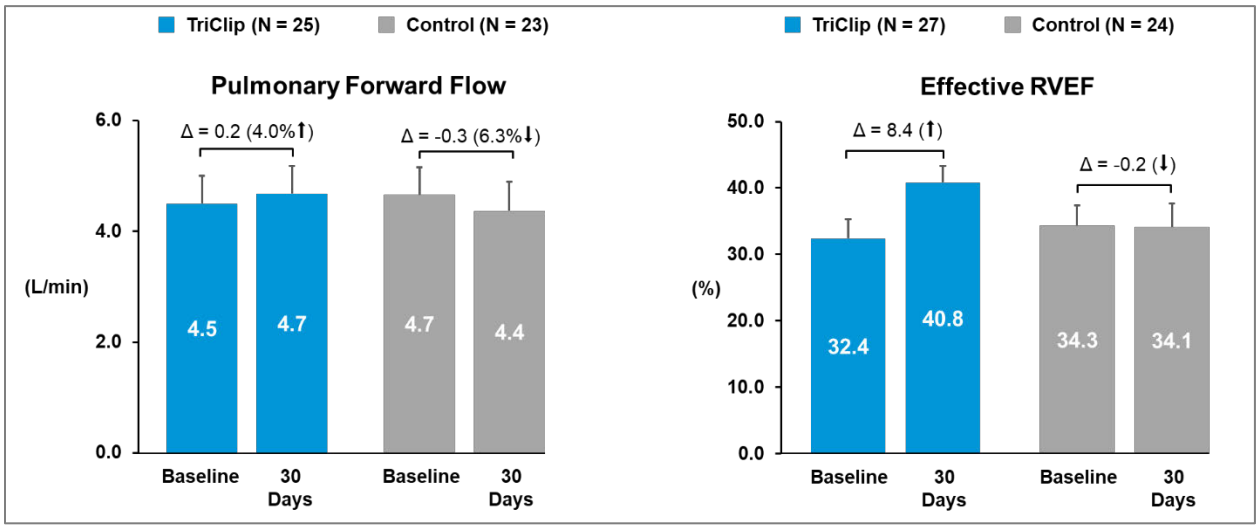
- At 30 days, substantial reductions in regurgitant volume and regurgitant fraction were observed in the Device group (-34.1 ± 28.2 mL and -27.8 ± 16.0 percent points) but not in the Control group (3.2 ± 22.1 mL and -2.3 ± 21.2 percent points), confirming the TR severity assessments by TTE.
- RVEDV and RV mass decreased in the Device group (-32.1 ± 33.5 mL and -4.7 ± 5.2 grams, respectively), whereas no reduction was observed in the Control group (3.3 ± 31.9 mL and 0.0 ± 6.0 grams, respectively).
- Pulmonary forward flow increased by 0.2 ± 0.9 L/min in the Device group while it decreased in the Control group (-0.3 ± 0.8 L/min) – see **Figure 11-2**.
- Effective RVEF increased by 8.4 ± 7.6 percentage points in the Device group while no improvement was seen in the Control group (-0.2 ± 4.5 percentage points) – see **Figure 11-2**.

Table 11-1: Change in TR Parameters and Right Heart Size at 30 Days (Assessed by MRI)

Parameter	Device (N=27)[a]	Control (N=26)[a]
Change in TR volume (mL)		
Mean ± SD (n)	-34.1 ± 28.2 (27)	3.2 ± 22.1 (24)
Median (Q1, Q3)	-28.0 (-52.0, -10.0)	2.0 (-13.0, 11.5)
Change in TR fraction (%)		
Mean ± SD (n)	-27.8 ± 16.0 (27)	-2.3 ± 21.2 (24)
Median (Q1, Q3)	-28.0 (-45.0, -13.8)	0.5 (-8.4, 6.0)
Change in RVEDV, mL		
Mean ± SD (n)	-32.1 ± 33.5 (27)	3.3 ± 31.9 (25)
Median (Q1, Q3)	-22.0 (-55.0, -7.0)	2.0 (-16.0, 16.0)
Change in RV mass (grams)		
Mean ± SD (n)	-4.7 ± 5.2 (27)	0.0 ± 6.0 (25)
Median (Q1, Q3)	-5.0 (-9.0, 0.0)	1.0 (-4.0, 5.0)
Change in RAEDV, mL		
Mean ± SD (n)	-8.7 ± 23.1 (27)	-4.0 ± 38.5 (26)
Median (Q1, Q3)	-9.0 (-21.0, 8.0)	-3.0 (-16.0, 22.0)
Change in Effective RVEF (%)		
Mean ± SD (n)	8.4 ± 7.6 (27)	-0.2 ± 4.5 (24)
Median (Q1, Q3)	8.1 (4.0, 15.0)	0 (-2.6, 2.5)
Change in RV function (RV free wall strain, %)		
Mean ± SD (n)	-2.0 ± 4.5 (27)	1.2 ± 6.1 (25)
Median (Q1, Q3)	-1.0 (-5.0, 1.0)	0.0 (-3.0, 3.0)
Change in Pulmonary Forward Flow (L/min)		
Mean ± SD (n)	0.2 ± 0.9 (25)	-0.3 ± 0.8 (23)
Median (Q1, Q3)	0.1 (-0.4, 0.9)	0.0 (-1.0, 0.3)

[a] Includes patients who had MRI performed at both baseline and 30 Days; excludes patients who had TV surgery prior to 30 days.
RVEDV: Right Ventricular End Diastolic Volume
RAEDV: Right Atrial End Diastolic Volume
RVEF: Right Ventricular Ejection Fraction

Figure 11-2: Pulmonary Forward Flow & Effective RVEF Assessed by Cardiac MRI



Error bars represent 95% CI (not adjusted for multiple testing).

11.2 Cardiac CT Results

Cardiac CT measurements at 30-day follow-up show similar improvements in the Device group. **Table 11-2** and **Table 11-3** provide quantification of change in right heart size at 30-day and 12-month follow-up, respectively, as assessed by CT, in the Randomized cohort.

- Tricuspid annular area showed substantial reduction (-201.2 ± 177.0 mm^2) in the Device group compared to the Control group (-49.3 ± 147.1 mm^2).
- RVEDV decreased substantially (-34.2 ± 32.8 mL) in the Device group whereas minimal change was noted in the Control group (-1.8 ± 30.3 mL).
- RV mass decreased in the Device group (-4.8 ± 7.4 grams) whereas there was no reduction in the Control group (0.3 ± 5.3 grams).
- The change in RAEDV at 30 days appeared somewhat different when measured by CT versus MRI, with CT showing slightly larger reductions than MRI in the Device group (CT: -20.3 mL vs. MRI: -8.7 mL), but similar measurements in the Control group (CT:-4.9 mL vs. MRI: -4.0 mL). However, both imaging modalities support reverse remodeling with the TriClip device relative to Control.

Table 11-2: Change in Right Heart Size at 30 Days (Assessed by Cardiac CT)

Parameter	Device (N=27)[a]	Control (N=29)[a]
Change in TV annular area (mm^2)		
Mean ± SD (n)	-201.2 ± 177.0 (26)	-49.3 ± 147.1 (29)
Median (Q1, Q3)	-195.0 (-290.0, -80.0)	-70.0 (-120.0, 80.0)
Change in RVEDV, mL		
Mean ± SD (n)	-34.2 ± 32.8 (26)	-1.8 ± 30.3 (29)
Median (Q1, Q3)	-36.5 (-60.0, -9.0)	-6.0 (-25.0, 16.0)
Change in RV mass (grams)		
Mean ± SD (n)	-4.8 ± 7.4 (26)	0.3 ± 5.3 (29)
Median (Q1, Q3)	-3.0 (-7.0, -1.0)	0.0 (-2.0, 4.0)
Change in RAEDV, mL		
Mean ± SD (n)	-20.3 ± 31.6 (26)	-4.9 ± 43.0 (29)
Median (Q1, Q3)	-21.5 (-32.0, -1.0)	-10.0 (-30.0, 15.0)
Change in RV function (RV free wall strain, %)		
Mean ± SD (n)	-1.3 ± 5.9 (22)	-0.5 ± 4.1 (26)
Median (Q1, Q3)	-2.5 (-6.0, 2.0)	-0.5 (-4.0, 2.0)

[a] Includes patients who had CT performed at both baseline and 30 days; excludes patients who had TV surgery prior to 30 days.
RVEDV: Right Ventricular End Diastolic Volume
RAEDV: Right Atrial End Diastolic Volume

Follow-up Cardiac CT data at 12 months confirm durability of the results observed at 30 days:

- Tricuspid valve annular area decreased (-195.0 ± 197.1 mm^2) in the Device group while there was almost no change in the Control group (-3.0 ± 142.8 mm^2).
- RVEDV showed a large reduction at 12 months in the Device group (-35.8 ± 26.4 mL reduction from baseline) while no improvement was seen in the Control group (-1.0 ± 38.1 mL).
- Consistent with 30-day CT measurements, RAEDV decreased by -19.5 ± 34.2 mL in the Device group whereas no reduction was observed in the Control group (4.4 ± 35.5 mL).
- RV mass showed reduction at 12 months in the Device group (-4.7 ± 4.9 grams) while no improvement was seen in the Control group (1.4 ± 6.5 grams).

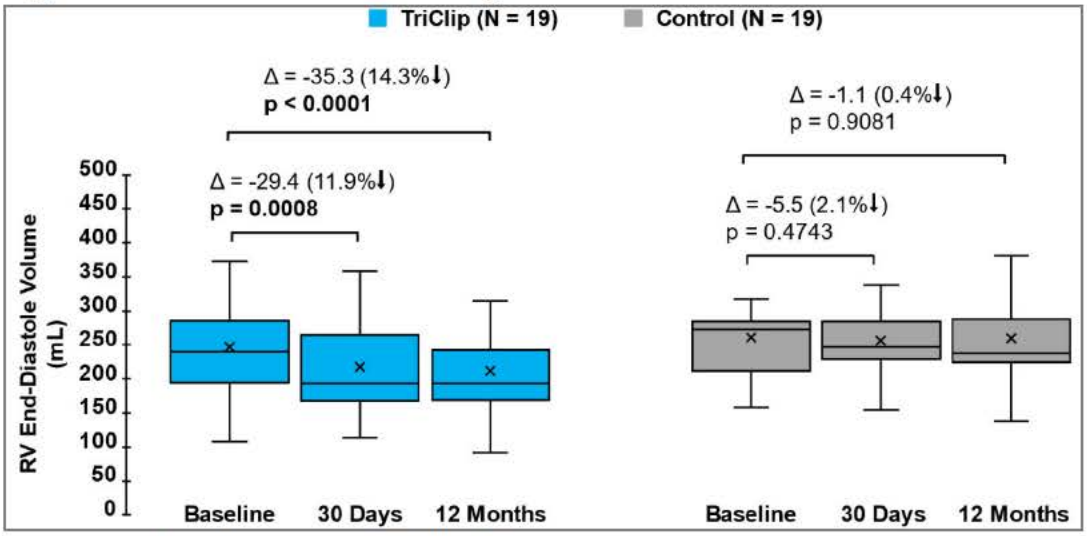
Table 11-3: Change in Right Heart Size at 12 months (Assessed by CT)

Parameter	Device (N=20)[a]	Control (N=20)[a]
Change in TV annular area (mm^2)		
Mean ± SD (n)	-195.0 ± 197.1 (20)	-3.0 ± 142.8 (20)
Median (Q1, Q3)	-205.0 (-305.0, -60.0)	-20.0 (-70.0, 60.0)
Change in RVEDV, mL		
Mean ± SD (n)	-35.8 ± 26.4 (20)	-1.0 ± 38.1 (20)
Median (Q1, Q3)	-38.0 (-58.5, -18.5)	-3.5 (-22.5, 12.5)
Change in RV mass (grams)		
Mean ± SD (n)	-4.7 ± 4.9 (20)	1.4 ± 6.5 (20)
Median (Q1, Q3)	-3.5 (-6.5, -1.0)	1.5 (-4.5, 5.0)
Change in RA end diastolic volume (RAEDV, mL)		
Mean ± SD (n)	-19.5 ± 34.2 (20)	4.4 ± 35.5 (20)
Median (Q1, Q3)	-18.0 (-31.5, -4.0)	5.0 (-14.0, 23.0)
Change in RV function (RV free wall strain, %)		
Mean ± SD (n)	-4.2 ± 7.2 (18)	-1.3 ± 5.4 (19)
Median (Q1, Q3)	-3.5 (-8.0, 2.0)	-2.0 (-5.0, 3.0)

[a] Includes patients who had CT performed at both baseline and 12 months; excludes patients who had TV surgery prior to 12 months.

Analysis of RVEDV measured by Cardiac CT in patients with data across baseline, 30 days and 12 months shows trends supportive of sustained reduction in the Device group but not in the Control group – see **Figure 11-3**.

Figure 11-3: RVEDV Assessed by Cardiac CT



p-values not based on pre-specified hypothesis tests
"x" symbol indicates mean; boxes indicate the 25th and 75th percentiles, and whiskers represent 1.5 interquartile range (IQR) below/above the first/third quartiles, respectively (whiskers stop at the minimum/maximum values if within the 1.5 IQR)

11.3 Cardiac Imaging Sub-Study Summary

The available imaging sub-study data confirm the significant reduction of TR in patients treated with TriClip relative to the Control group. There was a small increase in right atrial volume in the Device group noted on two-dimensional echocardiogram, but the gold standard CT measurements from this sub-study confirm *reduction* in right atrial and right ventricular volume in the Device group and no reduction in the Control group. In addition, MRI measurements showed improvement in right ventricular function in the Device group while no improvement was seen in the Control group. These high-resolution, three-dimensional data demonstrate sustained, favorable right heart reverse remodeling and improved right ventricular function with TriClip, which were not observed in the Control group.

12 ADDRESSING POTENTIAL BIAS IN OPEN-LABEL TRIAL

SUMMARY

- As the TRILUMINATE pivotal trial results are based on an open-label design and the trial met the primary endpoint driven by a patient-reported outcome (KCCQ-OS) alone, it can be hypothesized that trial patients' responses to the KCCQ were influenced by their knowledge of randomization and treatment received, which may have introduced bias in the patient-reported outcome, i.e., the improvement in health status with TriClip relative to the Control group is a "placebo effect". Several analyses were conducted to address the potential bias and to support a true treatment effect with TriClip:
    - *Substantial and Sustained TR Reduction:* Despite the presence of massive or torrential TR at baseline in 70% of the population, TriClip effectively reduced TR to moderate or less in a substantial proportion of patients (87% at 30 days), whereas only 5.4% of Control patients experienced such a reduction in TR.
    - *Association between KCCQ-OS change and TR Grade change:* Across all patients who underwent the TriClip procedure, a strong association was noted between KCCQ-OS change and TR grade change at 12 months. Such an association could not be observed if the health status improvement with TriClip relative to the Control group is a "placebo effect".
    - *Significant and Sustained Health Status Change:* The magnitude of treatment benefit of 10.4 points on KCCQ-OS at 12 months is larger than the expected magnitude of a placebo effect (~5-6 points).
    - *Durability of Benefit:* The treatment benefit of approximately 10 points in KCCQ-OS at 30 days was sustained through 6 months and 12 months. This is unlikely to be the case if awareness of treatment group is the only factor influencing the response to the KCCQ.
    - *Anatomical changes:* The Cardiac Imaging sub-study data confirmed TR reduction with TriClip and demonstrate sustained, favorable right heart reverse remodeling and improved RV function, which were not observed in the Control group
    - *Physiological Changes (Biomarkers):* Several biomarkers (liver and renal) showed favorable outcomes with the Device compared to Control.
- Improvement in objective measures such as right heart size and function and biomarkers cannot be attributed to patients' knowledge of treatment received. The totality of evidence presented demonstrates that the health status benefit seen with TriClip is a true benefit, supported by mechanistic and biological changes.

The TRILUMINATE Pivotal trial demonstrated that in patients with symptomatic severe TR, substantial health status improvement was achieved with the TriClip device compared to medical therapy alone. Although the KCCQ was administered by study personnel who were blinded to treatment group, it can be hypothesized that in this open-label trial, patients' responses to the questionnaire were influenced by their knowledge of randomization and treatment received. This section summarizes the totality of data that supports a true treatment effect of the device (i.e., not a placebo effect).

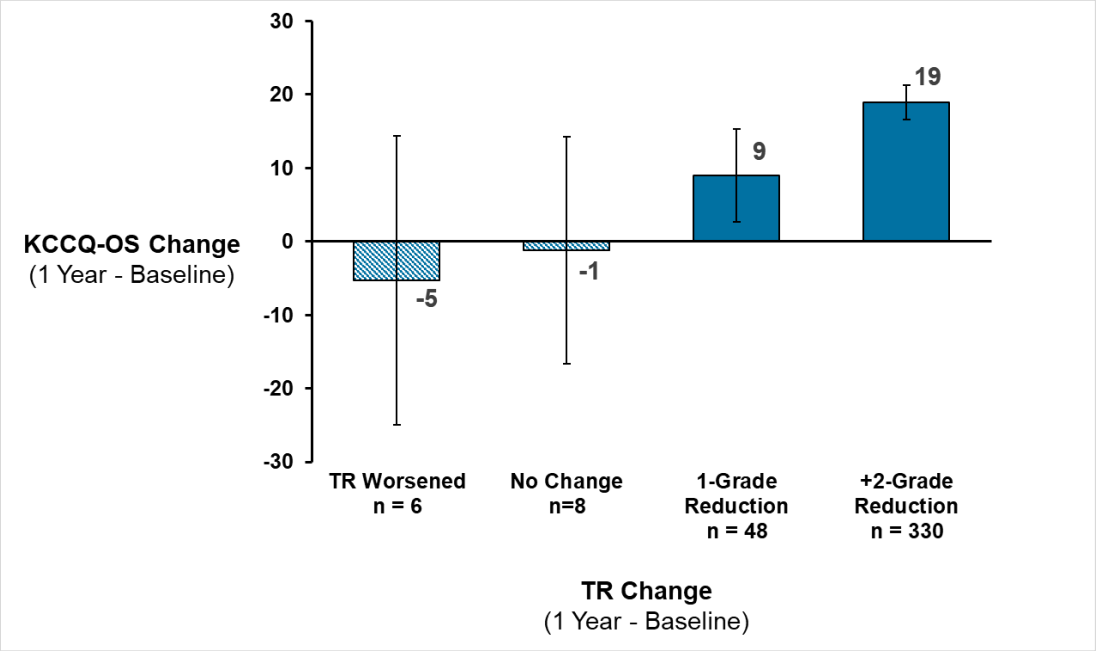
12.1 Substantial and Sustained Reduction in TR

TriClip was designed with the intent of treating and reducing TR. The trial demonstrated that TriClip effectively and substantially reduced TR in most patients in the Randomized cohort despite the presence of massive or torrential TR at baseline in 71%. The device showed substantial and clinically meaningful reduction in TR to moderate or less at 30 days in 87% of patients compared to only 5.4% in the Control group ($p<0.0001$). The reduction in TR was sustained, with 89% of patients at moderate or less TR at 12 months. The ability of TriClip to substantially reduce and sustain the reduction in TR was also observed in 79% of the more anatomically complex Single-arm cohort where 91% of patients had massive and torrential TR at baseline. The reduction in TR measured by echocardiography was confirmed via Cardiac MRI in the imaging sub-study, via substantially reduced regurgitant volume and regurgitant fraction measurements in the Device group but not in the Control group (**Section 11.1**).

12.2 Association between KCCQ-OS Change and TR Grade Change

All Device patients were aware of treatment, therefore an association between change in TR grade and change in KCCQ-OS supports that the health status improvements with TriClip reflects a real treatment benefit. When assessing only TriClip patients across all cohorts in the trial (Randomized, Single-arm, Roll-in), there is an association between KCCQ-OS change and TR grade change (**Figure 12-1**). Such an association cannot be a "placebo effect" since all patients received treatment with TriClip.

Figure 12-1: KCCQ-OS Change versus TR Grade Change at 12 Months (Randomized Device group, Single-arm Cohort, Roll-in Cohort)



Note: Patients who had TV surgery prior to 12 months are excluded.
Error bars represent 95% CI (not adjusted for multiple testing).
Striped bars represent data from <10 patients.

12.3 Significant and Sustained Health Status Change at 12 months favoring TriClip

As discussed below, the magnitude and durability of health status benefit from TriClip support a real treatment effect.

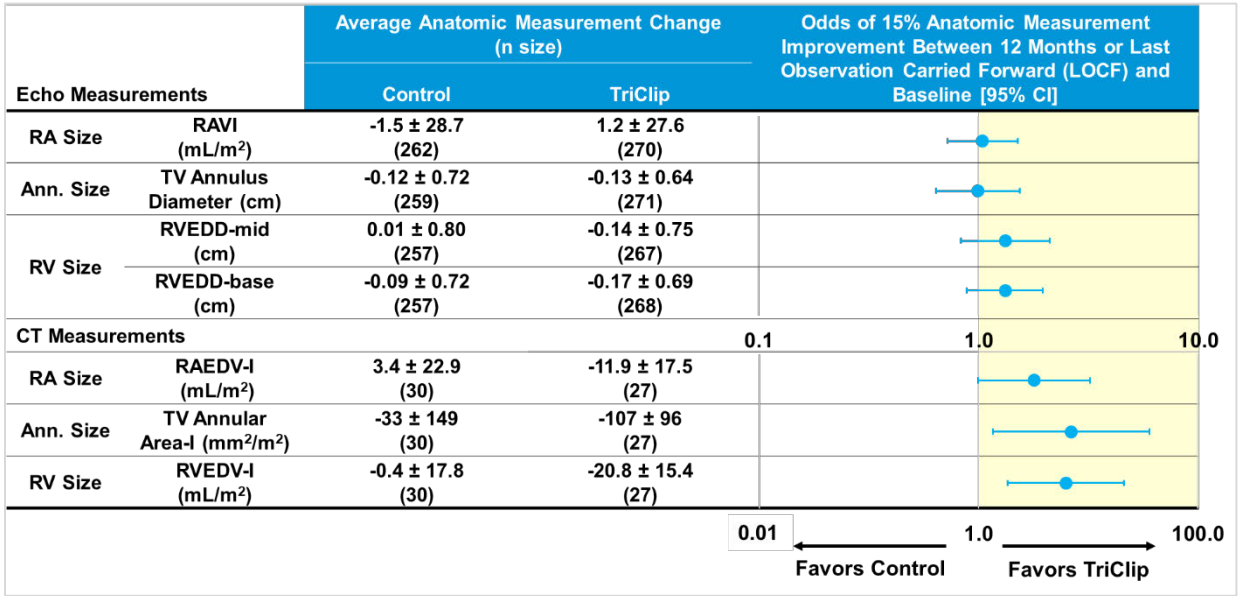
- *Magnitude (Effect size is larger than a "placebo effect")*: The magnitude of improvement in KCCQ-OS in the Device group (15.2 points) at 12 months requires a ***consistent*** "shift" in multiple categories of responses on the KCCQ. As discussed in Arnold et al. 2023's health status analysis from the TRILUMINATE Pivotal trial, the observed treatment benefit of 10.4 points in the trial is larger than the expected magnitude of a placebo effect (~5–6 points). The authors note: "*Although larger effects have been reported for the placebo arm of blinded randomized trials (Shah et al. 2022), it is important to distinguish the placebo response (i.e., the change from baseline in the placebo arm of a trial) from the placebo effect (i.e., the difference between a placebo and no treatment) (Hrobjartsson et al. 2011).*"
- *Durability (Health Status Benefit is Sustained at 12 months)*: The improvement in KCCQ-OS of approximately 10 points in the Device group over the Control group observed at 30 days was sustained through 6 months and 12 months. Such changes are unlikely to be sustained through multiple follow-up visits if

awareness of treatment group is the only factor influencing the response to the KCCQ. As noted in Arnold et al. 2023: "*Placebo effects are typically short-lived. The fact that the health status benefit of T-TEER was sustained without attenuation through 1 year of follow-up suggests a true biologic effect*."

12.4 Anatomical Changes

The available imaging sub-study data presented in **Section 11** demonstrate sustained, favorable right heart reverse remodeling and improved RV function with TriClip, which were not observed in the Control group of the Randomized cohort. **Figure 12-2** shows the odds of improvements in anatomic measurements in the Full Randomized Cohort (N=572) by treatment group, using data from 12 months or last available follow-up. The figure shows the odds of improvement (by at least 15% from baseline) in echocardiography-based RVEDD-mid and RVEDD-base tend to favor the Device group and the odds of improvement (by at least 15% from baseline) in CT-based indexed RAEDV, TV annular area and RVEDV favors the Device group. Together, these data support an anatomical benefit from TR reduction with TriClip, which cannot be attributed to knowledge of randomization or treatment received. These data provide a mechanistic explanation for the improvement in health status in the Device group relative to the Control group.

Figure 12-2: Change in Anatomic Measurements at 12 Months (Full Randomized Cohort, N=572)



If 12-month data were not available, last available follow-up was used for both TR grade and anatomic measurement.

12.5 Physiological Changes (Biomarkers)

Figure 12-3 explores cardiac, liver and renal function biomarkers by summarizing changes in biomarker by treatment group in the Full Randomized Cohort (N=572), using the data from 12 months or last available follow-up. The figure shows the odds of improvement in MELD-XI, GGT and eGFR from baseline by at least 15% favor the Device group. These data therefore provide a biological explanation for the improvement in health status in the Device group relative to the Control group.

Figure 12-3: Change in Biomarkers by TR Grade at 12 Months (Full Randomized Cohort, N=572)

		Average Biomarker Change (n size)		Odds of 15% Biomarker Improvement Between 12 Months LOCF and Baseline [95% CI]
		Control	TriClip	
Cardiac Function	BNP (pg/mL)	9.8 ± 226.5 (126)	29.6 ± 487.2 (142)	
	NT-proBNP (pg/mL)	-61.5 ± 1752 (106)	438 ± 2195 (116)	
Liver Function	MELD-XI	0.5 ± 3.3 (250)	-0.4 ± 3.3 (263)	
	GGT (U/L)	-1.0 ± 55.3 (179)	-10.9 ± 67.8 (191)	
Renal Function	eGFR (mL/min/1.73m^2)	-2.5 ± 13.9 (253)	0.8 ± 12.8 (266)	
	BUN (mg/dL)	0.9 ± 12.7 (249)	0.1 ± 14.4 (266)	

If 12-month data were not available, last available follow-up was used for both TR grade and biomarker.

12.6 Conclusions

The magnitude, durability, and consistency of improvement in health status with the TriClip device compared to medical therapy alone cannot be solely attributed to patient's knowledge of treatment group as change in health status was strongly associated with changes in TR grade in patients treated with the TriClip device. The benefits of TR reduction were observed in other objective measures such as right heart size and function and biomarkers, which cannot be attributed to patients' knowledge of treatment received, therefore, are unlikely to be "placebo effect." These analyses indicate a true treatment effect with TriClip.

13 SUMMARY OF FULL RANDOMIZED COHORT THROUGH 2 YEARS

SUMMARY

- After completion of 1-year follow-up, Control patients were allowed to receive the TriClip device if they continued to have ≥ severe TR and the tricuspid valve anatomy remained amenable for treatment with TriClip. Patients who were approved for and underwent the TriClip procedure are referred to as Crossovers.
- Although Crossover and Non-crossover patients had comparable baseline characteristics, at 1 year, Crossover patients had deteriorated from baseline more than Non-crossovers, which likely influenced the decision to receive treatment with TriClip. The rate of crossovers at 1 year was 50%, highlighting the unmet need for patients with symptomatic severe TR.
- A significant number of patients are still pending 2-year follow up. Preliminary results on TR reduction and KCCQ-OS changes for TriClip and Crossover through 2 years support the safety, effectiveness, and durable reduction in TR with TriClip.

Preliminary results through 2 years are summarized below. At the time of data cutoff, 160 patients (71 Device, 89 Control) were pending 2-year follow-up visits. After completion of 1-year follow-up, per protocol, Control patients were allowed to receive the TriClip device if they continued to have ≥ severe TR and the tricuspid valve anatomy remained amenable for treatment with TriClip. The decision to cross over was based on patient and physician preference. Patients who were approved for and underwent the TriClip procedure are referred to as Crossovers.

13.1 Crossover Discussion

Of 205 Control patients who completed 1-year follow-up, 102 (50%) patients crossed over at the time of data cutoff. Crossover patients underwent the TriClip procedure on average 76±51 days after completing the 1-year follow-up visit. At baseline, Crossover patients had slightly larger right ventricular and right atrial size than Non-crossover patients but otherwise had comparable baseline characteristics (**Table 13-1**).

Table 13-1: Summary of Baseline Characteristics for Crossovers and Non-crossovers

Characteristic	Crossover (N=102)	Non-crossover (N=103)
Age		
Mean ± SD (n)	77.0 ± 7.9 (102)	78.2 ± 7.2 (103)
Median (Q1,Q3)	77.5 (73.0, 83.0)	79.0 (75.0, 83.0)
Renal Disease	29.4% (30/102)	33.0% (34/103)
Liver Disease	11.8% (12/102)	4.9% (5/103)
Myocardial Infarction	4.9% (5/102)	7.8% (8/103)
Stroke	10.8% (11/102)	6.8% (7/103)
HFH in prior year	23.5% (24/102)	22.3% (23/103)
Prior Mitral/Aortic Intervention	32.4% (33/102)	34.0% (35/103)
CRT/ICD/Pacemaker	15.7% (16/102)	11.7% (12/103)
Coaptation gap (mm)		
Mean ± SD (n)	5.19 ± 1.83 (88)	5.13 ± 1.87 (81)
Median (Q1,Q3)	5.00 (4.00, 6.45)	5.00 (4.00, 7.00)
TR Severity		
Moderate or less	1.0% (1/100)	1.0% (1/97)
Severe	25.0% (25/100)	36.1% (35/97)
Massive	24.0% (24/100)	13.4% (13/97)
Torrential	50.0% (50/100)	49.5% (48/97)
RVEDD (base)		
Mean ± SD (n)	5.17 ± 0.75 (99)	4.93 ± 0.75 (98)
Median (Q1,Q3)	5.20 (4.70, 5.70)	4.80 (4.40, 5.40)
RVEDD (mid)		
Mean ± SD (n)	3.80 ± 0.74 (99)	3.56 ± 0.74 (98)
Median (Q1,Q3)	3.70 (3.30, 4.20)	3.50 (3.10, 4.00)
Right atrial volume (mL)		
Mean ± SD (n)	152.26 ± 74.00 (100)	137.71 ± 74.60 (99)
Median (Q1,Q3)	138.00 (93.97, 187.00)	121.50 (90.80, 162.40)
TAPSE (cm)		
Mean ± SD (n)	1.64 ± 0.46 (97)	1.67 ± 0.40 (95)
Median (Q1,Q3)	1.60 (1.36, 1.90)	1.60 (1.40, 1.90)
LVEF		
Mean ± SD (n)	59.13 ± 8.80 (91)	60.97 ± 8.12 (93)
Median (Q1,Q3)	59.30 (56.30, 64.90)	60.50 (57.30, 65.60)
KCCQ score		
Mean ± SD (n)	56.34 ± 23.55 (101)	55.23 ± 24.02 (103)
Median (Q1,Q3)	57.03 (36.72, 77.08)	53.13 (38.28, 75.52)
NYHA III/IV	56.9% (58/102)	50.5% (52/103)

Table 13-2 shows 1-year outcomes for Crossovers and Non-crossovers (i.e., outcomes at the year *prior to* crossover). At 1 year, Crossover patients had a higher proportion with torrential TR (69.6% vs. 44.6%) and NYHA Class III/IV (51.0% vs. 32.7%). Crossover patients also had less improvement in both KCCQ score (-0.06 ± 18.29 vs. 8.42 ± 18.73) and 6MWD (-22.38 ± 110.15 vs. -1.89 ± 92.70) from baseline than Non-crossover patients. Finally, Crossover patients had approximately two times the annualized rates of HFH (0.20 vs. 0.09 events/patient-year) and edema requiring hospitalization (0.12 vs. 0.06 events/patient-year) than Non-crossover patients.

In conclusion, Crossover and Non-crossover patients had comparable baseline characteristics but at 1 year, Crossover patients had deteriorated more than Non-crossovers, which likely influenced the decision to receive treatment with TriClip.

Table 13-2: 1-Year Outcomes for Crossovers and Non-crossovers *(Outcomes from the first year of follow-up prior to the decision to receive TriClip or remain on medical therapy)*

Outcome at 1 Year (i.e., Prior to Crossover)	Crossover (N=102)	Non-crossover (N=103)
TR Severity		
Moderate or less	1.0% (1/102)	13.0% (12/92)
Severe	14.7% (15/102)	21.7% (20/92)
Massive	14.7% (15/102)	20.7% (19/92)
Torrential	69.6% (71/102)	44.6% (41/92)
NYHA III/IV	51.0% (52/102)	32.7% (33/101)
KCCQ Change		
Mean ± SD (n)	-0.06 ± 18.29 (101)	8.42 ± 18.73 (102)
Median (Q1, Q3)	-1.04 (-11.72, 11.98)	5.86 (-1.45, 17.97)
6MWD Change		
Mean ± SD (n)	-22.38 ± 110.15 (89)	-1.89 ± 92.70 (90)
Median (Q1, Q3)	-15.24 (-60.00, 20.00)	1.00 (-45.00, 45.00)
HFH		
Number of Events	20	9
Total Follow Up (Patient-Years)	101.9	102.5
Annualized Rate	0.20	0.09
[95% CI]	[0.13, 0.30]	[0.05, 0.17]
Number of Patients with Events	13.7% (14/102)	6.8% (7/103)
Peripheral Edema Requiring Hospitalization		
Number of Events	12	6
Total Follow Up (Patient-Years)	101.9	102.5
Annualized Rate	0.12	0.06
[95% CI]	[0.07, 0.21]	[0.03, 0.13]
Number of Patients with Events	8.8% (9/102)	5.8% (6/103)

13.2 Discussion of Long-term Results

13.2.1 Effectiveness

Preliminary results in a small number of patients from the Full Randomized Cohort through 2 years are presented below. Paired analyses from 3 timepoints (baseline, 1 year and 2 years) among Device patients and among Crossover patients are presented for both TR and KCCQ-OS.

Table 13-3 evaluates TR reduction from baseline through 2 years across Device and Crossover patients. The table illustrates:

- Device and Crossover patients had similar proportions of massive and torrential TR at baseline (60% and 56%, respectively). At 1 year, TR was reduced to moderate or less for 95% of Device patients, whereas 81% of Crossover patients experienced massive or torrential TR. This highlights that the disease continued to progress for these Control patients.
- At 2 years, 91% of Device patients had moderate or less TR. Similarly, at 2 years (i.e., ~1-year post TriClip), 78% of Crossover patients experienced a reduction in TR to moderate or less.

Table 13-3: TR Severity through 2 Years (Randomized Device Patients and Crossovers, Paired Data Across Timepoints)

	Randomized Device (N=54)			Crossover (N=32)		
	Baseline	1 Year	2 Years	Baseline	1 Year	2 Years
TR Severity						
Trace/Mild	0%	54%	46%	0%	0%	50%
Moderate	7%	41%	44%	3%	0%	28%
Severe	33%	4%	6%	41%	19%	13%
Massive	32%	0%	2%	22%	25%	6%
Torrential	28%	2%	2%	34%	56%	3%
≤Moderate	**7%**	**95%**	**91%**	**3%**	**0%**	**78%**

The KCCQ-OS improvement in Randomized Device patients was sustained through 2 years (**Table 13-4**). KCCQ-OS at 2 years in Crossover patients (i.e., ~1 year post TriClip) improved relative to the 1-year timepoint by 10.9 points.

Table 13-4: KCCQ-OS through 2 Years (Randomized Device Patients and Crossovers, Paired Data Across Timepoints)

Visit/ KCCQ-OS	Randomized Device (N=58)	Crossover (N=35)
Baseline	55.5 ± 23.2 (58)	63.0 ± 24.0 (35)
Mean ± SD (n)	56.7 (36.2, 77.7)	69.5 (44.0, 82.0)
Median (Q1, Q3)	(8.9, 96.4)	(12.5, 97.9)
1 Year	74.5 ± 20.0 (58)	59.7 ± 22.5 (35)
Mean ± SD (n)	78.2 (62.0, 90.0)	62.0 (41.5, 74.7)
Median (Q1, Q3)	(22.1, 100.0)	(11.2, 95.1)
2 Years	71.1 ± 22.6 (58)	70.6 ± 19.6 (35)
Mean ± SD (n)	76.0 (56.8, 90.1)	72.7 (59.4, 83.3)
Median (Q1, Q3)	(12.5, 100.0)	(17.7, 100.0)

These data confirm that TriClip provides significant and sustained reduction in TR, with associated improvement in health status.

13.2.2 Safety

Safety through 30-days post Crossover TriClip procedure was assessed for Crossovers. **Table 13-5** shows that adverse event rates were comparable to or lower than those in Randomized Device patients (**Table 8-3** and **Table 9-5**).

Table 13-5: Adjudicated Adverse Events (30-Days Post Crossover TriClp Procedure, N=102)

Event	#Events	% Patients (n/N)	#Device Related Events	#Proc Related Events	#COVID-19 Related Events
Death (All-Cause)	1	1 (1.0%)	0	0	0
Cardiovascular	***0***	***0 (0.0%)***	***0***	***0***	***0***
Heart Failure-Related	0	0 (0.0%)	0	0	0
Non-Heart Failure-Related	0	0 (0.0%)	0	0	0
Non-Cardiovascular	***1***	***1 (1.0%)***	***0***	***0***	***0***
Hospitalization	**8**	**6 (5.9%)**	**0**	**0**	**0**
Heart Failure Hospitalization	6	5 (4.9%)	0	0	0
Other Cardiovascular Hospitalization	0	0 (0.0%)	0	0	0
Non-Cardiovascular Hospitalization	2	2 (2.0%)	0	0	0
Adjudicated Adverse Event					
Major Bleeding (≥BARC 3)	3	3 (2.9%)	0	1	0
New Onset Renal Failure	1	1 (1.0%)	0	0	0
Endocarditis Requiring Surgery	0	0 (0.0%)	0	0	0
Non-Elective Cardiovascular Surgery for TriClip Related AE	0	0 (0.0%)	0	0	0
Stroke	0	0 (0.0%)	0	0	0
TIA	0	0 (0.0%)	0	0	0
Myocardial Infarction	0	0 (0.0%)	0	0	0
TV Surgery	1	1 (1.0%)	0	0	0
TV Intervention	0	0 (0.0%)	0	0	0
Cardiogenic Shock	1	1 (1.0%)	0	0	1

13.3 Summary

Preliminary data through 2 years support the significant and sustained TR reduction and associated health status benefit for TriClip patients from the Randomized cohort. Half of the Control group deteriorated from baseline. One year after undergoing the Crossover TriClip procedure, Crossover patients experienced significant reduction in TR and associated changes in health status. No safety concerns were identified from the Crossover TriClip procedure. These preliminary data support the safety, effectiveness, and durable reduction in TR with TriClip.

14 POST MARKET PLANS

14.1 Learning analysis and Generalizability of Trial Results

Prior to enrolling in the analysis cohorts (Randomized and Single-arm) in the TRILUMINATE Pivotal trial, up to 3 Roll-in patients were permitted per implanter without prior TriClip experience. As shown in **Table 14-1**, the experience gained during the Roll-in phase contributed to considerable learning within the study, resulting in improvements in procedural success as well as in safety and clinical performance. Procedure and device times were substantially reduced, and device success rate was substantially improved from the Roll-in cohort to the analysis cohorts. Rates of major bleeding were also reduced from the Roll-in cohort. Other procedural events and safety outcomes through 12 months occurred at very low rates across all trial cohorts. TR reduction to moderate or less improved substantially from the Roll-in cohort to the analysis cohorts.

Table 14-1: Learning in TRILUMINATE Pivotal Trial

	Roll-in Cohort (N=141)	Analysis Cohorts		
		First 172 Randomized Treated Device Patients (N=172)	Single Arm Cohort (N=100)	Last 109 Randomized Treated Device Patients (N=109)
Procedural and Safety Outcomes				
Procedure Time	185 min	151 min	154 min	141 min
Device Time	112 min	90 min	84 min	79 min
Device Success	78%	89%	90%	95%
Procedure- or Device-Related Death at 30 Days	0.7%	0%	0%	0%
Procedure- or Device-Related HFH at 30 Days	0%	0.6%	0%	0%
Major Bleeding at 30 Days	7.1%	5.2%	4%	0%
New Onset Renal Failure at 30 Days	0.7%	1.2%	0%	0%
Non-elective Cardiovascular Surgery for TriClip Related AE at 30 Days	0.7%	0%	0%	0%
Safety Outcomes through 12 Months				
SLDA through 12 Months	9.9%	7.0%	7.0%	2.8%
Effectiveness				
TR ≤ Moderate at 30 Days	68%	87%	80%	92%

The following contains a discussion on generalizability of trial results. A total of 5 sites contributed 118 (33.7%) of the 350 patients in the Primary Analysis Population and 168 (29.4%) of the 572 patients in the Full Randomized Cohort. Given the substantial contribution from these top 5 enrolling sites to both datasets, it is important to evaluate whether the top 5 enrolling sites drove the overall trial outcomes. Recall that the primary endpoint was driven by the KCCQ-OS component, which was shown to be associated with TR reduction (**Section 12.2**). Thus, to explore generalizability, **Table 14-2** summarizes TR grade distribution at 30-day and 12-month follow-up at the top 5

enrolling sites vs. all other sites in each cohort and **Table 14-3** summarizes the KCCQ-OS in the two treatment groups. **Table 14-2** shows that in both the Primary Analysis Population and the Full Randomized Cohort, and at both timepoints, TR reduction to moderate or less in the Device group was comparable between the top 5 enrolling sites and all other sites, with the maximum difference being less than 6 ppts. TR reduction to mild or less in the Device group was also comparable, with the maximum difference being less than 7 ppts. **Table 14-3** shows that in both cohorts, KCCQ-OS changes are larger in the Device group than the Control group by approximately 10 points at both top enrolling sites and all other sites.

Table 14-2: TR Grade through 12-month Follow-up at Top 5 Enrolling Sites vs. All Other Sites (Primary Analysis Population, N=350 and Full Randomized Cohort, N=572)

Primary Analysis Population (N=350)								
TR Severity	30-Day				12-Month			
	Top 5 Enrolling Sites		All Other Sites		Top 5 Enrolling Sites		All Other Sites	
	Device (N=60)	Control (N=58)	Device (N=115)	Control (N=117)	Device (N=60)	Control (N=58)	Device (N=115)	Control (N=117)
Trace/Mild	54.5%	2.0%	47.7%	1.0%	49.1%	2.1%	51.6%	6.3%
Moderate	36.4%	8.2%	37.4%	2.0%	39.6%	6.3%	36.3%	1.0%
≤Moderate	**90.9%**	**10.2%**	**85.0%**	**3.0%**	**88.7%**	**8.3%**	**87.9%**	**7.3%**
Full Randomized Cohort (N=572)								
TR Severity	30-Day				12-Month			
	Top 5 Enrolling Sites		All Other Sites		Top 5 Enrolling Sites		All Other Sites	
	Device (N=84)	Control (N=84)	Device (N=201)	Control (N=203)	Device (N=84)	Control (N=84)	Device (N=201)	Control (N=203)
Trace/Mild	53.2%	1.5%	50.3%	0.6%	49.2%	1.7%	50.8%	4.5%
Moderate	35.4%	7.4%	38.7%	3.4%	41.0%	8.3%	36.9%	0.7%
≤Moderate	**88.6%**	**8.9%**	**89.0%**	**4.0%**	**90.2%**	**10.0%**	**87.7%**	**5.2%**

Table 14-3: Change in KCCQ-OS at 12 Months at Top 5 Enrolling Sites vs. All Other Sites (Primary Analysis Population, N=350 and Full Randomized Cohort, N=572)

Primary Analysis Population (N=350)				
KCCQ-OS Mean ± SD	Top 5 Enrolling Sites		All Other Sites	
	Device (N=60)	Control (N=58)	Device (N=115)	Control (N=117)
Baseline	60.7 ± 22.4	57.2 ± 21.9	57.8 ± 23.0	55.2 ± 25.1
12-Month	77.5 ± 17.8	61.7 ± 21.8	72.1 ± 21.7	60.2 ± 22.1
Change	16.8 ± 23.0	4.5 ± 18.0	14.3 ± 22.0	5.0 ± 18.6
Full Randomized Cohort (N=572)				
KCCQ-OS Mean ± SD	Top 5 Enrolling Sites		All Other Sites	
	Device (N=84)	Control (N=84)	Device (N=201)	Control (N=203)
Baseline	61.2 ± 21.4	56.8 ± 22.6	58.1 ± 22.4	55.4 ± 24.4
12-Month	77.0 ± 17.4	61.1 ± 22.8	73.1 ± 21.0	59.5 ± 22.7
Change	15.8 ± 22.4	4.4 ± 18.8	15.0 ± 23.0	4.1 ± 19.1

The consistency of TR reduction between top 5 enrolling sites and all other sites along with the consistency in larger KCCQ-OS changes in the Device group than the Control group support the generalizability of TriClip in the ability to reduce TR and associated health status benefit.

14.2 Physician Training

To ensure proper use of the TriClip System, Abbott has developed a robust training and education program for physicians. The post market product training will be consistent with Abbott's Global Commercial TriClip and TRILUMINATE Product Training Plans for Physicians and Sites. New physician implanters and echocardiography physicians will learn how to use the TriClip System and follow critical procedural and imaging steps necessary to complete the TriClip procedure safely and effectively. New physician implanters will also receive hands-on practice using a TriClip System demonstration unit with heart models that simulate clinical use and will complete a procedural skills assessment. Both physician implanter and echocardiography physician must complete the TriClip System training requirements prior to initial account opening. Once completed, training accreditation, and documentation thereof, will be issued by Abbott's training staff.

14.3 Post Approval Clinical Program

Abbott is committed to continuing to collect and report on the safety, effectiveness and durability of treatment with TriClip in patients with symptomatic severe TR despite medical therapy, and the impact of TR reduction to clinical and health status endpoints, through the following:

1) **Continuing follow-up of TRILUMINATE Pivotal trial** patients through 5 years, with annual reports to FDA per post approval requirements: The last patient was enrolled in the trial in June 2022. All patients are expected to complete 5-year follow-up by July 2027.
    - The following secondary endpoints will be assessed after all randomized patients complete the 2-year follow-up:
        - Recurrent HFH at 2 years
        - Freedom from all-cause mortality, TV surgery, and TV intervention at 2 years
    - Incidence of the following events will be reported annually through 5 years:
        - Death (All-cause, Cardiovascular)
        - Hospitalizations (Cardiovascular, HFH, Non-cardiovascular)
        - TV Surgery
        - Peripheral edema requiring hospitalization
        - Ascites
        - IV diuretic administration (including outpatient clinics)
    - Change in KCCQ-OS, SF-36 physical and mental component summary scores, NYHA class (from III/IV to I/II), 6MWD, BNP/NT-proBNP, gamma-GGT, eGFR and MELD score annually through 5 years from baseline
    - Change in the following echocardiography endpoints will be reported annually through 5 years from baseline:
        - TR Severity
        - Proximal Isovelocity Surface Area (PISA) Effective Regurgitant Orifice Area (EROA)
        - PISA Regurgitant Volume
        - Vena Contracta Width
        - Tricuspid Valve Annulus Diameter
        - RVEDD-mid
        - RVEDD-base
        - Right Atrial Volume (RAV)
        - Cardiac Output
        - Inferior Vena Cava Dimension
        - TV Diastolic Mean Gradient

2) **Initiating a post-approval study** to evaluate the safety and effectiveness of the TriClip System: Important considerations for the post-approval study include ensuring representation from a diverse population with a broad range of anatomies, as well as patients with significant left ventricular dysfunction or pulmonary hypertension. This will be a prospective, single-arm, multi-center, real-world study with a proposed sample size of 2000 patients. Consecutive patients entered in the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapies (TVT) registry (STS/ACC TVT Registry | STS) will be analyzed and summarized every year from the date of FDA approval of TriClip. Baseline characteristics and data from the index procedure, and from 30 days and 12 months will be collected through the registry. Survival and hospitalization data from months 24 to 60 will be obtained through linkage with Centers for Medicare and Medicaid Services (CMS) claims database.

15 BENEFIT-RISK CONCLUSIONS

Severe TR is an abnormal condition which can result in debilitating symptoms, physical and social limitations, and poor quality-of-life. Patients with TR experience fatigue, declining exercise capacity, swelling of the abdomen, legs, or veins of the neck, abnormal heart rhythms, and shortness of breath with activity, which can significantly impact patients' health status. Given the lack of satisfactory treatment options, there is a significant unmet need to treat symptomatic severe TR. TriClip was granted Breakthrough Device Designation by the FDA because of this clear unmet need and the lack of satisfactory treatment options.

The TRILUMINATE Pivotal trial was designed for patients who had symptomatic severe TR, whose symptoms were likely due to the TR and not due to other untreated cardiac conditions that could confound the trial results. This is consistent with the proposed indication whereby a heart team will ensure the patient is receiving optimal medical therapy. The trial results demonstrate safety, effectiveness, and durability of the TriClip device in reducing TR in these patients, and consequently improving the health status. TriClip clearly addresses an unmet patient need with a favorable benefit/risk profile as discussed below.

15.1 Benefits

The totality of data from the Randomized cohort, Single-arm cohort, Cardiac Imaging sub-study, and longer-term follow-up demonstrated that the TriClip device is effective in reducing TR in the indicated population. Importantly, this reduction in TR was associated with a corresponding improved health status measured by the Kansas City Cardiomyopathy Questionnaire and supported by physiological and anatomical changes.

The primary endpoint of the Randomized cohort was met, demonstrating superiority of the TriClip device compared to medical therapy alone, and was driven by change in the KCCQ overall summary score, with no reduction in mortality/tricuspid valve surgery or heart failure hospitalization. At 30 days, reduction of TR to moderate or less was achieved in 87% of the Device group, whereas only 5.4% of the Control group experienced such a reduction ($p<0.0001$). Furthermore, the reduction in TR severity at 30 days following TriClip implant was sustained at 12 months, with moderate or less TR in 89% of Device patients, whereas TR remained severe or greater in a majority (92%) of patients in the Control group.

The reduction in TR with TriClip was accompanied by significant improvements in health status compared to medical therapy alone. Consistent improvement was observed across all domains of the KCCQ, favoring the TriClip device over medical therapy alone. Analyses showed the change in KCCQ overall summary score is associated with change in TR severity post TriClip implant. Improvement in heart failure symptoms measured by New York Heart Association class also favored the TriClip

device. Analyses of biomarkers indicated that TriClip is associated with improved liver and renal function. Although improvement in 6-Minute Walk Distance was not demonstrated in the Primary Analysis Population, the Full Randomized cohort demonstrated improvement favoring TriClip.

The Single-arm cohort also met its primary endpoint. Despite being more technically challenging, TR reduction to moderate or less was achieved in 80% of patients at 30 days in this cohort and these patients experienced meaningful improvement in health status of the same magnitude as the Randomized cohort.

Lastly, data from the Cardiac Imaging sub-study demonstrated favorable right heart reverse remodeling and improved right heart function with the TriClip device, which were not observed with medical therapy alone. These data provide supporting evidence for a mechanistic explanation for the health status improvement for patients receiving the device.

Collectively, the analyses indicate that the health status improvement with the TriClip device in this open-label trial is a true treatment benefit and cannot be attributed solely to the knowledge of treatment received. Data from the Full Randomized Cohort of 572 patients strengthen the conclusions from the Primary Analysis Population.

15.2 Risks

The TriClip device has a favorable safety profile. 98.3% of patients in the Randomized cohort were free of major adverse events at 30 days, with no operative mortality or urgent cardiac surgery for TriClip-related adverse events, and low rates of cardiovascular mortality and new onset renal failure. Through 12 months, there were no device embolizations or device thromboses, and the need for new permanent pacemaker implantation was low and comparable between Device and Control groups.

Despite being more anatomically complex, the TriClip device was also safe in the Single-arm cohort and there were no procedure- or device-related deaths, no device thrombosis, and no device embolization through 12 months. Although Single-arm patients had more advanced disease than Randomized patients, adverse event rates in this cohort were comparable to Device patients in the Randomized cohort. The low events rates and favorable safety profile provide assurance that intervention with TriClip in these anatomically complex patients exposes them to low risk.

15.3 Overall Conclusions

There is an unmet need to treat patients with symptomatic severe TR as these patients have limited treatment options. Patients with TR tend to be elderly with a dilated right heart, and it is important to intervene when the right heart has the capacity for reverse remodeling and patients can benefit from TR reduction.

The TRILUMINATE Pivotal trial demonstrated the TriClip System to be a highly effective therapy for reducing severe tricuspid regurgitation and led to substantial improvements

in health status at 12 months. The TriClip System was not associated with any mortality, and procedure- or device-related adverse event rates were low. The trial results provide evidence that repair of the tricuspid valve with the TriClip System is superior to medical therapy in improving health status and is a safe and effective treatment option for patients with severe TR. The health status improvement with TriClip is supported by physiological and anatomical changes. These data provide supporting evidence for a mechanistic explanation for the health status improvement for patients receiving the device. Collectively, despite the absence of improvement in death and HFH, the analyses indicate that the health status improvement with the TriClip device in this open-label trial is a true treatment benefit and cannot be attributed solely to the knowledge of treatment received.

In conclusion, for a patient population that needs symptom relief from severe TR, the TriClip device offers a safe, compelling, and reliable treatment option with little to no added risk. With the favorable benefit to risk profile of the TriClip System, a historically untreated population will have a viable treatment option to improve heart failure symptoms and health status.

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17 APPENDICES

17.1 Appendix 1 – Biomarkers at Baseline, Subgroup Analyses and Descriptive Endpoints

I. Biomarkers at Baseline (Primary Analysis Population N=350, Full Randomized Cohort N=572, Single-arm Cohort N=100)

Table A-1: Biomarkers at Baseline

Biomarker	Indication	Description	Normal Range[a]	Primary Analysis Population (N=350) Mean ± SD	Full Randomized Cohort (N=572) Mean ± SD	Single-arm Cohort (N=100) Mean ± SD
ALT (U/L)	Liver function	Liver enzyme, elevated values can indicate impaired liver function.	7-41	20.9 ± 11.0	21.2 ± 13.6	19.1 ± 9.0
AST (U/L)		Liver enzyme, elevated values can indicate impaired liver function.	12-38	26.6 ± 9.7	27.0 ± 10.6	26.2 ± 8.9
Bilirubin (mg/dL)		A red blood cell byproduct, can be elevated in diseases of the liver, gallbladder, or bile ducts.	0.3-1.3	0.9 ± 0.7	0.9 ± 0.6	1.0 ± 0.5
GGT (U/L)		Enzyme, present in various organ membranes, but primarily used as a marker for liver dysfunction.	9-58	91.8 ± 96.3	83.0 ± 87.7	83.1 ± 68.5
MELD score		A numerical value that is used to predict mortality in individuals with liver disease; it is calculated from a formula using serum creatinine, serum bilirubin, and INR.	6-40[b]	14.8 ± 5.9	14.3 ± 5.7	15.1 ± 5.6
Serum Creatinine (mg/dL)	Renal function	A muscle waste product that is excreted by the kidneys. Elevated serum creatinine can indicate impaired kidney function.	F: 0.5-0.9 M: 0.6-1.2	F: 1.2 ± 0.5 M: 1.5 ± 0.5	F: 1.2 ± 0,5 M: 1.4 ± 0.5	F: 1.2 ± 0.4 M: 1.5 ± 0.6
eGFR (mL/min/1.73 m^2)		A value used to monitor the progression of kidney disease over time. Its formula considers age, race, sex, and serum creatinine.	>60	55.5 ± 20.2	56.7 ± 21.0	53.8 ± 21.6
BUN (mg/dL)		Commonly used alongside creatinine; elevated levels can suggest renal impairment. More specifically, BUN measures the amount of blood nitrogen that comes from urea, a protein waste product normally filtered by the kidneys.	8-20	30.5 ± 17.1	29.5 ± 16.7	31.5 ± 14.9
Serum Sodium (mmol/L)	Renal and cardiac function	An electrolyte that plays a key role in the body's water balance. Heart failure can create an environment of fluid overload leading to low serum sodium levels, or hyponatremia. Impaired kidney function can also lead to abnormal serum sodium levels. Hyponatremia has been shown to be associated with increased short-term mortality in heart failure patients.	136-146	138.5 ± 3.5	138.7 ± 3.4	138.5 ± 3.1
Hemoglobin (g/dL)	Cardiac function	A protein in red blood cells that carries oxygen to tissues. In heart failure, a low serum hemoglobin (anemia) can be a sign that the heart is not pumping blood effectively to tissues. Anemia has been associated with reduced survival in heart failure patients.	F:12.0-15.8 M: 13.3-16.2	F: 12.5 ± 2.1 M: 12.6 ± 2.0	F: 12.7 ± 1.9 M: 12.6 ± 2.0	F: 12.4 ± 1.5 M: 12.5 ± 2.0

Biomarker	Indication	Description	Normal Range[a]	Primary Analysis Population (N=350) Mean ± SD	Full Randomized Cohort (N=572) Mean ± SD	Single-arm Cohort (N=100) Mean ± SD
BNP (pg/mL)		A hormone produced by the heart in response to increased blood volume. It is commonly increased in patients with heart failure and increases further during acute heart failure exacerbations.	<100	369.2 ± 317.7	373.8 ± 356.7	496.5 ± 631.6
NT-proBNP (pg/mL)		Related to BNP but is not biologically active. NT-proBNP has shown strong prognostic value of mortality in heart failure patients.	Age < 75: <125 Age ≥ 75: < 450	Age < 75: 2753 ± 5062 Age ≥ 75: 2255 ± 2541	Age<75: 2064 ± 3887 Age≥75: 2156 ± 2152	Age<75: 1371 ± 1372 Age≥75: 2254 ± 1554
CK (U/L)	Organ damage	An enzyme produced by various tissues. Serum CK is used as a marker of damage to CK-rich tissues, such as in the setting of myocardial infarction or acute kidney injury.	F: 30-135 M: 55-170	F: 73.5 ± 62.7 M: 88.7 ± 64.7	F: 72.5 ± 53.4 M: 89.4 ± 61.9	F:78.2 ± 57.5 M: 94.6 ± 45.7

F: Female; M: Male

[a] Source: Loscalzo J. Harrison's Cardiovascular Medicine. 3 ed: McGraw Hill, 2016

[b] Higher scores predict higher mortality. Scores less than 10-15 are generally considered "low"

II. Subgroup Analyses

This section contains subgroup analyses for the primary endpoint of the Randomized cohort (for both Primary Analysis Population and Full Randomized Cohort) and the Single-arm cohort.

Table A-2: Subgroup Analyses Results for Components of the Primary Endpoint (Primary Analysis Population, N=350)

Baseline Variable		All-cause mortality or TV surgery at 12 months		HFH at 12 months		KCCQ-OS improvement ≥15 points at 12 months	
		KM estimate[a]	p-value[a]	Annualized rate (per pt-year)	p-value[a]	Proportion of Patients	p-value[a]
Pre-specified subgroups							
Sex	Male (n=158)	Device: 12.0% Control: 14.9%	0.6676	Device: 0.25 Control: 0.23	0.4378	Device: 40.0% Control: 16.7%	0.5793
	Female (n=192)	Device: 7.3% Control: 6.7%		Device: 0.20 Control: 0.13		Device: 56.3% Control: 34.1%	
TR Severity	Severe (n=93)	Device: 4.5% Control: 2.1%	0.4029	Device: 0.16 Control: 0.13	0.8905	Device: 55.0% Control: 22.2%	0.4632
	> Severe (n=239)	Device: 10.7% Control: 14.4%		Device: 0.25 Control: 0.21		Device: 48.0% Control: 24.7%	
NYHA	II (n=149)	Device: 7.0% Control: 9.0%	0.8346	Device: 0.10 Control: 0.15	0.1444	Device: 33.8% Control: 17.1%	0.5996
	III/IV (n=201)	Device: 11.0% Control: 11.8%		Device: 0.31 Control: 0.19		Device: 63.3% Control: 34.6%	
TR Etiology	Primary (n=21)	Device: 0.0% Control: 0.0%	n/a[c]	Device: 0.00 Control: 0.00	n/a[c]	Device: 77.8% Control: 16.7%	0.0839
	Secondary (n=323)	Device: 9.9% Control: 11.7%		Device: 0.23 Control: 0.19		Device: 47.4% Control: 26.0%	

[a] Interaction p-value from Cox regression model (for mortality/TV surgery), Poisson regression for HFH, and Breslow-Day test for KCCQ-OS.

[b] Not calculated due to 0 event rates

Table A-3: Subgroup Analyses Results for Components of the Primary Endpoint (Full Randomized Cohort, N=572)

Baseline Variable		All-cause mortality or TV surgery at 12 months		HFH at 12 months		KCCQ-OS improvement ≥15 points at 12 months	
		KM estimate[a]	p-value[a]	Annualized rate (per pt-year)	p-value[a]	Proportion of Patients	p-value[a]
Pre-specified subgroups							
Sex	Male (n=235)	Device: 10.1% Control: 15.8%	0.0572	Device: 0.22 Control: 0.24	0.9389	Device: 38.8% Control:17.6%	0.9625
	Female (n=337)	Device: 9.7% Control: 5.2%		Device: 0.14 Control: 0.16		Device: 56.9% Control: 31.4%	
TR Severity	Severe (n=148)	Device: 2.9% Control: 2.9%	0.9341	Device: 0.11 Control: 0.08	0.4772	Device: 53.7% Control: 21.7%	0.4009
	> Severe (n=395)	Device: 12.4% Control:12.2%		Device: 0.21 Control: 0.25		Device: 47.8% Control: 24.8%	
NYHA	II (n=257)	Device: 7.0% Control: 8.9%	0.4685	Device: 0.11 Control: 0.15	0.3771	Device: 34.1% Control: 16.8%	0.5337
	III/IV (n=315)	Device: 12.2% Control: 10.4%		Device: 0.23 Control: 0.22		Device: 62.9% Control: 33.3%	
TR Etiology	Primary (n=28)	Device: 0.0% Control: 0.0%	n/a[b]	Device: 0 Control: 0.07	n/a[b]	Device: 72.7% Control: 15.4%	0.0964
	Secondary (n=533)	Device: 10.4% Control: 10.2%		Device: 0.18 Control: 0.21		Device: 47.8% Control: 25.4%	

[a] Interaction p-value from Cox regression model (for mortality/TV surgery), Poisson regression for HFH, and Breslow-Day test for KCCQ-OS.
[b] Not calculated due to 0 event rates

Table A-4: Subgroup Analyses Results for Components of the Primary Endpoint (Single-arm Cohort, N=100)

Baseline Variable		All-cause mortality at 12 months		KCCQ-OS improvement ≥10 points at 12 months	
		KM estimate	p-value[a]	Proportion of Patients	p-value[a]
Pre-specified subgroups					
Sex	Male (n=47)	17.4% (8)	0.4215	34.3% (12/35)	0.0011
	Female (n=53)	11.5% (6)		71.4% (30/42)	
TR Severity	Severe (n=9)	11.1% (1)	0.7178	75.0% (6/8)	0.2378
	> Severe (n=87)	15.3% (13)		53.0% (35/66)	
NYHA	II (n=41)	7.7% (3)	0.1436	47.1% (16/34)	0.2407
	III/IV (n=59)	18.6% (11)		60.5% (26/43)	
TR Etiology	Primary (n=9)	0.0% (0)	0.1987	44.4% (4/9)	0.4987
	Secondary (n=85)	16.9% (14)		56.5% (35/62)	

[a] Log-rank test p-value for All-cause mortality and Chi-squared test p-value for KCCQ-OS.

III. Key Descriptive Endpoints

Days to Treatment Visit

The average time from randomization to Treatment visit was 11–13 days for the Device group and 9–10 days for the Control group (**Table A-5**).

Table A-5: Days from Randomization to Treatment Visit

Days from Randomization to Treatment Visit	Primary Analysis Population (N=350)		Full Randomized Cohort (N=572)	
	Device (N=172)	Control (N=174)	Device (N=281)	Control (N=286)
Mean ± SD (n) Median (Q1, Q3) Range (min, max)	11.1 ± 14.9 (172) 7.0 (4.0, 12.5) (0, 108)	9.0 ± 8.5 (174) 8.0 (5.0, 12.0) (0, 95)	12.6 ± 16.2 (281) 8.0 (5.0, 13.0) (0, 135)	9.6 ± 8.3 (286) 9.0 (6.0, 13.0) (-2, 95)

Procedural Results

The TriClip procedure was performed under general anesthesia via echocardiographic and fluoroscopic guidance. Procedural results are summarized in **Table A-6**. The device was successfully implanted in >98% of attempts with an average of 2 clips per patient and a maximum of 4 clips. The second-generation system (TriClip G4) was used in approximately half the procedures in the Primary Analysis Population and almost three-quarters of patients in the Full Randomized Cohort. Total procedure time, defined as the time between the earliest insertion of either the TEE probe or steerable guide catheter and the removal of the last catheter and TEE probe, averaged 2.5 hours. Device time, defined as the time between insertion of the steerable guide catheter and retraction of the TriClip delivery system into the steerable guide catheter, averaged 1.5 hours. Fluoroscopy duration averaged half an hour.

Table A-6: Index Procedure Results

Characteristic	Primary Analysis Population Treated Device Patients (N=172)	Full Randomized Cohort Treated Device Patients (N=281)
Number of Clips Implanted Mean ± SD (n) Median (Q1, Q3) Range (min, max)	2.2 ± 0.7 (172) 2.0 (2.0, 3.0) (0.0, 4.0)	2.1 ± 0.7 (281) 2.0 (2.0, 2.0) (0.0, 4.0)
0 Clips*	1.2% (2/172)	1.1% (3/281)
1 Clip	10.5% (18/172)	14.9% (42/281)
2 Clips	61.0% (105/172)	60.5% (170/281)
3 Clips	24.4% (42/172)	20.6% (58/281)
4 Clips	2.9% (5/172)	2.8% (8/281)
5 Clips	0.0% (0/172)	0.0% (0/281)

Characteristic	Primary Analysis Population Treated Device Patients (N=172)	Full Randomized Cohort Treated Device Patients (N=281)
Device Used TriClip (first-generation)	47.1% (81/172)	29.9% (84/281)
TriClip G4	52.9% (91/172)	70.1% (197/281)
Total Number of Clips Implanted	374	588
NT	14.4% (54/374)	10.0% (59/588)
XT	44.1% (165/374)	32.0% (188/588)
NTW	6.1% (23/374)	5.6% (33/588)
XTW	35.3% (132/374)	52.4% (308/588)
Total Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 151.0 ± 71.7 (171) 143.0 (98.0, 187.0)	 147.2 ± 72.0 (279) 135.0 (95.0, 182.0)
Device Time (min) Mean ± SD (n) Median (Q1, Q3)	 89.7 ± 66.4 (168) 75.5 (44.5, 110.0)	 85.6 ± 63.0 (274) 70.0 (43.0, 107.0)
Fluoroscopy Duration (min) Mean ± SD (n) Median (Q1, Q3)	 31.9 ± 23.5 (171) 27.9 (14.3, 41.0)	 30.7 ± 23.2 (280) 26.1 (15.0, 38.0)

*Two patients with 0 clips (both in the Primary Analysis Cohort) implanted during the index procedure had successful implants during a second TriClip procedure.

Procedural Outcomes

Technical, device and procedural success are summarized in **Table A-7**. Technical success at exit from procedure room (defined as 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) was achieved in >98%. Device success (defined as 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 ≥1 grade improvement in TR severity, no embolization, single leaflet device attachment-SLDA, or para-device complications) was achieved in >88%. Procedural success (defined as Device success, and no device or procedure related serious adverse event) at 30 days post-procedure was achieved in >87%.

Table A-7: Procedural Outcomes at Index Procedure

Characteristic	Primary Analysis Cohort Treated Device Patients (N=172)	Full Randomized Cohort Treated Device Patients (N=281)
Technical Success at Exit from Procedure Room[a]	98.8% (170/172)	98.9% (278/281)
Device Success at 30-Days Post-Procedure[b]	88.9% (144/162)	91.4% (243/266)
Procedural Success at 30-Days Post-Procedure[c]	87.0% (141/162)	89.1% (237/266)

[a] 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.
[b] Device Success at 30 days: 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, no SLDA, absence of para-device complications[5]). Not assessed in 10 patients due to missing TR grade at either baseline or 30 days
[c] Procedural Success at 30 days: Device success, and no device or procedure related SAE

Discharge Information

Table A-8 summarizes the post-procedure and discharge status for patients in whom a TriClip procedure was attempted. Length of hospital stay averaged 1.5 days. ICU stay occurred in <10%, and average ICU duration in cases where ICU stay occurred was 1.5 days. Most patients were discharged home (>97.7%) and there was no in-hospital death.

Table A-8: Index Procedure Discharge Information

Characteristic	Primary Analysis Cohort Treated Device Patients (N=172)	Full Randomized Cohort Treated Device Patients (N=281)
Length of Stay in Hospital[a] (days) Mean ± SD (n) Median (Q1, Q3) Range (min, max)	 1.6 ± 1.4 (172) 1.0 (1.0, 2.0) (0, 10)	 1.5 ± 1.3 (281) 1.0 (1.0, 1.0) (0, 10)
ICU Stay	9.9% (17/172)	8.5% (24/281)
ICU Duration (days) Mean ± SD (n) Median (Q1, Q3) Range (min, max)	 1.5 ± 1.0 (17) 1.0 (1.0, 1.0) (1, 4)	 1.5 ± 0.9 (24) 1.0 (1.0, 2.0) (1, 4)
Discharge Status		
Home	97.7% (168/172)	97.9% (275/281)
Hospice Care	0.0% (0/172)	0.0% (0/281)
Rehabilitation Center	0.0% (0/172)	0.4% (1/281)
Nursing Home	2.3% (4/172)	1.8% (5/281)
Death	0.0% (0/172)	0.0% (0/281)

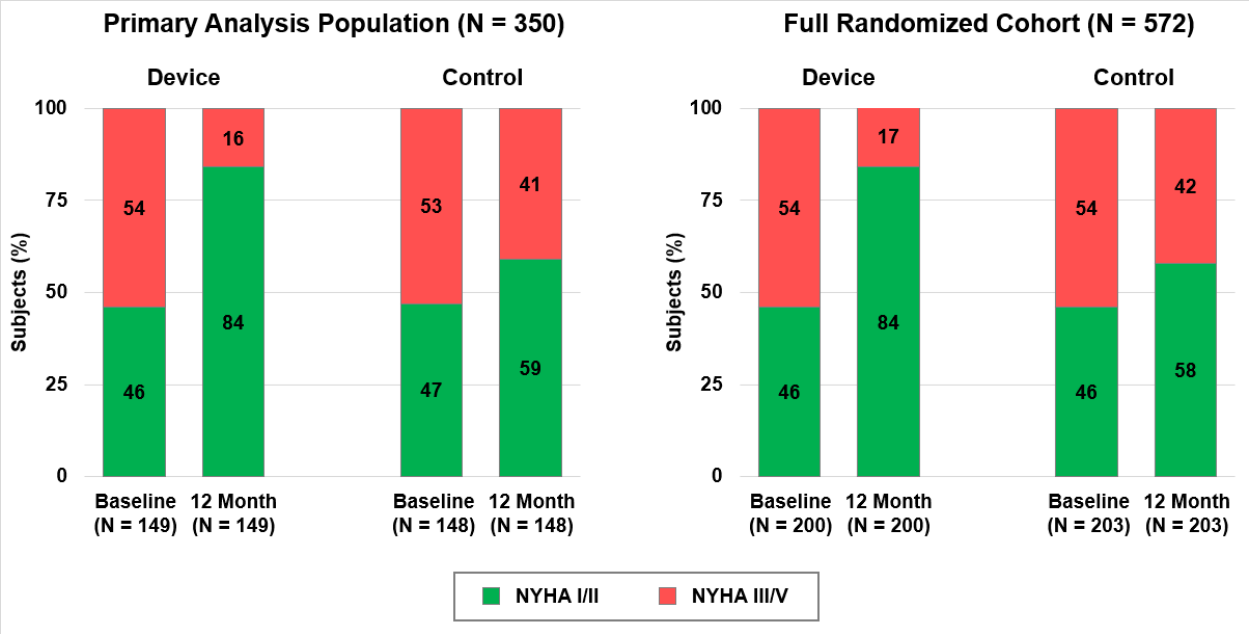
[a] Days from index procedure to discharge

[5] Defined as a CEC adjudicated event that was determined to be device related

NYHA Functional Class

NYHA functional class for the Device and Control groups (paired analysis) is shown in **Figure A-1.** The proportion of patients categorized as NYHA functional class I/II at 12 months was 84% for the Device group compared to 59% for the Control group.

Figure A-1: NYHA Functional Class (Paired Analysis, Primary Analysis Population and Full Randomized Cohort)



Edema, Ascites and IV Diuretic Use

In both cohorts, peripheral edema requiring hospitalization and ascites through 12 months were lower in Device patients than Control patients in terms of both annualized rates and proportion of patients (**Table A-9**). IV diuretic use was comparable between treatment groups in both cohorts.

Table A-9: Edema, Ascites and Days on IV Diuretic Use at 12 Months

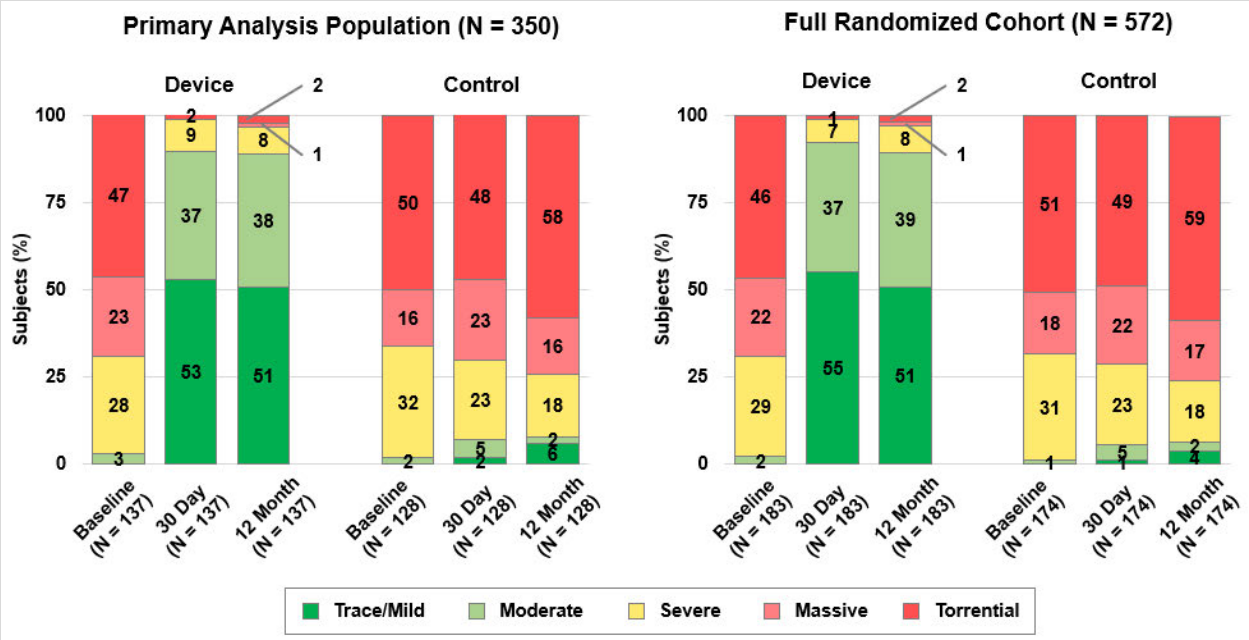
	Primary Analysis Population (N=350)		Full Randomized Cohort (N=572)	
	Device (N=175)	Control (N=175)	Device (N=285)	Control (N=287)
Peripheral Edema Requiring Hospitalization				
Number of Events	4	18	6	28
Total Follow Up (Patient-Years)[a]	160.4	161.5	250.2	250.4
Annualized Rate [95% CI][b]	0.02 [0.01, 0.07]	0.11 [0.07, 0.18]	0.02 [0.01, 0.05]	0.11 [0.08, 0.16]
Number of Patients with Events	1.7% (3/175)	7.4% (13/175)	1.8% (5/285)	7.7% (22/287)
Difference [95% CI][c]	-5.7% [-10.7%, -1.3%]		-5.9% [-9.7%, -2.5%]	
Ascites				
Number of Events	3	11	7	15
Total Follow Up (Patient-Years)[a]	160.4	161.5	250.2	250.4
Annualized Rate [95% CI][b]	0.02 [0.01, 0.06]	0.07 [0.04, 0.12]	0.03 [0.01, 0.06]	0.06 [0.04, 0.10]
Number of Patients with Events	1.7% (3/175)	6.3% (11/175)	2.1% (6/285)	4.9% (14/287)
Difference [95% CI][c]	-4.6% [-9.3%, -0.4%]		-2.8% [-6.1%, 0.3%]	
IV Diuretics Usage (Including Outpatient Clinics)				
Number of Days	191	159	257	241
Total Follow Up (Patient-Years)[a]	160.4	161.5	250.2	250.4
Annualized Rate [95% CI][c]	1.19 [1.03, 1.37]	0.98 [0.84, 1.15]	1.03 [0.91, 1.16]	0.96 [0.85, 1.09]
Number of Patients with Events	14.9% (26/175)	13.1% (23/175)	12.6% (36/285)	13.9% (40/287)
Difference [95% CI][d]	1.7% [-5.6%, 9.1%]		-1.3% [-6.9%, 4.3%]	

[a] The total follow-up in patient-years is calculated as the sum of follow-up patient-years for each patient through either 1 year or time of last follow-up if withdrawn prior to 1 year.
[b] The annualized event rate is calculated as total number of events divided by total follow-up.
[c] The annualized event rate is calculated as total number of days on IV diuretics divided by total follow-up.
[d] By Newcombe score method. IV Diuretics during the index procedure hospitalization or during the additional procedure hospitalization that was not due to an adverse event are excluded.

Durability in TR Reduction at 12 Months

Figure A-2 presents paired TR severity at baseline and 12 months for Device and Control patients. In the Primary Analysis Population, the substantial reduction in TR severity to moderate or less at 30 days in 90% of Device patients was sustained to 12 months in 89%, whereas Control patients did not experience a reduction in TR severity at 12 months (moderate or less in 8%). Similar results are observed in the Full Randomized Cohort.

Figure A-2: TR Severity at Baseline and 12 Months (Paired Analysis, Primary Analysis Population and Full Randomized Cohort)



Transthoracic Echocardiography Measurements

Table A-10 summarizes changes in paired echocardiography measurements from baseline to 12 months. Consistent with the significant reduction in TR severity seen in the Device group, PISA EROA, PISA regurgitant volume and vena contracta width all showed substantial decreases from baseline to 12 months in the Device group whereas no substantial differences were noted in the Control group. However, no substantial changes through 12 months were observed in terms of cardiac size or function measured by echocardiography for either group.

Table A-10: Echocardiography Measurements (Paired Analysis, Primary Analysis Population, N=350)

Parameter	Device (N=175)	Control (N=175)
TR Parameters		
Change in PISA EROA (cm^2)		
Mean ± SD (n)	-0.44 ± 0.33 (115)	-0.04 ± 0.31 (127)
Median (Q1, Q3)	-0.42 (-0.56, -0.26)	0.00 (-0.16, 0.12)
Change in PISA Regurgitant Volume (mL)		
Mean ± SD (n)	-33.84 ± 20.48 (115)	-1.99 ± 23.56 (127)
Median (Q1, Q3)	-33.20 (-44.90, -21.40)	-1.30 (-12.40, 10.21)
Change in Vena Contracta Width (SL, 4-Ch View, cm)		
Mean ± SD (n)	-0.52 ± 0.48 (139)	0.03 ± 0.44 (136)
Median (Q1, Q3)	-0.48 (-0.77, -0.26)	0.00 (-0.30, 0.32)
Other Echocardiography Parameters		
Change in Tricuspid Annulus Diameter (End-Diastole, Apical 4Ch, cm)		
Mean ± SD (n)	-0.09 ± 0.64 (140)	-0.11 ± 0.74 (135)
Median (Q1, Q3)	-0.10 (-0.50, 0.30)	-0.17 (-0.50, 0.30)
Change in RV End Diastolic Diameter Mid (4Ch, cm)		
Mean ± SD (n)	-0.18 ± 0.73 (140)	-0.02 ± 0.85 (134)
Median (Q1, Q3)	-0.20 (-0.60, 0.20)	0.10 (-0.50, 0.50)
Change in RV End Diastolic Diameter Base (4Ch, cm)		
Mean ± SD (n)	-0.21 ± 0.71 (142)	-0.12 ± 0.76 (134)
Median (Q1, Q3)	-0.15 (-0.70, 0.20)	-0.10 (-0.60, 0.40)
Change in Right Atrial Volume (Single Plane Simpson's, mL)		
Mean ± SD (n)	7.78 ± 55.92 (140)	-2.13 ± 54.14 (136)
Median (Q1, Q3)	8.17 (-22.48, 28.25)	-4.35 (-29.90, 21.90)
Change in RV TAPSE (cm)		
Mean ± SD (n)	-0.13 ± 0.45 (141)	0.00 ± 0.48 (132)
Median (Q1, Q3)	-0.10 (-0.43, 0.10)	0.01 (-0.20, 0.30)
Change in Cardiac Output (L/min)		
Mean ± SD (n)	-0.05 ± 1.89 (136)	0.03 ± 1.40 (131)
Median (Q1, Q3)	-0.14 (-0.98, 0.63)	-0.04 (-0.88, 0.86)
Change in Inferior Vena Cava Diameter (cm)		
Mean ± SD (n)	-0.09 ± 0.56 (135)	-0.01 ± 0.56 (136)
Median (Q1, Q3)	-0.04 (-0.48, 0.34)	0.00 (-0.34, 0.32)
Change in TV Diastolic Mean Gradient (CW, mmHg)		
Mean ± SD (n)	1.15 ± 1.28 (136)	0.07 ± 0.58 (126)
Median (Q1, Q3)	0.86 (0.32, 1.89)	0.02 (-0.31, 0.43)

17.2 Appendix 2 – Data Tables for Roll-in Cohort

Table A-11: Baseline Characteristics, Echocardiography Parameters and Cardiac Medication (Roll-in Cohort, N=141)

Characteristic	Roll-in Cohort (N=141)
Baseline Characteristic	
Age	
Mean ± SD	78.4 ± 8.5
≥ 75 years	68.8%
Female	61.7%
Caucasian[a]	86.5%
Renal disease	29.8%
Liver disease	11.3%
Stroke/TIA	9.2%
Hypertension	84.4%
Atrial fibrillation	91.5%
COPD	18.4%
HFH	
HFH in prior year, %patients	25.5%
HFH rate in prior year, per patient-year	36.9%
CRT/ICD/Pacemaker	18.4%
Prior mitral/aortic intervention	36.9%
NYHA III/IV	65.2%
KCCQ-OS, Mean ± SD	52.0 ± 21.0
6MWD (m), Mean ± SD	231.4 ± 108.8
Key Echocardiography Parameters	
TR Severity	
Moderate[b]	1.5%
Severe	30.5%
Massive	22.9%
Torrential	45.0%
Secondary Etiology	90.5%
Coaptation gap, mm	5.9 ± 2.4
Heart size/function (Mean ± SD)	
Tricuspid annulus diameter, cm	4.3 ± 0.7
RVEDD-base, cm	5.1 ± 0.9
RVEDD-mid, cm	3.7 ± 0.8
Right atrial volume, mL	154.3 ± 89.7
Right ventricular TAPSE, cm	1.6 ± 0.4
Cardiac output, L/min	4.5 ± 1.7
LVEF (Mean ± SD)	59.2 ± 10.5
LVEF ≤ 40%	7.0%
LVEF ≤ 50%	14.8%

[a] Among patients who disclosed race (5 patients did not disclose race due to local regulation)

[b] Patients with moderate TR qualified for the trial with ≥severe TR based on the screening echocardiogram

Table A-12: Safety and Effectiveness Results (Roll-in Cohort, N=141)

	Roll-in Cohort (N=141)
30-Day Outcomes (%)	
All-Cause Death	***0.7%***
Procedure- or Device-Related	0.7%
Cardiovascular	0.7%
Endocarditis Requiring Surgery	0.0%
Non-Elective Cardiovascular Surgery for TriClip Related AE	0.7%
HFH	***2.1%***
Procedure- or Device-Related	0.0%
Major Bleeding (≥ BARC 3)	7.1%
New Onset Renal Failure	0.7%
Stroke	0.0%
TIA	0.0%
Myocardial Infarction	0.7%
Cardiogenic Shock	0.0%
SLDA	6.4%
New Permanent Pacemaker Implantation	0.0%
12-Month Outcomes (%)	
All-Cause Death	***15.6%***
Procedure- or Device-Related	0.7%
Cardiovascular	12.1%
HFH	***17.0%***
Procedure- or Device-Related	0.0%
Stroke	2.8%
TIA	1.4%
TV Surgery	1.4%
Cardiogenic Shock	0.0%
Device Embolization	1.4%
Device Thrombosis	0.0%
New Permanent Pacemaker Implantation	1.7%
SLDA	9.9%
TR ≤ moderate at 30 days (%)	68.4%
TR ≤ moderate at 12 months (%)	82.1%
KCCQ-OS change from baseline to 12 months (Mean ± SD)	19.3 ± 22.2
NYHA class I/II at 12 months (%)	75.5%
6MWD change from baseline to 12 months (Mean ± SD), meters	33.3 ± 106.3

17.3 Appendix 3 – Kansas City Cardiomyopathy Questionnaire

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

Original US English

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

Original US English

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

Original US English

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way all of the time	**I felt that way most of the time**	**I occasionally** felt that way	**I rarely** felt that way	**I never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Original US English