SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Mitral Valve Repair Device
Device Trade Name:	MitraClip NT Clip Delivery System MitraClip NTR/XTR Clip Delivery System
Device Procode:	NKM
Applicant Name and Address:	Abbott Vascular Inc. 3200 Lakeside Drive Santa Clara, CA 95054
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100009/S028
Date of FDA Notice of Approval:	March 14, 2019

The original PMA P100009 was approved on October 24, 2013 where the MitraClip Clip Delivery System was indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR $\geq$ 3+) due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation. The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100009B.pdf.) and is incorporated by reference herein.

The MitraClip Clip Delivery System has since been phased out and is no longer in commercial distribution. The MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System are design iterations of the MitraClip Clip Delivery System. The former was approved under P100009/S015 on May 10, 2016; the latter was approved under P100009/S025 on May 23, 2018.

The current supplement was submitted to expand the indication for the MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System to include secondary MR.

II. INDICATIONS FOR USE

The MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), are

indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

III. CONTRAINDICATIONS

The MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System are contraindicated in patients with the following conditions:

- Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen
- Active endocarditis of the mitral valve
- Rheumatic mitral valve disease
- Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System labeling.

V. DEVICE DESCRIPTION

The MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System are design iterations of the MitraClip Clip Delivery System approved under the original PMA. The differences between the three design iterations (collectively known as the MitraClip System) are summarized in Table 1.

Table 1: Design Iterations of the MitraClip System

Device	Device Modifications
MitraClip Clip Delivery System	Original device
MitraClip NT Clip Delivery System	Gripper material change from Elgiloy to Nitinol
MitraClip NTR/XTR Clip Delivery System	Modifications to the delivery catheter (NTR) and Clip Implant (XTR)

Same as the MitraClip Clip Delivery System, the MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System each consists of two major components: the Clip Delivery System and the Steerable Guide Catheter, as illustrated in Figure 1.

The Clip Delivery System includes the Delivery Catheter, the Steerable Sleeve, and the MitraClip Device. The Delivery Catheter consists of a long, flexible hydrophilic-coated multi-lumen shaft secured to the MitraClip Implant at the distal end and to a handle at its

proximal end. It is used to actuate and deploy the MitraClip Device. The Steerable Sleeve is used to position and orient the Clip Delivery System and MitraClip Device in the appropriate location above the mitral valve. The MitraClip Device is a percutaneously implanted mechanical clip manufactured with metal alloys and polyester fabric (clip cover), as shown in Figure 2. It grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle.

Figure 1: MitraClip System

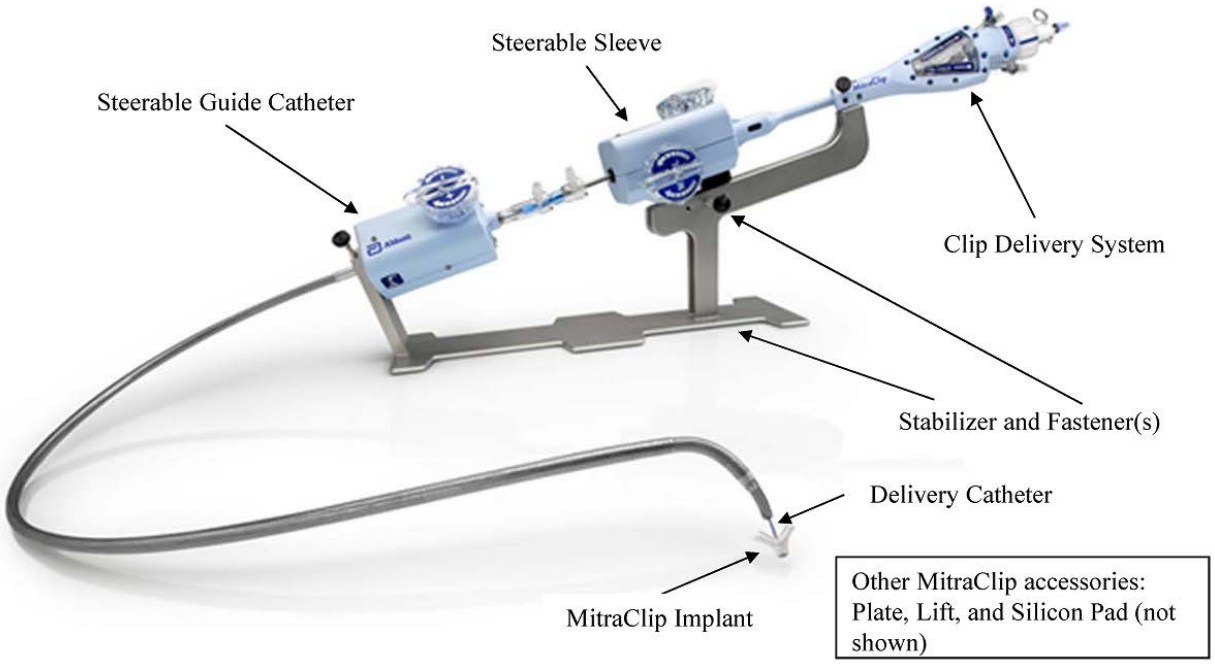
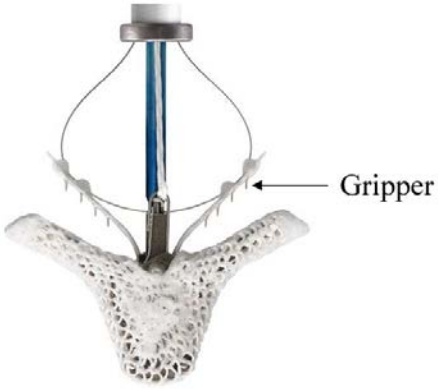


Figure 2: MitraClip Implant



The Steerable Guide Catheter (including a dilator) is a Class II device cleared under various 510(k)s. It provides a conduit into the left side of the heart through the interatrial septum and

provides the user with torque control and the ability to direct and orient the distal end of the catheter.

In addition, several accessories are used in conjunction with the MitraClip System, including: (1) a Stabilizer, (2) a Lift, (3) a Support Plate, (4) a Silicone Pad, and (5) Fasteners. These accessories are Class I devices.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of secondary MR, including surgical repair or replacement of the mitral valve and GDMT (including cardiac resynchronization therapy (CRT) and coronary revascularization when appropriate). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The MitraClip System is commercially available for patients with secondary MR in the following countries: all countries in the European Union, Australia, Brazil, Colombia, Costa Rica, Hong Kong, Indonesia, Israel, Japan, Kuwait, Lebanon, New Zealand, Norway, Saudi Arabia, Singapore, Turkey, United Arab Emirates, and Vietnam. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Death
- Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex)
- Aneurysm or pseudo-aneurysm
- Arrhythmias
- Atrial fibrillation
- Atrial septal defect requiring intervention
- Arterio-venous fistula
- Bleeding
- Cardiac arrest
- Cardiac perforation
- Hemorrhage requiring transfusion
- Hypotension/ hypertension
- Infection
- Injury to mitral valve complicating or preventing later surgical repair
- Lymphatic complications
- Mesenteric ischemia
- MitraClip Implant erosion, migration or malposition
- MitraClip Implant thrombosis
- MitraClip System component(s) embolization
- Mitral stenosis

- Cardiac tamponade/pericardial effusion
- Chordal entanglement/rupture
- Coagulopathy
- Conversion to standard valve surgery
- Deep venous thrombus (DVT)
- Dislodgement of previously implanted devices
- Dizziness
- Drug reaction to anti-platelet/ anticoagulation agents/contrast media
- Dyskinesia
- Dyspnea
- Edema
- Emboli (air, thrombus, MitraClip Implant)
- Emergency cardiac surgery
- Endocarditis
- Esophageal irritation
- Esophageal perforation or stricture
- Failure to deliver MitraClip to the intended site
- Failure to retrieve MitraClip System
- components
- Fever or hyperthermia
- Gastrointestinal bleeding or infarct
- Hematoma
- Hemolysis
- Mitral valve injury
- Multi-system organ failure
- Myocardial infarction (MI)
- Nausea/vomiting
- Pain
- Peripheral ischemia
- Prolonged angina
- Prolonged ventilation
- Pulmonary congestion
- Pulmonary thrombo-embolism
- Renal insufficiency or failure
- Respiratory failure/atelectasis/ pneumonia
- Septicemia
- Shock, anaphylactic or cardiogenic
- Single leaflet device attachment (SLDA)
- Skin injury or tissue changes due to exposure to ionizing radiation
- Stroke or transient ischemic attack (TIA)
- Urinary tract infection
- Vascular trauma, dissection or occlusion
- Vessel spasm
- Vessel perforation or laceration
- Worsening heart failure (HF)
- Worsening mitral regurgitation
- Wound dehiscence

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

IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA. No additional preclinical study was performed for the current application.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the MitraClip Clip Delivery System for patients with symptomatic, moderate-to-severe or severe secondary MR whose symptoms and MR severity persist despite maximally tolerated GDMT in the U.S. and Canada under IDE G120024 (entitled

"COAPT Trial"). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System were not used in the pivotal trial. However, based on the similarities between these two design iterations and the MitraClip Clip Delivery System, the results obtained on the MitraClip Clip Delivery System are considered applicable to the MitraClip NT Clip Delivery System and MitraClip NTR/XTR Clip Delivery System.

A. Study Design

Patients were enrolled between December 27, 2012, and June 23, 2017. The database for this Panel Track Supplement reflected data collected through August 3, 2018, and included 614 randomized patients. There were 78 investigational sites.

The COAPT Trial was a prospective, randomized (1:1; MitraClip + GDMT vs. GDMT alone), open-label, multicenter investigational study intended to demonstrate: (1) MitraClip was safe in subjects with secondary MR, and (2) MitraClip could reduce recurrent HF hospitalization as compared to the GDMT Control group. The randomization was further stratified by study site and by cardiomyopathy etiology (e.g., ischemic or non-ischemic). The planned sample size of the trial was 760, including 150 roll-in subjects.

The COAPT Trial was conducted under the oversight of several independent committees, including: (1) a Steering Committee, which provided scientific and medical input on trial design, data collection, data analyses, and interpretation of results; (2) an independent Eligibility Committee, which confirmed that each subject was on optimal therapy including GDMT prior to being considered for the trial and that the subject was not appropriate for mitral valve surgery, even if randomized to the Control group; (3) a Central Echocardiography Core Laboratory (ECL), which was responsible for reviewing subject's screening echocardiography images to determine if the subject met the MR severity eligibility criterion prior to the subject being considered eligible for the trial, and for assessing MR severity and left ventricular measurements, along with other measures, at baseline and follow-ups; (4) a Clinical Events Committee (CEC), which adjudicated all adverse events per pre-established definitions (blinding was maintained whenever feasible); (5) a Data Monitoring Committee (DMC), which monitored the safety of subjects throughout trial; and (6) a Contract Research Organization, which participated in source data verification.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the COAPT Trial was limited to patients who met the following inclusion criteria:

   - Symptomatic functional MR (≥ 3+) due to cardiomyopathy of either ischemic or non-ischemic etiology determined by assessment of a qualifying transthoracic echocardiogram (TTE) obtained within 90 days and transesophageal echocardiogram

(TEE) obtained within 180 days prior to subject registration, with MR severity based principally on the TTE study, confirmed by the ECL. The ECL may request a transesophageal echocardiogram (TEE) to confirm MR etiology.

- In the judgment of the HF specialist investigator at the site, the subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and HF (e.g., with CRT, revascularization, and/or GDMT. The Eligibility Committee must concur that the subject has been adequately treated.
- New York Heart Association (NYHA) Functional Class II, III or ambulatory IV.
- The Local Site Heart Team (cardiothoracic surgeon and HF specialist investigators) and the Central Eligibility Committee concur that surgery will not be offered as a treatment option and that medical therapy was the intended therapy for the subject, even if the subject was randomized to the Control group.
- Left Ventricular Ejection Fraction (LVEF) was ≥ 20% and ≤ 50% within 90 days prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI).
- Left Ventricular End Systolic Dimension (LVESD) was ≤ 70 mm assessed by site based on a TTE obtained within 90 days prior to subject registration.
- The primary regurgitant jet was non-commissural, and in the opinion of the MitraClip implanting investigator can successfully be treated by the MitraClip. If a secondary jet exists, it must be considered clinically insignificant.
- Creatine Kinase-MB (CK-MB) obtained within prior 14 days < local laboratory ULN (Upper Limit of Normal).
- Transseptal catheterization and femoral vein access was determined to be feasible by the MitraClip implanting investigator.
- Age 18 years or older.
- The subject or the subject's legal representative understands and agrees that should he/she be assigned to the Control group, he/she will be treated with medical therapy and conservative management without surgery and without the MitraClip, either domestically or abroad. If the subject would actively contemplate surgery and/or MitraClip if randomized to Control, he/she should not be registered in this trial.
- The subject or the subject's legal representative has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group and returning for all required post-procedure follow-up visits, and has provided written informed consent.

Patients were <u>not</u> permitted to enroll in the COAPT Trial if they met any of the following clinical or anatomical exclusion criteria:

- Chronic Obstructive Pulmonary Disease (COPD) requiring continuous home oxygen therapy or chronic outpatient oral steroid use.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Coronary artery bypass grafting (CABG) within 30 days prior to subject registration.
- Percutaneous coronary intervention within 30 days prior to subject registration.

- Transcatheter aortic valve replacement (TAVR) within 30 days prior to subject registration.
- Tricuspid valve disease requiring surgery.
- Aortic valve disease requiring surgery or transcatheter intervention.
- Cerebrovascular accident within 30 days prior to subject registration.
- Severe symptomatic carotid stenosis (> 70% by ultrasound).
- Carotid surgery or stenting within 30 days prior to subject registration.
- American College of Cardiology (ACC)/American Heart Association (AHA) Stage D heart failure.
- Presence of any of the following:
  - Estimated pulmonary artery systolic pressure (PASP) > 70 mm Hg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the catheterization laboratory was able to reduce the pulmonary vascular resistance (PVR) to < 3 Wood Units or between 3 and 4.5 Wood Units with v wave less than twice the mean of the pulmonary capillary wedge pressure
  - Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
  - Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
  - Hemodynamic instability requiring inotropic support or mechanical heart assistance
- Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction, as assessed by site.
- Implant of any CRT or CRT with cardioverter-defibrillator (CRT-D) within the last 30 days prior to subject registration.
- Mitral valve orifice area < 4.0 cm^2 assessed by site based on a TTE within 90 days prior to subject registration.
- Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in MR by the MitraClip. This evaluation was based on TEE evaluation of the mitral valve within 180 days prior to subject registration and includes:
  - Insufficient mobile leaflet available for grasping with the MitraClip device
  - Evidence of calcification in the grasping area
  - Presence of a significant cleft in the grasping area
  - Lack of both primary and secondary chordal support in the grasping area
  - Leaflet mobility length < 1 cm
- Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
- Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
- Life expectancy < 12 months due to non-cardiac conditions.
- Modified Rankin Scale (MRS) ≥ 4 disability.
- Status 1 heart transplant or prior orthotopic heart transplantation.

- Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated).
- Active infections requiring current antibiotic therapy.
- Subjects in whom TEE was contraindicated or high risk.
- Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically.
- Pregnant or planning pregnancy within next 12 months.
- Currently participating in an investigational drug or another device study that has not reached its primary endpoint. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
- Subject belongs to a vulnerable population per investigator's judgment or subject has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at 1 week (phone contact), 30 days, 6 months, 12 months, 18 months, 24 months, and annually thereafter through 5 years. Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and health status/quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Safety Endpoint:

The primary safety endpoint was a composite of SLDA, device embolizations, endocarditis requiring surgery, ECL confirmed mitral stenosis requiring surgery, left ventricular assist device (LVAD) implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery at 12 months. The proportion of subjects free from the primary safety endpoint events was tested against a pre-specified performance goal (PG) of 88% for the Safety Analysis population, as defined in Section X.B.

Primary Effectiveness Endpoint:

The primary effectiveness endpoint was recurrent HF hospitalizations through 24 months, with the following null and alternative hypotheses:

$$H_0: RRR \leq 0$$
$$H_A: RRR > 0$$

where *RRR* is the relative risk reduction in the rate of recurrent HF hospitalization due to

treatment with the MitraClip device as compared to the Control group. The primary effectiveness endpoint was analyzed when the last subject completed 12 months of follow-up. Hypothesis testing was performed using the Joint Frailty Model to adjust for the competing risk of death.[1-3]

Secondary Endpoints:

An ordered list of powered secondary endpoints, as shown in Table 2, was included in a hierarchical testing scheme, which were carried out after both the primary safety and effectiveness endpoints were met.

Table 2: Ordered List of Secondary Endpoints for Hierarchical Testing

Order	Secondary Endpoint	Alternative Hypothesis
#1	Proportion of MR severity ≤ 2+ at 12 months	$H_A: P_D - P_C \neq 0$
#2	All-cause mortality at 12 months	$H_A: HR < 1.5$
#3	Hierarchical composite of all-cause mortality and recurrent HF hospitalization (analyzed when the last subject completes 12 months of follow-up)	H_A: Either rate of death or rate of recurrent HF hospitalization is lower in the Device group compared to the Control group.
#4	Change in quality of life (QoL) at 12 months from baseline, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)	$H_A: \mu_D - \mu_C \neq 0$
#5	Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 12 months over baseline	$H_A: \mu_D - \mu_C \neq 0$
#6	Recurrent hospitalizations - all-cause (analyzed when the last subject completes 12 months of follow-up)	$H_A: RRR \neq 0$
#7	Proportion of New York Heart Association (NYHA) Functional Class I/II at 12 months	$H_A: P_D - P_C \neq 0$
#8	Change in Left Ventricular End Diastolic Volume (LVEDV) at 12 months over baseline	$H_A: \mu_D - \mu_C \neq 0$
#9	All-cause mortality at 24 months	$H_A: HR \neq 1$
#10	Freedom from all-cause mortality, stroke, myocardial infarction, or non-elective cardiovascular surgery for device related complications in the MitraClip group at 30 days	$H_A: P_D(30) > 0.80$

P: proportion; μ: mean.
HR: hazard ratio; *RRR*: relative risk reduction.
Subscript D: Device; Subscript C: Control.

B. Accountability of PMA Cohort

At the time of database lock, a total of 614 subjects were randomized in this trial, including 302 Device subjects and 312 Control subjects.

There were four different analysis populations defined in the protocol: Intention-to-Treat (ITT) population, Per Protocol (PP) population, As Treated (AT) population, and Safety Analysis (SA) population, as summarized in Table 3 and Figure 3. The primary analysis for safety was the Safety Analysis, and that for effectiveness was the ITT analysis.

Table 3: Analysis Populations

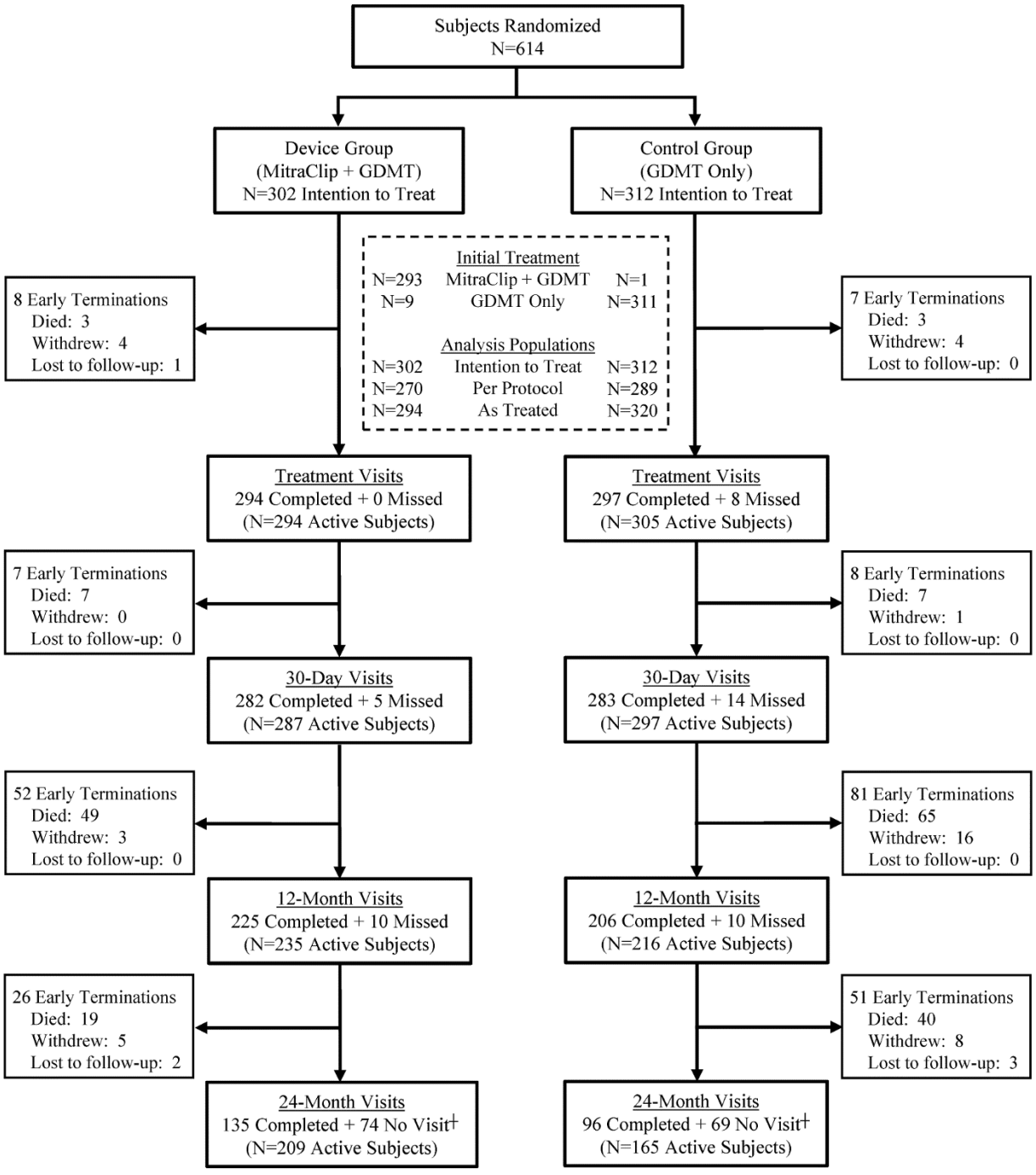
Analysis Population	Definition	Number of Patients	
		Device	Control
Intention-to-Treat (ITT)	All randomized subjects	302	312
As Treated (AT)	Randomized subjects who received the treatment as randomized	294	320
Per Protocol (PP)	Subjects who met major inclusion and none of the major exclusion criteria and received the treatment as randomized	270	289
Safety Analysis (SA)	All ITT subjects in the Device group with an attempted implant procedure*	293	

*Attempted implant procedure is defined as administration of anesthesia for the MitraClip procedure.

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population are typical for an HF study performed in the U.S., as shown in Table 4. The two study groups were well-balanced, with no significant difference in patient demographics and baseline characteristics.

Figure 3: Disposition of COAPT Randomized Subjects



†Denotes visits that were expected from, missed by or not due from subjects active in the study at the time of the data cut-off.

Table 4: Patient Demographics and Baseline Characteristics (ITT Population)

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Age at Registration (year)	71.7 ± 11.8 (302)	72.8 ± 10.5 (312)	0.2186
Male	66.6% (201/302)	61.5% (192/312)	0.1953
Race/Ethnicity			
White or Caucasian	74.5% (225/302)	74.4% (232/312)	0.9673
Non-white	25.5% (77/302)	25.6% (80/312)	
Height (cm)	170.8 ± 10.4 (301)	169.9 ± 10.8 (306)	0.2500
Weight (kg)	78.8 ± 17.2 (301)	78.4 ± 20.1 (307)	0.8002
Body Mass Index (kg/m^2)	27.0 ± 5.8 (300)	27.1 ± 5.9 (305)	0.9880
Serum Creatinine (mg/dL)	1.8 ± 1.2 (300)	1.8 ± 1.4 (306)	0.8362
Creatinine Clearance (mL/min)	50.9 ± 28.5 (299)	47.8 ± 25.0 (302)	0.1552
Creatinine Clearance ≤ 60 mL/min	71.6% (214/299)	75.2% (227/302)	0.3189
BNP (pg/mL)	1014.8 ± 1086.0 (208)	1017.1 ± 1212.8 (209)	0.9833
NT-proBNP (pg/mL)	5174.3 ± 6566.6 (74)	5943.9 ± 8437.6 (85)	0.5194
Elevated BNP or NT-proBNP prior to Enrollment	93.4% (267/286)	93.1% (282/303)	0.8898
Extremely High Risk for MV Surgery	68.6% (205/299)	69.9% (218/312)	0.7258
KCCQ Overall Summary Score	53.2 ± 22.8 (302)	51.6 ± 23.3 (309)	0.3907
Six Minute Walk Test Distance (meters)	249.6 ± 123.8 (296)	234.5 ± 123.5 (305)	0.1359
NYHA Functional Class			
Class I	0.3% (1/302)	0.0% (0/311)	0.4927
Class II	42.7% (129/302)	35.4% (110/311)	0.0623
Class III	51.0% (154/302)	54.0% (168/311)	0.4532
Class IV	6.0% (18/302)	10.6% (33/311)	0.0371
SF-36 Quality of Life Physical Component Score	33.0 ± 9.1 (299)	32.6 ± 10.0 (308)	0.6336

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
SF-36 Quality of Life Mental Component Score	46.7 ± 12.7 (299)	45.3 ± 13.0 (308)	0.1883
Cardiovascular Event History			
Ischemic Cardiomyopathy	60.9% (184/302)	60.6% (189/312)	0.9292
Non-Ischemic Cardiomyopathy	39.1% (118/302)	39.4% (123/312)	
Prior TIA	8.6% (26/302)	5.4% (17/312)	0.1250
Prior Stroke	12.3% (37/302)	11.2% (35/312)	0.6906
Prior Stroke or TIA	18.5% (56/302)	15.7% (49/312)	0.3505
Prior Myocardial Infarction	51.7% (156/302)	51.3% (160/312)	0.9262
Coronary Artery Disease (CAD)	72.2% (218/302)	73.1% (228/312)	0.8044
Hypertension	80.5% (243/302)	80.4% (251/312)	0.9963
Hypercholesterolemia	55.0% (166/302)	52.2% (163/312)	0.4988
Angina	16.9% (51/302)	23.4% (73/312)	0.0446
Chronic Obstructive Pulmonary Disease	23.5% (71/302)	23.1% (72/312)	0.8990
Arrhythmia Event History	66.6% (201/302)	64.4% (201/312)	0.5783
Ventricular Fibrillation	5.6% (17/302)	8.0% (25/312)	0.2421
Ventricular Flutter	0.0% (0/302)	0.0% (0/312)	1.0000
Ventricular Tachycardia	24.8% (75/302)	22.4% (70/312)	0.4842
Atrial Flutter	10.3% (31/302)	10.9% (34/312)	0.7990
Atrial Fibrillation	55.6% (168/302)	51.0% (159/312)	0.2465
Atrial Fibrillation or Flutter	57.3% (173/302)	53.2% (166/312)	0.3095
Any Hospitalization 12 months prior to enrollment	67.5% (204/302)	65.1% (203/312)	0.5148
Heart Failure	58.3% (176/302)	56.1% (175/312)	0.5838
Other-Cardiovascular	11.6% (35/302)	9.3% (29/312)	0.3523
Non-Cardiovascular	7.9% (24/302)	7.1% (22/312)	0.6734
Co-morbidity			
Diabetes	35.1% (106/302)	39.4% (123/312)	0.2680
Peripheral Vascular Disease	17.2% (52/302)	18.3% (57/312)	0.7334
Renal Disease	57.0% (172/302)	56.7% (177/312)	0.9555

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
History of Anemia	22.5% (68/302)	24.4% (76/312)	0.5901
History of Major Bleeds or Bleeding Disorder	7.6% (23/302)	7.1% (22/312)	0.7884
STS Replacement Score (%)	7.8 ± 5.5 (302)	8.5 ± 6.2 (312)	0.1565
STS Repair Score (%)	5.6 ± 5.6 (302)	6.0 ± 5.4 (312)	0.3939
Prior Cardiac Interventions			
Coronary Artery Bypass Craft (CABG)	40.1% (121/302)	40.4% (126/312)	0.9359
PTCA/Stents/Atherectomy	43.0% (130/302)	49.0% (153/312)	0.1364
Device Implantation			
None	33.1% (100/302)	33.0% (103/312)	0.9790
ICD	30.1% (91/302)	32.4% (101/312)	0.5496
CRT-P	1.7% (5/302)	1.9% (6/312)	0.8028
CRT-D	36.4% (110/302)	33.0% (103/312)	0.3747
Pacemaker	6.0% (18/302)	8.0% (25/312)	0.3191
Defibrillator (ICD or CRT-D)	62.6% (189/302)	61.5% (192/312)	0.7898
Resynchronization (CRT-D or CRT-P)	38.1% (115/302)	34.9% (109/312)	0.4185
Pacing (CRT-P or Pacemaker)	7.3% (22/302)	9.9% (31/312)	0.2422
Prior Cardiac Valve Interventions			
Aortic Valve Intervention	3.3% (10/302)	4.5% (14/312)	0.4523
Pulmonic Valve Intervention	0.0% (0/302)	0.0% (0/312)	1.0000
Tricuspid Valve Intervention	0.0% (0/302)	0.0% (0/312)	1.0000
Mitral Valve Intervention	0.3% (1/302)	0.0% (0/312)	0.4919
Echocardiographic Core Laboratory Measures			
Mitral regurgitation severity			
3+: Moderate-to-Severe	49.0% (148/302)	55.3% (172/311)	0.1186
4+: Severe	51.0% (154/302)	44.7% (139/311)	
Effective Regurgitant Orifice Area (EROA, cm^2)	0.41 ± 0.15 (289)	0.40 ± 0.15 (302)	0.4203
Left Ventricular Ejection Fraction (LVEF, %)	31.3 ± 9.1 (281)	31.3 ± 9.6 (294)	0.9717
≤ 40 %	82.2% (231/281)	82.0% (241/294)	0.9418
Left Ventricular End Systolic Dimension (LVESD, cm)	5.3 ± 0.9 (301)	5.3 ± 0.9 (306)	0.8172

Demographics and Baseline Characteristics	Summary Statistics*		P-Value†
	Device (N=302)	Control (N=312)	
Left Ventricular End Diastolic Dimension (LVEDD, cm)	6.2 ± 0.7 (301)	6.2 ± 0.8 (307)	0.7958
Left Ventricular End Systolic Volume (LVESV, mL)	135.5 ± 56.1 (281)	134.3 ± 60.3 (294)	0.8085
Left Ventricular End Diastolic Volume (LVEDV, mL)	194.4 ± 69.2 (281)	191.0 ± 72.9 (294)	0.5667
LVEDV Index (mL/m^2)	102.3 ± 33.7 (279)	100.6 ± 35.0 (288)	0.5570
Right Ventricular Systolic Pressure (RVSP, mmHg)	44.0 ± 13.4 (253)	44.6 ± 14.0 (275)	0.6090
Medication Use at Baseline			
Beta-blocker	91.1% (275/302)	89.7% (280/312)	0.5802
ACEI, ARB or ARNI	71.5% (216/302)	62.8% (196/312)	0.0218
Mineralocorticoid receptor antagonist	50.7% (153/302)	49.7% (155/312)	0.8076
Nitrate	6.3% (19/302)	8.0% (25/312)	0.4084
Hydralazine	16.6% (50/302)	17.6% (55/312)	0.7243
Diuretic	89.4% (270/302)	88.8% (277/312)	0.8048
Chronic oral anticoagulant	46.4% (140/302)	40.1% (125/312)	0.1155
Aspirin	57.6% (174/302)	64.7% (202/312)	0.0699
P2Y12 receptor inhibitor	25.2% (76/302)	22.8% (71/312)	0.4843
Statin	62.6% (189/302)	60.6% (189/312)	0.6095

*Continuous measures - Mean ± SD; categorical measures - % (no./total no.).
†P-values are from *t*-test for continuous variables and from Chi-square test or Fisher's exact test when Cochran's rule is not met for categorical variables. All p-values displayed are two-sided and for information only.

D. Safety and Effectiveness Results

1. Primary Safety Endpoint

The rate of freedom from device-related complications at 12 months was 96.6%, with a lower 95% confidence limit of 94.8%, which was higher than the pre-specified performance goal of 88% ($p<0.0001$), as shown in Figure 4. As such, the COAPT Trial met its primary safety endpoint. A breakdown of the composite primary safety endpoint events is presented in Table 5.

Figure 4: Kaplan-Meier Curve of the Primary Safety Endpoint (SA Population)

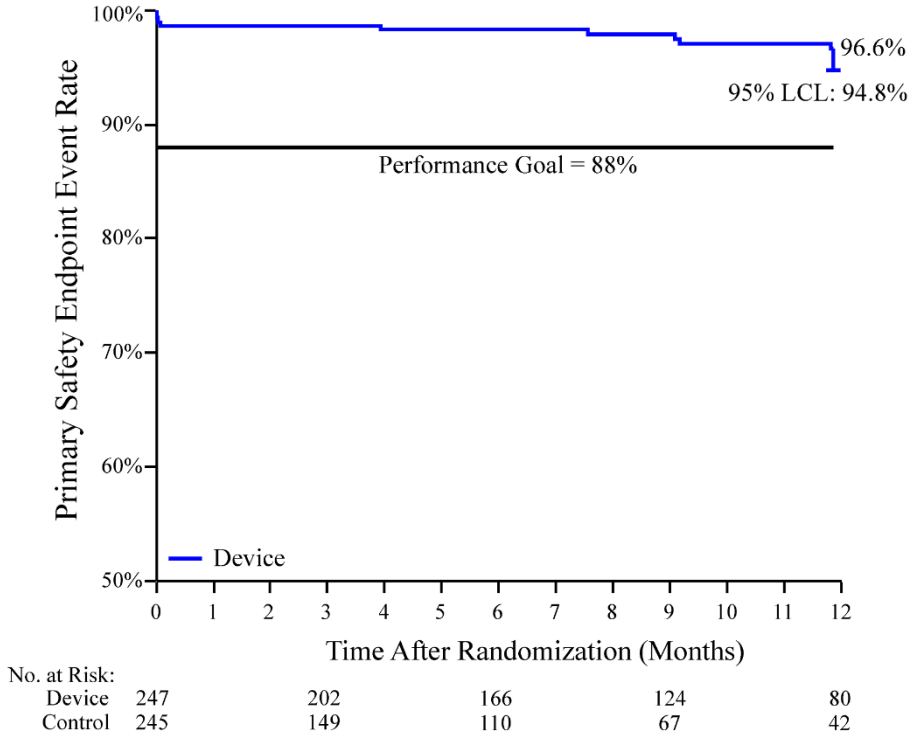


Table 5: Outcomes of the Primary Safety Endpoint Components (SA Population)

Event	Summary Statistics* (N = 293)
Device-related complications at 12 months	9 (3.4%)
-- Single leaflet device attachment	2 (0.7%)
-- Device embolization	1 (0.3%)
-- Endocarditis requiring surgery	0 (0.0%)
-- Mitral stenosis requiring surgery	1 (0.3%)
-- LVAD implant	3 (1.2%)
-- Heart transplant	2 (0.8%)
-- Any device-related complication requiring non-elective cardiovascular surgery	1 (0.3%)

*# events (Kaplan-Meier rate)

2. Primary Effectiveness Endpoint

A total of 160 and 283 HF hospitalizations occurred within 24 months in the Device and Control groups, respectively. The annualized rates (events per patient-year) of HF hospitalization were 0.358 in the Device group and 0.679 in the Control group, with a hazard ratio (HR) of 0.525 (upper 95% confidence limit: 0.664), representing a 47.5% reduction in the risk of recurrent HF hospitalization by the Joint Frailty Model in favor of the Device

($p<0.0001$), as summarized in Table 6 and Figure 5. Therefore, the COAPT Trial met its primary effectiveness endpoint. The successes of the primary safety endpoint and the primary effectiveness endpoint were confirmed by the AT analysis, PP analysis, and sensitivity analysis.

Table 6: Recurrent HF Hospitalization through 24 Months – Primary Effectiveness Endpoint (ITT Population)

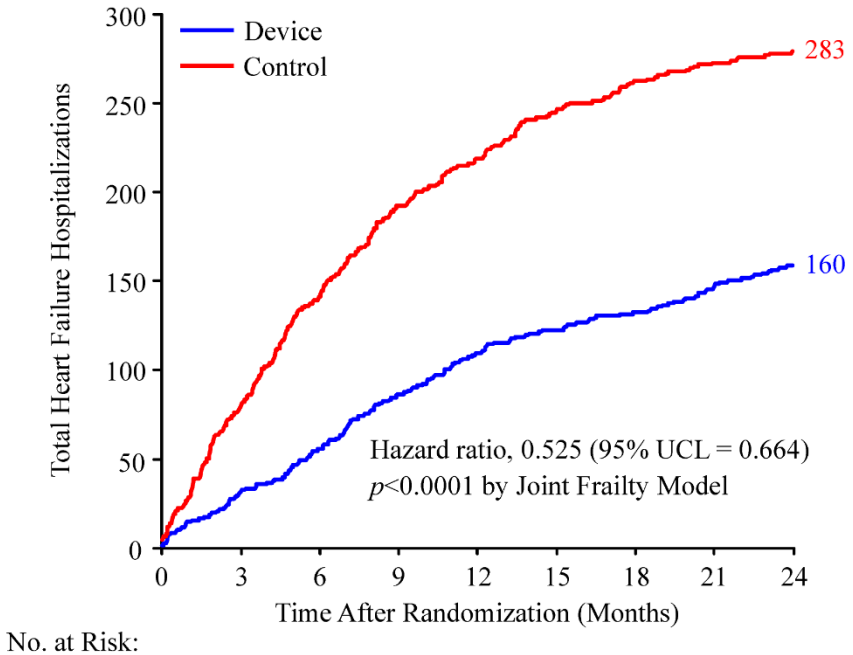
	Device (N=302)	**Control (N=312)**	**Hazard Ratio - Device vs. Control [95% CI]**	**Relative Risk Reduction - Device vs. Control [95% CI]**	**P-Value**
Number of Subjects*	92 (30.5%)	151 (48.4%)			
Number of Events	160	283			
Total Follow-Up (patient-years)*	446.5	416.8			
Annualized Rate [95% CI]†	0.358 [0.307, 0.418]	0.679 [0.604, 0.763]			
Joint Frailty Model			0.525 [-, 0.664]	0.475 [0.336, -]	< 0.0001

*The total follow-up in patient-years was calculated as the sum of follow-up patient-years for each subject through 24 months at the time of data cut-off or end of study, whichever was earlier.

†The annualized rate was calculated as total number of HF hospitalization events divided by total follow-up years through 24 months.

Note: (1) Hospitalizations that were adjudicated by the CEC as related to HF using the pre-specified protocol definition were included as events in the analysis; (2) Hospitalizations for MV surgery, LVAD implant or heart transplant during the follow-up period were treated as HF hospitalizations; and (3) For subjects in the Control group who received the MitraClip device due to HF or cardiac symptoms, the hospitalizations for the MitraClip procedure were treated as HF hospitalizations.

Figure 5: Total HF Hospitalization through 24 Months (ITT Population)



3. Powered Secondary Endpoints

Hypothesis testing was performed on 10 pre-specified secondary endpoints using a hierarchical test procedure, as shown in Table 7.

Table 7: Summary of Hierarchical Secondary Endpoints (ITT Population)

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
#1 Proportion of MR Severity ≤ 2+ at 12 Months; % (no./total no.) [95% CI]	94.8% (199/210) [90.82%, 97.36%]	46.9% (82/175) [39.29%, 54.53%]	-	-	< 0.0001
#2 All-Cause Mortality at 12 Months (Non-inferiority);† Kaplan-Meier estimate (SE) of event rate	19.1% (2.3%)	23.2% (2.4%)	0.809 [-, 1.085]	-	0.0003

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
#3 Finkelstein-Schoenfeld Analysis of a Hierarchical Composite of All-Cause Mortality and Recurrent HF Hospitalization through 24 Months	-	-	-	-	< 0.0001
#4 Change in KCCQ Overall Summary Score at 12 Months over Baseline; least square means (SE) [95% CI]	12.50 (1.82) [8.93, 16.08]	-3.56 (1.85) [-7.21, 0.08]	16.07 [10.97, 21.17]	-	< 0.0001
#5 Change in 6MWD at 12 Months over Baseline; least square means (SE) [95% CI]	-2.17 (9.12) [-20.10, 15.76]	-60.03 (8.99) [-77.69, -42.36]	57.86 [32.67, 83.05]	-	< 0.0001
#6 All-Cause Recurrent Hospitalizations through 24 Months;† annualized rate [95% CI]	1.062 [0.970, 1.162]	1.464 [1.352, 1.585]	0.760 [0.602, 0.960]	-	0.0213
#7 Proportion of NYHA Functional Class of I/II at 12-Month; % (no./total no.) [95% CI]	72.2% (171/237) [65.98%, 77.76%]	49.6% (115/232) [42.96%, 56.19%]	-	-	< 0.0001
#8 Change in Left Ventricular End Diastolic Volume at 12 Months over Baseline; least square means (SE) [95% CI]	-3.71 (5.08) [-13.71, 6.28]	17.06 (5.10) [7.03, 27.08]	-20.77 [-34.93, -6.62]	-	0.0041

Secondary Endpoints (hierarchical order)	Device (N=302)	Control (N=312)	HR or Difference [95% CI]	Lower 95% confidence limit	P-Value*
#9 All-Cause Mortality through 24 Months;† Kaplan-Meier estimate (SE) of event rate	29.1% (2.8%)	46.1% (3.2%)	0.615 [0.463, 0.816]	-	0.0008
#10 Estimate of Freedom from All-Cause Mortality, Stroke, MI or Non-Elective Cardiovascular Surgery for Device-Related Complications at 30 Days; % (no./total no.)	96.9% (284/293)	-	-	94.7%	<0.0001

*All p-values were tests for superiority, except for the secondary endpoint of mortality at 12 months (#2), which was a test for non-inferiority, and for the secondary endpoint of freedom from composite of all-cause mortality, stroke, MI or non-elective cardiovascular surgery for device-related complications at 30 days (#10), which was compared against a performance goal.

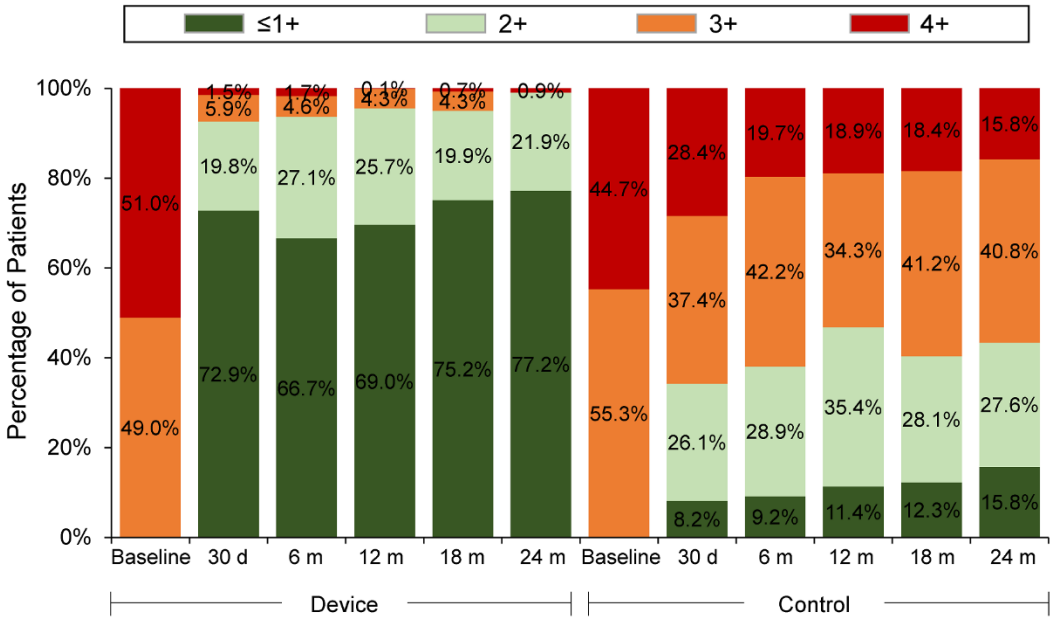
†Analyzed when the last subject completed the 12-month follow-up.

Note: (1) Imputation of worst clinical outcomes for subjects experiencing HF death prior to 12 months for the changes in KCCQ, 6MWD, LVEDV and NYHA class. (2) Continuous endpoints (KCCQ, 6MWD, and LVEDV) were analyzed using Analysis of Covariance (ANCOVA). (3) HR – Hazard Ratio; CI – Confidence Interval; SE – Standard Error.

All powered secondary endpoints were met, as summarized below:

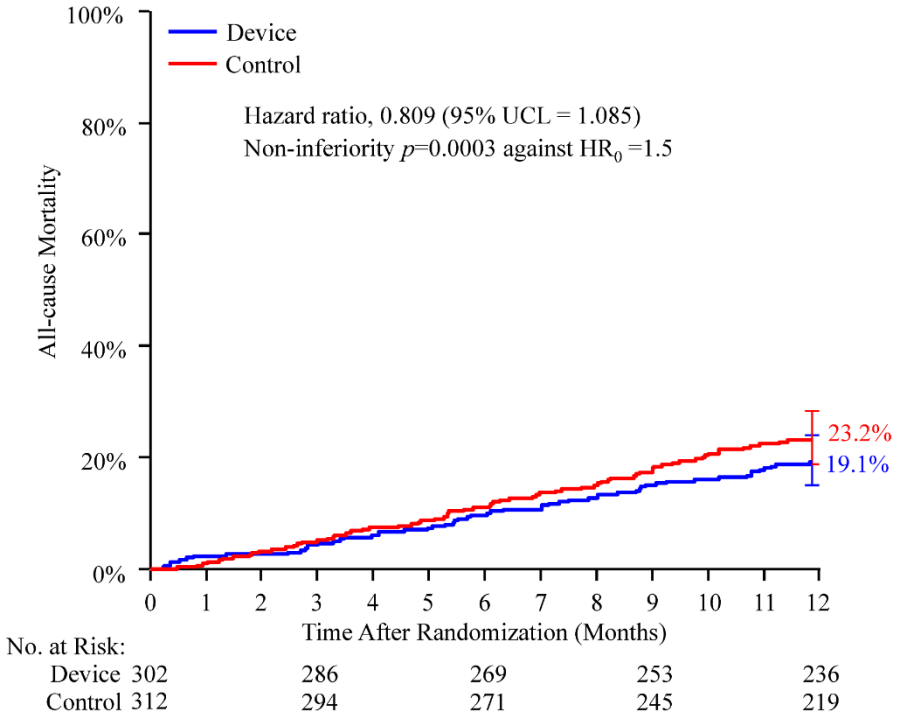
(1) There were significantly more subjects with MR severity ≤ 2+ in the Device group than in the Control group at 12 months (94.8% vs. 46.9%). The MR severity grades over time in both groups are shown in Figure 6.

Figure 6: MR Severity Grades over Time (ITT Population)



(2) The Device group was found to be non-inferior to the Control group in all-cause mortality at 12 months (19.1% vs. 23.2%), as shown in Figure 7.

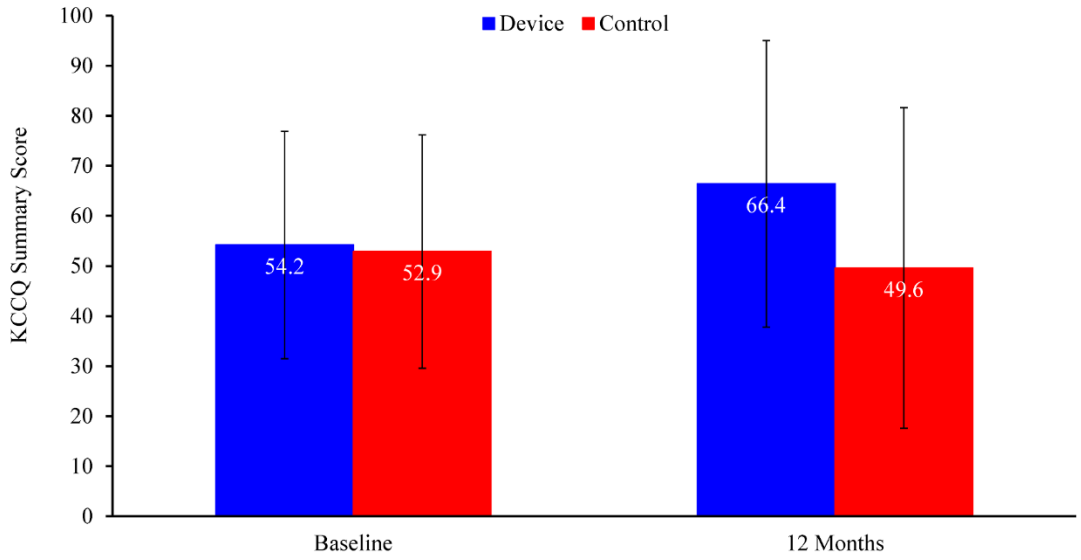
Figure 7: Kaplan-Meier Curve of All-Cause Mortality through 12 Months (ITT Population)



(3) Subjects in the Device group experienced a significant reduction in the hierarchical composite of all-cause mortality and recurrent HF hospitalization compared to those in the Control group.

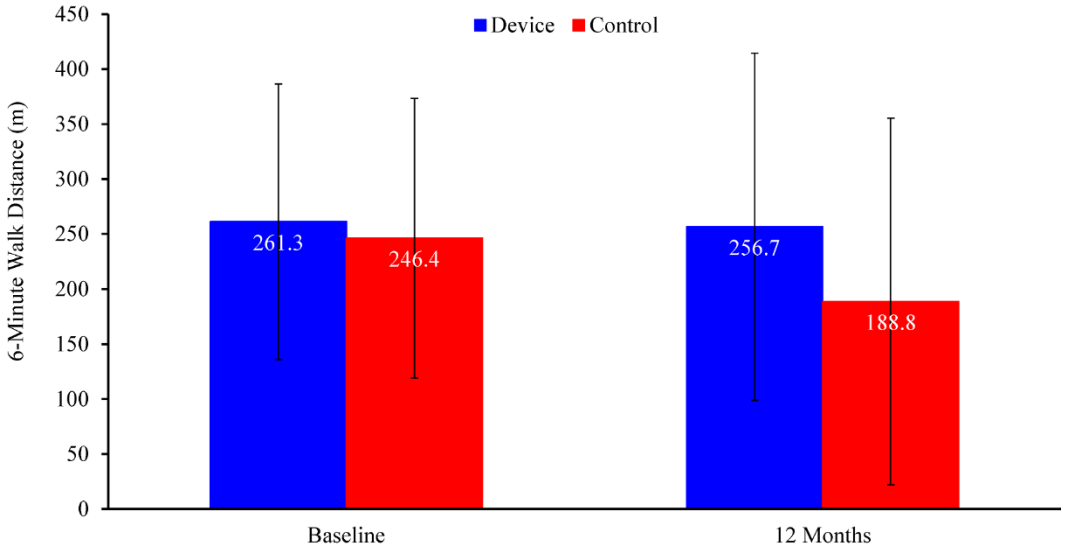
(4) Subjects in the Device group experienced a significantly greater improvement in QoL (as assessed by the change in KCCQ Overall Summary Score at 12 months over baseline) compared to those in the Control group (12.50 vs. -3.56), as shown in Figure 8.

Figure 8: KCCQ Overall Summary Score at Baseline and 12 Months (ITT Population)



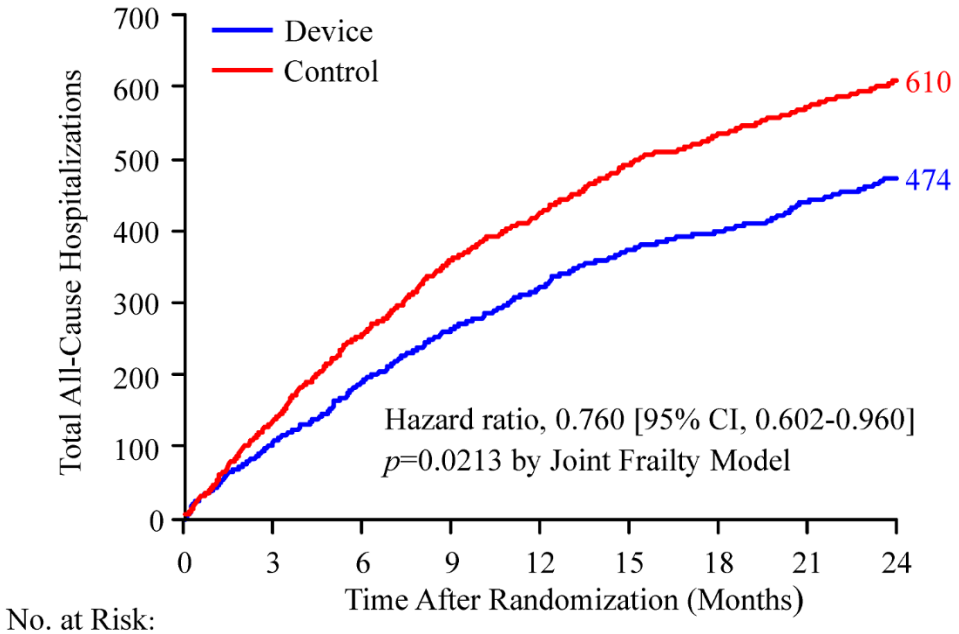
(5) Subjects in the Device group experienced significantly greater preservation of functional capacity (as assessed by the change in 6MWD at 12 months over baseline) compared to those in the Control group (-2.17 m vs. -60.03 m), as shown in Figure 9.

Figure 9: 6MWD at Baseline and 12 Months (ITT Population)



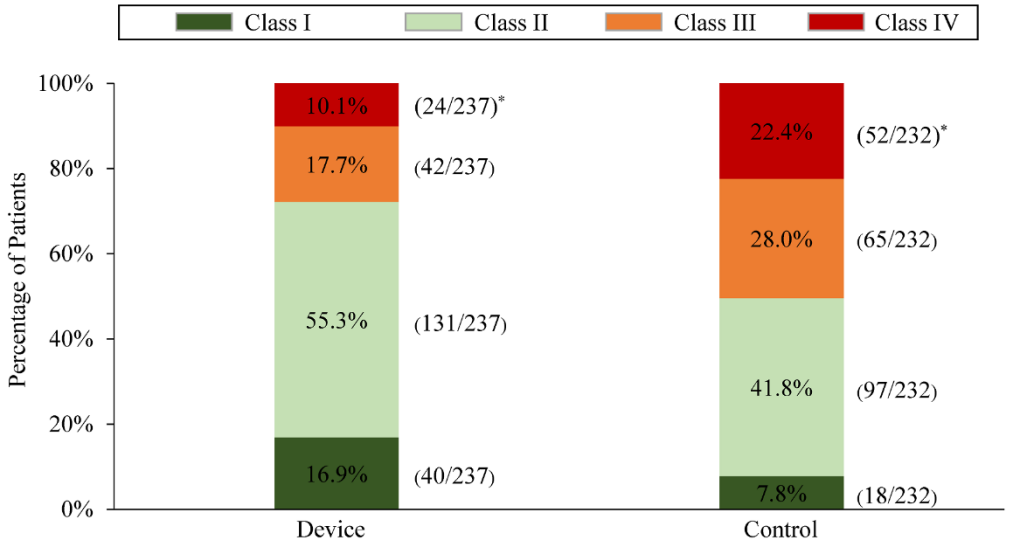
(6) Subjects in the Device group experienced a significantly lower annualized rate (events per patient-year) of all-cause hospitalizations compared to those in the Control group (1.062 vs. 1.464). The total all-cause hospitalization through 24 months is shown in Figure 10.

Figure 10: Total All-Cause Hospitalization through 24 Months (ITT Population)



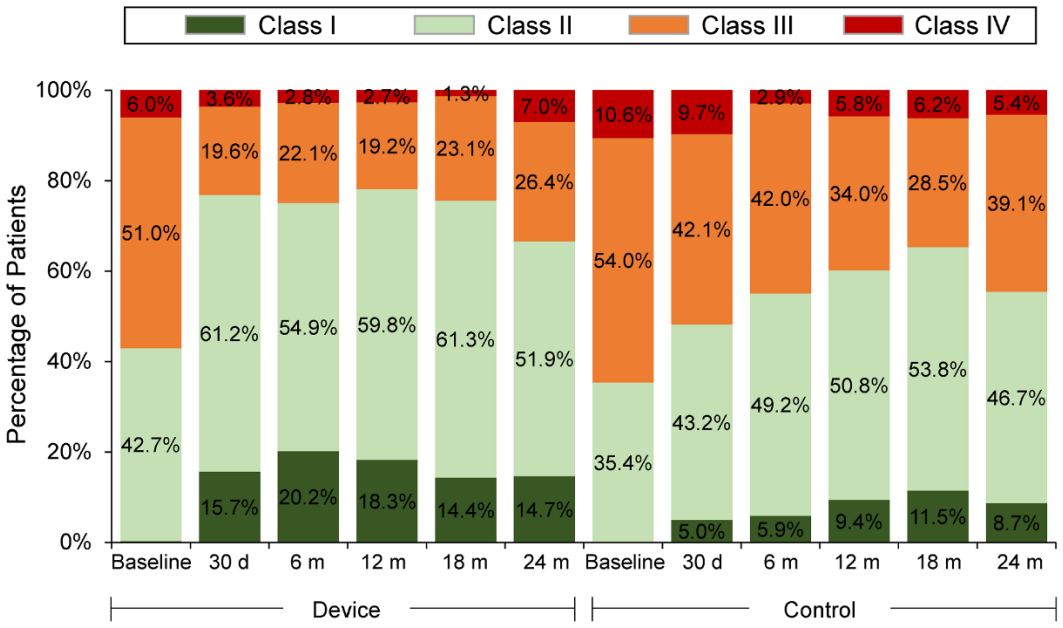
(7) Subjects in the Device group experienced a significantly greater improvement in NYHA Functional Class at 12 months compared to those in the Control group (Class I or II: 72.2% vs. 49.6%), as shown in Figure 11, where subjects who died prior to 12 months were imputed as having NYHA Class IV. The NYHA Functional Class (unimputed) through 24 months is shown in Figure 12.

Figure 11: NYHA Functional Class at 12 Months (ITT Population)



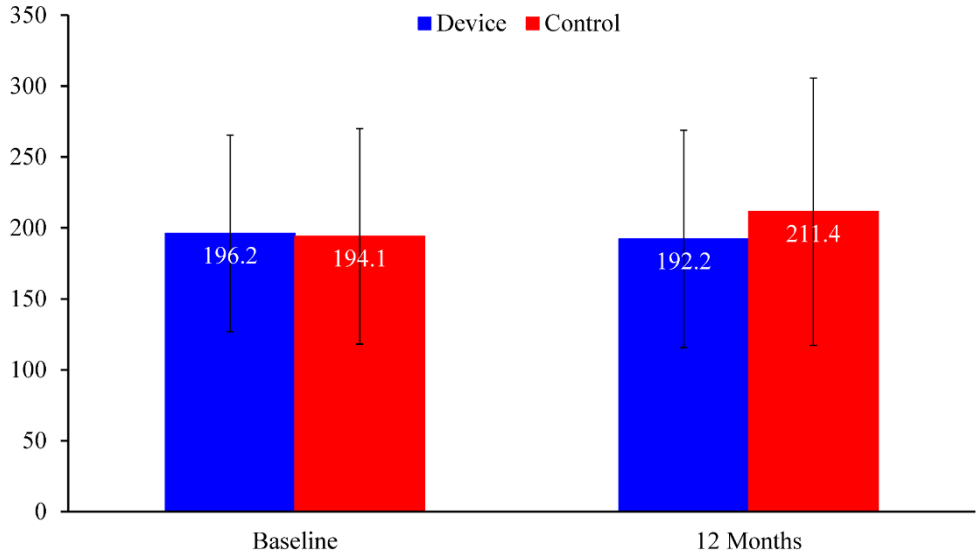
*Subjects died of HF prior to 12 months were imputed as having NYHA Class IV (Device group: 18; Control group: 41)

Figure 12: NYHA Functional Class through 24 Months (ITT Population)



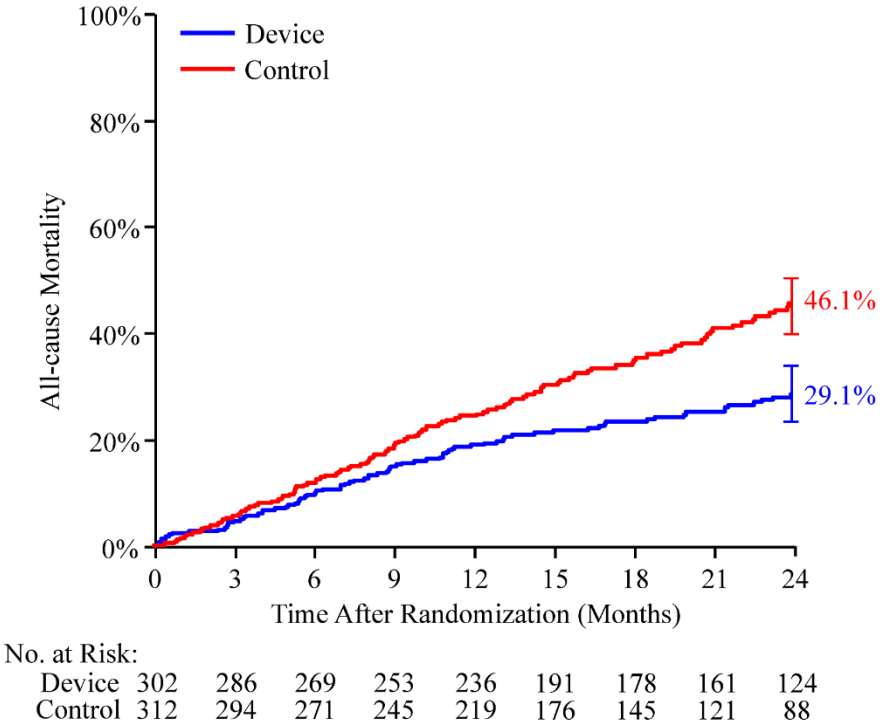
(8) Subjects in the Device group experienced significantly greater reduction in LVEDV between baseline and 12 months compared to those in the Control group (-3.71 mL vs. 17.06 mL), as shown in Figure 13. However, while this endpoint demonstrated superiority of the device when analyzed per protocol, the finding appears to be primarily related to pre-specified imputation of LVEDV values for subjects who died of HF prior to completing the 12-month follow-up. Specifically, subjects who died prior to 12 months were assigned the worst LVEDV change between baseline and 12 months observed for any subject in the analysis (126 mL). Because subjects in the Control group had a numerically higher (41 vs. 18) incidence of HF-related mortality than those in the Device group and the worst change in LVEDV was extreme, calculations for the LVEDV change from baseline in the Control group patients could be skewed mathematically to the larger end. It should be noted that neither clinically nor statistically significant difference in LVEDV change from baseline to 12 months was observed between the Device and Control groups based on un-imputed unpaired and paired analyses, or based on a responder analysis.

Figure 13: LVEDV Change from Baseline to 12 Months (ITT Population)



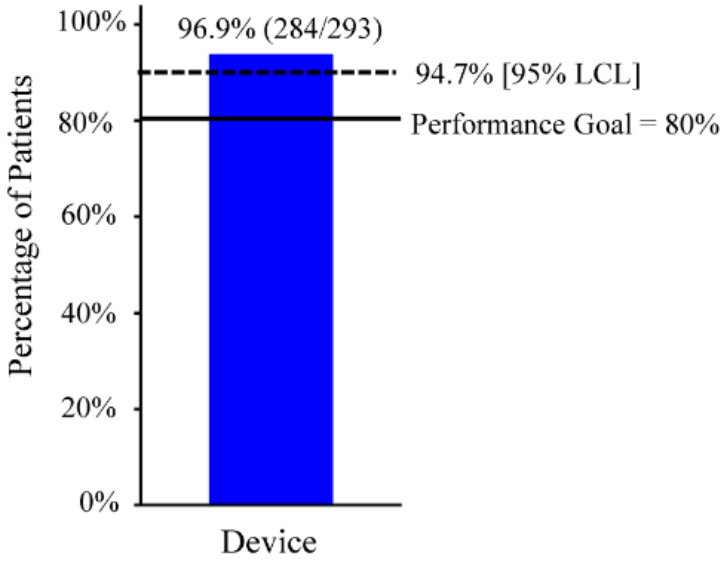
(9) Subjects in the Device group experienced significantly lower all-cause mortality at 24 months compared to those in the Control group (Kaplan-Meier estimate: 29.1% vs. 46.1%), as shown in Figure 14. The number needed to treat (NNT) to save one life within 24 months was 5.9 (95% CI: [3.9, 11.7]).

Figure 14: Kaplan-Meier Curve of All-Cause Mortality through 24 Months (ITT Population)



(10) The rate of freedom from all-cause mortality, stroke, MI, or non-elective cardiovascular surgery for device-related complications at 30 days was 96.9%, with a lower 95% confidence limit of 94.7%, which met the prespecified performance goal of 80%, as shown in Figure 15.

Figure 15: Freedom from All-Cause Mortality, Stroke, MI or Non-Elective Cardiovascular Surgery for Device-Related Complications at 30 Days (SA Population)



4. Adverse Events

The adverse events that occurred in the trial through 24 months are presented in Table 8.

Table 8: CEC-Adjudicated Adverse Events through 24 Months (SA Population)

Events	0-30 Days		0-12 Months		0-24 Months	
	Device	Control	Device	Control	Device	Control
All-cause mortality*	2.3% (7)	1.0% (3)	19.1% (57)	23.2% (70)	29.1% (80)	46.1% (121)
Cardiovascular	2.3% (7)	0.6% (2)	13.8% (40)	19.4% (57)	23.2% (60)	37.0% (93)
Heart failure	0.7% (2)	0.6% (2)	6.2% (17)	13.8% (39)	12.0% (28)	25.9% (61)
Stroke	0.7% (2)	0.0% (0)	2.9% (8)	2.9% (8)	4.4% (11)	5.1% (11)
Transient ischemic attack	0.0% (0)	0.0% (0)	1.1% (3)	1.1% (3)	1.1% (3)	1.1% (3)
Endocarditis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
ECL confirmed mitral stenosis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
LVAD implant	0.0% (0)	1.0% (3)	0.8% (2)	3.9% (11)	3.0% (6)	7.1% (16)

Events	0-30 Days		0-12 Months		0-24 Months	
	Device	Control	Device	Control	Device	Control
Heart transplant	0.0% (0)	0.0% (0)	0.8% (2)	2.2% (6)	1.4% (3)	3.6% (8)
Myocardial Infarction†	0.3% (1)	0.0% (0)	NA	NA	NA	NA
Major bleeding†	5.0% (15)	1.0% (3)	NA	NA	NA	NA
Iatrogenic ASD requiring intervention	0.7% (2)	NA	0.7% (2)	NA	0.7% (2)	NA
Device-related complications requiring non-elective CV surgery	0.3% (1)	NA	0.3% (1)	NA	0.3% (1)	NA

*Include adjudicated death events and deaths from the national death registry (for subjects who were lost to follow-up or withdrew from the COAPT study).
†Events were adjudicated up to 30 days post treatment visit.
Note: (1) Kaplan-Meier rate (# patients with events). Include only each patient's first occurrence of each event. (2) The follow-up duration was calculated from the randomization date. (3) ECL: Echocardiography Core Laboratory; LVAD: Left Ventricular Assists Device; ASD: Atrial Septal Defect; CV: Cardiovascular.

5. Subgroup Analyses

Pre-specified Analyses:

The primary safety and primary effectiveness endpoints were examined across the following 4 subgroups:

- Sex (male vs. female)
- Etiology of cardiomyopathy (ischemic vs. non-ischemic)
- LVEF (> 40% vs. ≤ 40%)
- Extreme surgical risk status (yes vs. no, as determined by the Central Eligibility Committee)

There was no clinically significant difference among the subgroups for the primary safety outcome, and there were no clinically significant interaction effects between treatment and subgroups for the primary effectiveness outcome.

Post hoc Analyses:

The results of the "Mitra-FR Trial," a trial conducted similarly to the COAPT Trial, became available about a month prior to the COAPT Trial results.[4,5] The Mitra-FR Trial was conducted solely in France by a group of independent investigators at 37 centers. The trial was designed to examine whether percutaneous mitral valve repair using the MitraClip

device could improve clinical outcomes in patients who have chronic HF with reduced LVEF and severe secondary MR. The trial randomized (1:1) a total of 304 subjects into two study groups: MitraClip + medical therapy (Device group) and medical therapy alone (Control group). The trial results showed that there was no significant difference between the Device group and the Control group in the primary composite endpoint of all-cause mortality or unplanned HF hospitalization at 12 months (54.6% vs. 51.3%). Specifically, the rate of all-cause mortality was 24.3% in the Device group and 22.4% in the Control group; the rate of unplanned HF hospitalization was 48.7% in the Device group and 47.4% in the Control group.

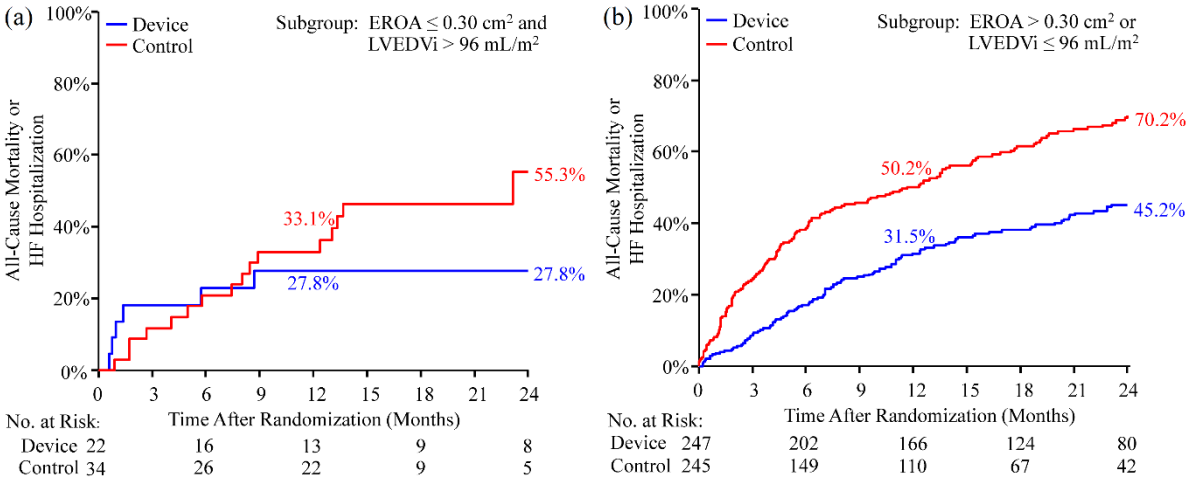
A comparison of the baseline characteristics of the subjects enrolled in the COAPT Trial and the Mitra-FR Trial suggests that differences existed between the two trials. Specifically, the Mitra-FR subjects on average had less severe MR and more dilated left ventricles as compared to the COAPT subjects, as indicated by the effective regurgitant orifice area (EROA) and left ventricular end-diastolic volume index (LVEDVi), respectively, shown in Table 9.

Table 9: Comparison in EROA and LVEDVi between Mitra-FR and COAPT

Baseline Characteristics	Mitra-FR	COAPT
EROA (mean ± SD; cm^2)	0.31 ± 0.11	0.41 ± 0.15
LVEDVi (mean ±SD; mL/m^2)	135 ± 35	101 ± 34

To explore potential correlation between the clinical outcomes and the baseline EROA and LVEDVi, a *post hoc* subgroup analysis was conducted on the COAPT dataset, by comparing the composite rate of all-cause mortality or HF hospitalization between subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2 and those with an EROA > 0.30 cm^2 or an LVEDVi ≤ 96 mL/m^2. Thresholds for this analysis were chosen to reflect the lower bound of the EROA (0.30 cm^2) defining, along with other parameters, Grade III (or 3+) MR as per the 2017 ASE Recommendation for Noninvasive Evaluation of Native Valvular Regurgitation and the median LVEDVi value in the COAPT Trial (96 mL/m^2).[5] A total of 22 subjects in the Device group and 34 subjects in the Control group had an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2. The results of the subgroup analysis are shown in Figure 16. Similar to the Mitra-FR patient population, among COAPT subjects with relatively less severe MR and larger left ventricles, those in the Device group did not experience a clinically meaningful benefit for all-cause mortality or HF hospitalization at the 12-month timepoint compared to those in the Control group (33.1% vs. 27.8%; Figure 16a). For the remaining COAPT subjects (those with an EROA > 0.3 cm^2 or an LVEDVi $\leq 96 mL/m^2$; Figure 16b), the difference in all-cause mortality or HF hospitalization seen in the overall population was maintained. This finding appears to shed some light on the discrepancies between the overall results of the COAPT and Mitra-FR Trials.

Figure 16: Subgroup Analysis Stratified by EROA and LVEDVi



Despite the absence of benefit of reduced all-cause mortality or HF hospitalization in the subgroup with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2, clinically meaningful improvements in the overall 6MWD (as shown in Figure 17; 11 subjects in the Device group and 26 subjects in the Control group had 6MWD values) and KCCQ (as shown in Figure 18; 15 subjects in the Device group and 27 subjects in the Control group had KCCQ values) compared to baseline were observed in Device group patients, an effect not observed in the same sub-population of the Control group. However, because of the nature of the *post hoc* subgroup analysis and the small sample size in the subgroup with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2, no statistical or clinical intra-group inferences can be made.

Figure 17: 6MWD for Subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2

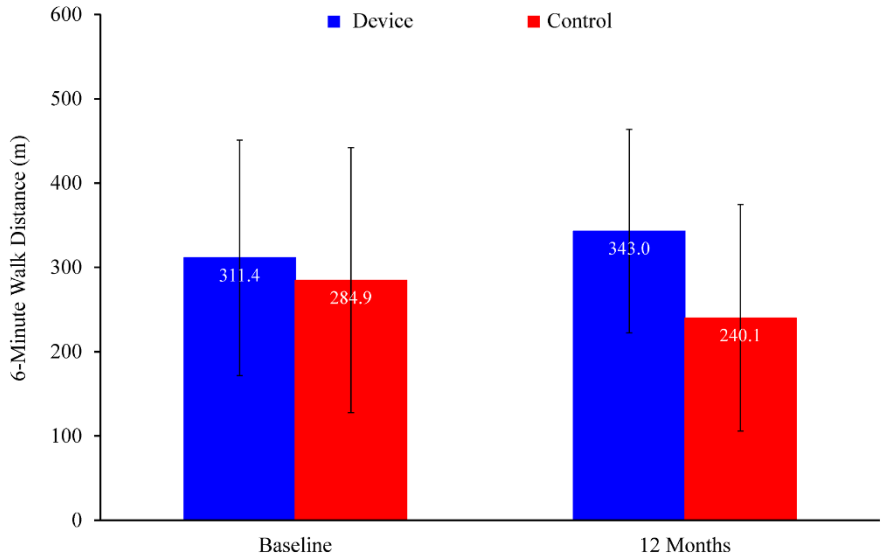
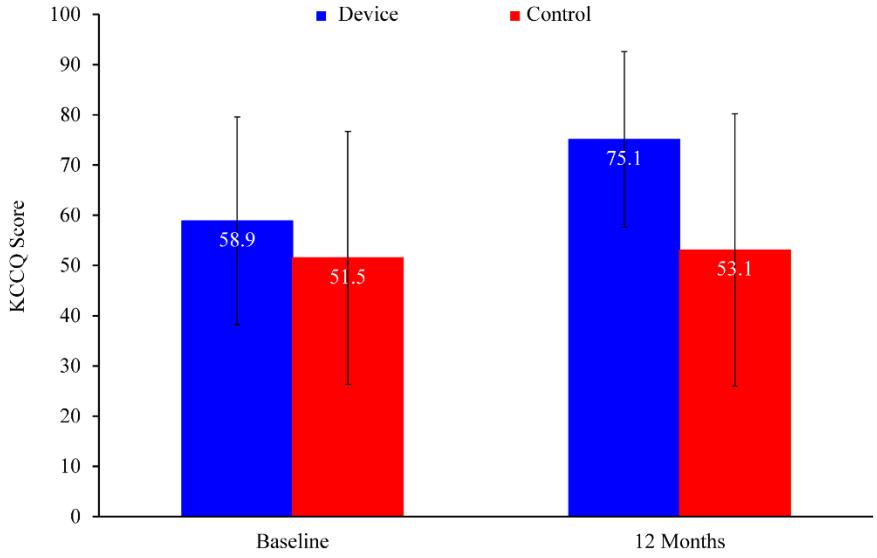


Figure 18: KCCQ Score for Subjects with an EROA ≤ 0.30 cm^2 and an LVEDVi > 96 mL/m^2



6. Procedural Data

The procedural data of the Device group are summarized in Table 10.

Table 10: Procedural Data Summary for Device Subjects – AT Population

Procedure Data	Device (N=294)
MitraClip Procedure Attempted	100.0%
Implant Rate	98.0%
Number of Clips Implanted	
0 Clip	2.0%
1 Clip	36.4%
2 Clips	53.1%
3 Clips	8.2%
4 Clips	0.3%
Total Number of Clips Implanted	495
Total Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 163.0 ± 117.5 (294) 146.5 (108.0, 199.0)

Procedure Data	Device (N=294)
Device Procedure Time (min) Mean ± SD (n) Median (Q1, Q3)	 118.8 ± 63.3 (283) 106.0 (73.0, 148.0)
Device Time (min) Mean ± SD (n) Median (Q1, Q3)	 82.6 ± 80.6 (288) 65.5 (40.0, 100.0)
Fluoroscopy Duration (min) Mean ± SD (n) Median (Q1, Q3)	 33.91 ± 23.15 (285) 29.50 (18.60, 43.00)

7. Pediatric Extrapolation

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

(11) Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical trial included 641 investigators of which none was a full-time or part-time employee of the sponsor and nineteen (19) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3
- Significant payment of other sorts: 14
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 2

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

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

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical trial, subjects in the Device group had a significantly lower annualized rate of recurrent HF hospitalizations and all-cause recurrent hospitalizations, respectively, as compared to those in the Control group (0.358 vs. 0.679 and 1.062 vs. 1.464, respectively).

The MitraClip device was found to be generally effective in reducing secondary MR; the proportion of subjects in the Device group with an MR severity grade of 3+ or more decreased from 100% at baseline to 7.4% at 30 days post randomization. There was a significantly greater proportion of subjects having an MR severity grade of 2+ or less in the Device group than in the Control group at 12 months post randomization (94.8% vs. 46.9%).

The difference in the effectiveness in reducing secondary MR between MitraClip + GMDT (Device) and GDMT alone (Control) was further manifested through the different degrees of improvements seen in QoL, NYHA class, functional capacity, and the rate of HF hospitalization between the two study groups. Subjects in the Device group experienced a significantly greater improvement in KCCQ Overall Summary Score at 12 months over baseline compared to those in the Control group (12.50 vs. -3.56), and a greater proportion of subjects in the Device group had an NYHA Functional Class of I or II at 12 months compared to those in the Control group (72.2% vs. 49.6%). In addition, subjects in the Device group experienced significantly greater preservation of functional capacity as assessed by the change in 6MWD at 12 months over baseline compared to those in the Control group (-2.17 m vs. -60.03 m).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the clinical study conducted to support approval of the expanded indication for use as described above.

The pivotal clinical trial has shown that the 12-month rate of freedom from device-related complications (including SLDA, device embolizations, endocarditis requiring surgery, ECL confirmed mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device related complications requiring non-elective cardiovascular surgery) was 96.6%. In addition, the Device group was found to be non-inferior to the Control group in all-cause mortality at 12 months (Kaplan-Meier estimate:19.1% vs. 23.2%) and superior to the Control group in all-cause mortality at 24 months (Kaplan-Meier estimate: 29.1% vs. 46.1%).

C. Benefit-Risk Conclusions

The probable benefits of the MitraClip System include reduced secondary MR, improved heart failure classification (NYHA), improved QoL (KCCQ), better preserved functional capacity (6MWD), increased survival, and reduced hospitalizations.

The probable risks of the MitraClip System include device and procedure related complications such as death, stroke, SLDA, device embolization, myocardial infarction, major bleeding, iatrogenic atrial septal defect requiring intervention, and complications requiring non-elective cardiovascular surgery.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for the MitraClip System.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the MitraClip System for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) MR in patients with an LVEF ≥ 20% and ≤ 50%, and an LVESD ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

XIII. CDRH DECISION

CDRH issued an approval order on March 14, 2019. The final condition of approval cited in the approval order is described below.

The applicant must conduct the following post-approval study (PAS) and active surveillance study:

1. *Continued Follow-up of the COAPT Trial Pivotal Cohort*: This study will consist of all living subjects who were enrolled in the COAPT Trial pivotal cohort at participating institutions.

   The objective of this PAS is to characterize the clinical outcomes annually through 5 years post-procedure, unless noted otherwise. The key safety and effectiveness endpoints include all-cause mortality, stroke, single leaflet device attachment, device embolization, endocarditis requiring surgery, ECL confirmed mitral stenosis requiring surgery, HF related hospitalization, NYHA classification, 6MWD through 2 years, KCCQ score through 2 years, 36-Item Short Form Survey (SF-36) score through 2 years, mitral valve surgery (including type of surgery), new use of CRT, new use of single or dual chamber pacemaker, LVAD implant, heart transplant, additional MitraClip device intervention or *de novo* MitraClip device intervention, including reason for intervention, number of hospitalizations and reason for hospitalization (i.e., HF, cardiovascular, non-cardiovascular) through 2 years, number of days alive and out of hospital, number of days hospitalized, proportion of subjects living in the baseline location, new onset of permanent atrial fibrillation, mitral stenosis, clinically significant ASD that requires intervention, and dosages of GDMT.

2. *Registry-Based Continued Access Protocol (CAP) Cohort and Real-World Use Surveillances*: The applicant has agreed to work with the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry to ensure that FDA surveillances occur for the registry-based CAP cohort per approved protocol and for commercial uses of the MitraClip Systems for the secondary (or functional) mitral MR indication. The surveillances will be carried out to characterize the clinical outcomes of the CAP cohort annually through 5 years post-procedure and to assess the real-world use of the commercial MitraClip System to ensure that the device is used in appropriate circumstances, respectively. The surveillance of the CAP cohort will consist of all living CAP subjects who were enrolled at participating institutions, and the surveillance of the real-world use will involve a minimum of 100 representative institutions across the United States and a total of 5000 consecutively treated patients at these participating institutions. Patients will be followed through 5 years post procedure. The clinical data through one (1) year will be collected through the TVT Registry. The follow-up data (including all-cause mortality, stroke, repeat procedure for mitral valve-related dysfunction, and hospitalization) from year 2 through year 5 post procedure will be obtained through linking the TVT data with the Centers for Medicare and Medicaid Services (CMS) claims database.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to health from use of the device: See indications, contraindications, warnings, precautions, and adverse events in the device labeling.

Post-approval requirements and restrictions: See approval order.

XV. REFERENCES

[1] Rogers JK, Pocock SJ, McMurray JJV, Granger CB, Michelson EL, Östergren J, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology with application to charm-preserved. *European Journal of Heart Failure* 2014; 16:33–40.

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