SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Prosthesis, mitral valve, percutaneously delivered
Device Trade Name:	SAPIEN M3 Transcatheter Mitral Valve Replacement System
Device Procode:	NPU
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P250019
Date of FDA Notice of Approval:	December 22, 2025
Breakthrough Device:	Granted breakthrough device designation on June 13, 2024, because the device can provide for more effective treatment of an irreversibly debilitating disease; as well as represents a breakthrough technology and is in the best interest of patients.

II. INDICATIONS FOR USE

The SAPIEN M3 transcatheter mitral valve replacement system (SAPIEN M3 system) is indicated for the treatment of symptomatic moderate-to-severe or severe mitral regurgitation (MR) in patients who are deemed unsuitable for surgery or transcatheter edge-to-edge repair (TEER) therapy by a multidisciplinary heart team.

The SAPIEN M3 system is also indicated for the treatment of symptomatic mitral valve dysfunction (moderate-to-severe or severe MR, severe mitral stenosis (MS), or moderate MR with moderate MS) associated with mitral annular calcification (MAC) in patients who are deemed unsuitable for surgery or TEER therapy by a multidisciplinary heart team.

III. CONTRAINDICATIONS

The SAPIEN M3 system is contraindicated in patients who cannot tolerate any anticoagulation/antiplatelet regime or intraprocedural heparin; or who have active bacterial endocarditis or other infections.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the SAPIEN M3 system labeling.

V. DEVICE DESCRIPTION

The SAPIEN M3 system consists of the SAPIEN M3 transcatheter heart valve (model 9880TFX29M), SAPIEN M3 dock steerable catheter (Model 9880DDS), SAPIEN M3 dock, Edwards 23F guide sheath (model 9880GS), Edwards Commander M delivery system (model 9880CM29), and SAPIEN M3 crimper (model 9880CR).

The SAPIEN M3 transcatheter heart valve, as shown in Figure 1, is a bioprosthesis comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, three bovine pericardial tissue leaflets, polyethylene terephthalate (PET) fabric inner skirt, and full-frame outer skirt. The valve frame inflow and outflow are covered with expanded polytetrafluoroethylene (ePTFE). All bovine pericardium is treated according to the Carpentier-Edwards ThermaFix process.

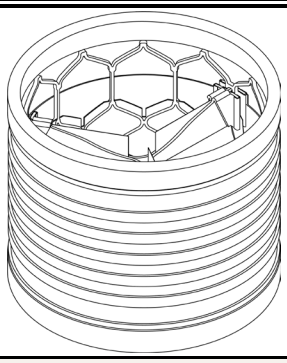

Figure 1. SAPIEN M3 Transcatheter Heart Valve.

The SAPIEN M3 dock steerable catheter, as shown in Figure 2, is comprised of a dock, steerable catheter, dock handle, a hydrophilic coated removable sleeve, and device preparation accessories. The steerable catheter is used for delivery of the SAPIEN M3 dock to its intended location. The removable sleeve covers the dock during encircling and is designed to facilitate encircling of the mitral apparatus and is removed after the dock is positioned in the anatomy. The sleeve has a radiopaque marker that aids in visualization. The dock handle aids in advancing and/or retrieving the dock and can be locked to the steerable catheter. A release assembly at the proximal end of the dock handle allows for suture slack or suture tension. The suture can be cut to release the dock from the dock handle.

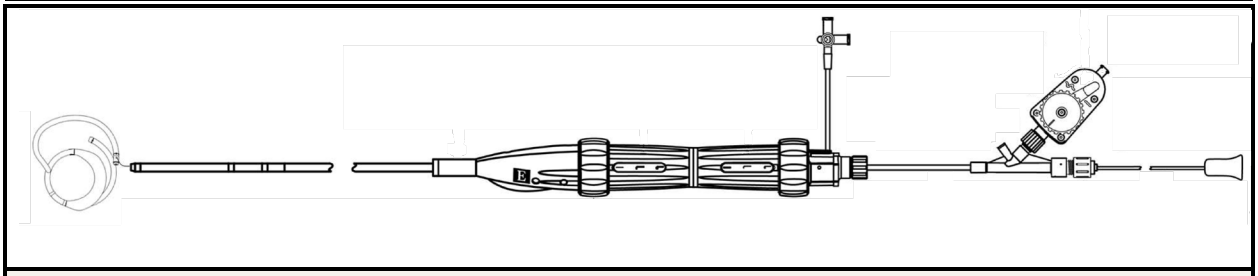

Figure 2. SAPIEN M3 Dock Steerable Catheter.

The SAPIEN M3 dock, as shown in Figure 3, is comprised of a nitinol core that is covered with ePTFE tubing and PET braid, with a self-expanding paravalvular leak (PVL) guard made of a PET covered nitinol braid. The dock encircles the native mitral leaflets which applies an inward force to the mitral apparatus, pulling the leaflets and chordae to the dock center and approximating the papillary muscles, to provide a landing zone for the SAPIEN M3 valve. The dock includes one (1) radiopaque marker to visualize proper deployment positioning within the anatomy, and two (2) radiopaque markers to visualize final deployment positioning of the PVL guard. The PVL guard expands at the medial commissure of the native mitral valve.

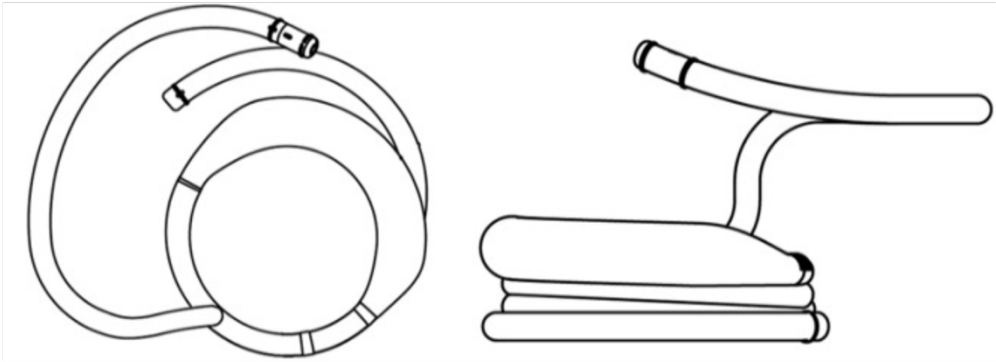

Figure 3. SAPIEN M3 Dock.

The Edwards 23F guide sheath, as shown in Figure 4, is comprised of an articulating hydrophilic coated guide sheath and a hydrophilic coated introducer. The sheath provides venous vascular access to cardiac structures enabling the introduction and removal of SAPIEN M3 devices. The guide sheath has a radiopaque soft tip, and a flex wheel which flexes the guide sheath towards the flush port. The introducer is compatible with a 0.035 inch (0.89 mm) guidewire.

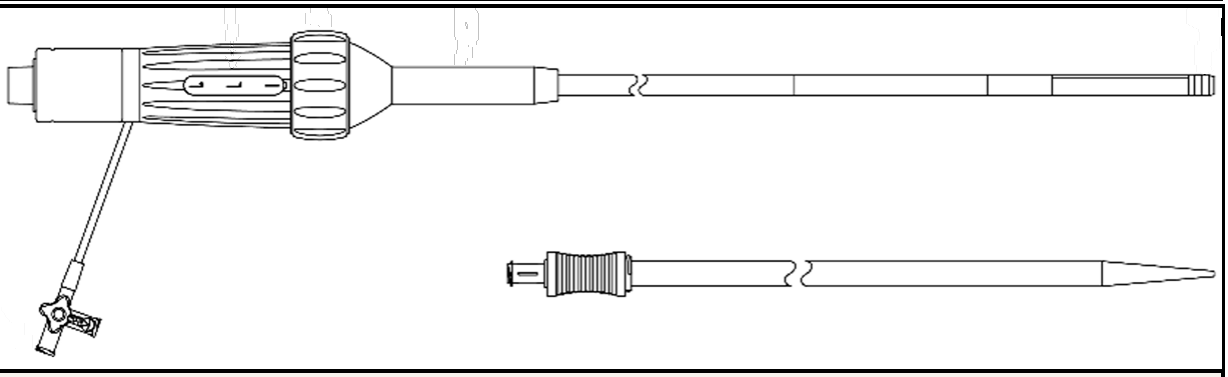

Figure 4. Edwards 23F Guide Sheath and Introducer.

The Edwards Commander M delivery system, as shown in Figure 5, is comprised of a balloon catheter and flex catheter with a tapered tip. The Edwards Commander M delivery system is used for delivery of the SAPIEN M3 valve. The handle contains a flex wheel and a balloon lock and the balloon catheter has radiopaque markers. The radiopaque markers indicate the flex catheter and guide sheath position during deployment and define the crimp location for the valve.

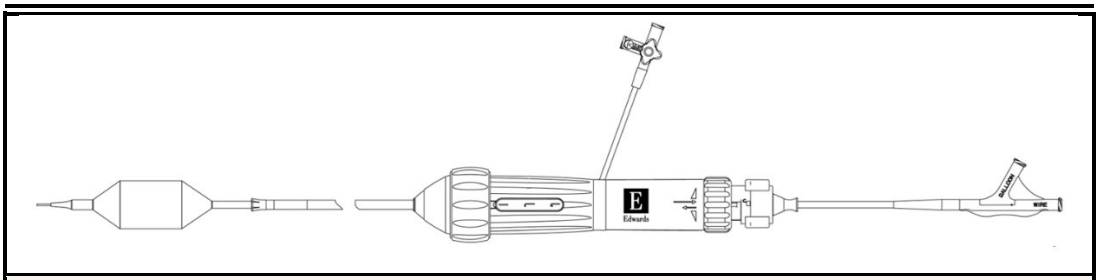

Figure 5. Edwards Commander M Delivery System.

The SAPIEN M3 crimper, as shown in Figure 6, is comprised of a housing and compression mechanism. The crimper reduces the diameter of the SAPIEN M3 valve while compressing it onto the delivery system. The Crimp Stopper is used to crimp the valve to its intended diameter.

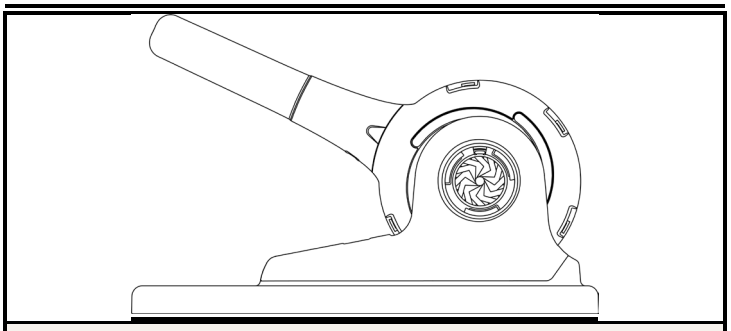

Figure 6. SAPIEN M3 Crimper.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are limited treatment options for patients with symptomatic moderate-to-severe or severe MR and those with mitral valve dysfunction due to severe MAC who are deemed unsuitable for surgery or TEER therapy due to comorbidities or anatomy. For both patient groups, medical therapy does not address the underlying disease condition and offers limited benefit in symptom management. For the latter patient group, additional treatment options include balloon mitral valvuloplasty and transcatheter mitral valve replacement performed transapically. 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 SAPIEN M3 system is commercially available in the European Economic Area, as well as in the United Kingdom and Switzerland. It 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 SAPIEN M3 system:

- Death
- Stroke or neurological dysfunction
- Cardiovascular injury – cardiac structure complications
- Cardiovascular injury – vascular complications
- Cardiovascular injury – access related complications
- Heart failure or low cardiac output/worsening of heart failure
- Renal insufficiency or renal failure
- Cardiogenic shock
- Cardiac arrest
- Pericardial effusion or cardiac tamponade
- Thromboembolism including air, calcific valve material, or thrombus
- Retroperitoneal bleed
- Arrhythmia
- Hypertension or hypotension
- New or worsening valvular regurgitation
- Bleeding/hematoma/hemorrhage
- Hemolysis that may require transfusion or intervention
- Device/valve thrombosis
- Respiratory insufficiency or respiratory failure
- Paravalvular or transvalvular leak
- Device deterioration (wear, fracture, calcification, or other)
- Reoperation/reintervention

- Device explants
- Pleural effusion
- Left ventricular outflow tract (LVOT) obstruction
- Emergency cardiac surgery
- Conversion to cardiac surgery
- Thoracic bleeding
- Valve stenosis
- Myocardial infarction
- Pulmonary edema
- Transient ischemic attack including clusters
- Device migration, malposition or embolization
- Infection including septicemia and endocarditis
- Allergic reaction to anesthesia, contrast media, or device materials
- Deterioration of native valve (leaflet tear/tearing, leaflet retraction, leaflet thickening, or other)
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Nonstructural valve dysfunction
- Atrial septal defect
- Syncope
- Conduction system defect which may require a permanent pacemaker
- Skin burn
- Mechanical failure of delivery system, and/or accessories
- Valve deployment in an unintended location
- Abnormal lab values (including electrolyte imbalance)
- Angina
- Anemia
- Fever
- Inflammation
- Pain or changes at the access site

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Nonclinical laboratory studies on the SAPIEN M3 system were performed in accordance with but not limited to: ISO 5840-1:2021*, Cardiovascular implants – Cardiac valve prostheses – Part 1: General Requirements*, and ISO 5840-3:2021, *Cardiovascular implants – Cardiac valve prostheses – Part 3: Heart valve substitutes implanted by transcatheter techniques*, along with relevant FDA guidance documents.

1. Biocompatibility

Biocompatibility assessments were completed on the SAPIEN M3 system in accordance with ISO 10993-1, *Biological Evaluation of Medical Devices - Part 1: Evaluation and testing within a risk management process*, and the FDA Guidance for Industry and Food and Drug Administration Staff, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*. The required testing for each component was determined based on the nature and duration of body contact per ISO 10993-1. The test articles consisted of patient-contacting device components after exposure to all manufacturing processes, including sterilization. The crimper is defined as a non-contacting device. However, the crimper jaws have wet product contact with the valve during crimping. Therefore, testing conducted on the valve by inference qualifies the crimper jaws. The biocompatibility test results for the SAPIEN M3 valve, SAPIEN M3 dock, SAPIEN M3 dock steerable catheter, Edwards 23F guide sheath, and Commander M delivery system are summarized in the tables below.

Table 1. Summary of SAPIEN M3 Valve and Dock Biocompatibility Assessments.

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method	Non-cytotoxic
Sensitization	Guinea pig maximization test	Non-sensitizing
Irritation/ Intracutaneous Reactivity	Rabbit intracutaneous reactivity test	Non-irritating
Pyrogenicity	Rabbit pyrogen test – materials mediated	Non-pyrogenic
Acute systemic toxicity	Mouse systemic injection test	Not inducing significantly greater biological reactions than the control extracts
Implantation	4-week rabbit intramuscular implantation test	No significant microscopic evidence of cytotoxicity relative to the control
	90-day systemic toxicity in rabbits via intramuscular implantation	No toxicity of biological significance relative to the control
Hemocompatibility	*In vitro* hemolysis (indirect contact)	Non-hemolytic
	In vitro hemolysis (direct contact)	Non-hemolytic
	Complement activation test	No risk to activate complement

Biological Effect Per ISO 10993-1	Test Method	Results
	In vivo thrombogenicity with domestic sheep	No evidence of clinically significant thrombosis or thromboembolism after implantation for up to 20 weeks
Genotoxicity	Ames assay – plate incorporation	Non-mutagenic
	Chromosomal aberration assay	Non-clastogenic
Physicochemical	Chemical characterization of volatile organic compounds, semivolatile organic compounds, nonvolatile organic compounds, elements and toxicological risk assessment	Compounds detected and identified in extracts of the test articles were present at levels that would not be expected to pose any significant risk of adverse systemic toxicological effects

Table 2. Summary of SAPIEN M3 Dock Steerable Catheter Biocompatibility Assessments.

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method	Non-cytotoxic
Sensitization	Guinea pig maximization test	Non-sensitizing
Irritation/ Intracutaneous Reactivity	Rabbit intracutaneous reactivity test	Non-irritating
Pyrogenicity	Rabbit pyrogen test – materials mediated	Non-pyrogenic
Acute systemic toxicity	Mouse systemic injection test	Not inducing significantly greater biological reactions than the control extracts
Hemocompatibility	*In vitro* hemolysis (indirect contact)	Non-hemolytic
	In vitro hemolysis (direct contact)	Non-hemolytic
	Partial thromboplastin time test	No impact on the Unactivated Partial Thromboplastin Time
	Platelet and leukocyte count test	No impact on platelet and leukocyte counts

Biological Effect Per ISO 10993-1	Test Method	Results
	Complement activation test	No risk to activate complement
	In vivo thrombogenicity with domestic pigs	No clinically significant risk of thrombosis or thromboembolism

Table 3. Summary of Edwards 23F Guide Sheath Biocompatibility Assessments.

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method	Non-cytotoxic
Sensitization	Guinea pig maximization test	Non-sensitizing
Irritation/ Intracutaneous Reactivity	Rabbit intracutaneous reactivity test	Non-irritating
Pyrogenicity	Rabbit pyrogen test – materials mediated	Non-pyrogenic
Acute systemic toxicity	Mouse systemic injection test	Not inducing significantly greater biological reactions than the control extracts
Hemocompatibility	*In vitro* hemolysis (indirect contact)	Non-hemolytic
	In vitro hemolysis (direct contact)	Non-hemolytic
	Partial thromboplastin time test	No impact on the Unactivated Partial Thromboplastin Time
	Platelet and leukocyte count test	No impact on platelet and leukocyte counts
	Complement activation test	No risk to activate complement
	In vivo thrombogenicity with domestic pigs	No clinically significant risk of thrombosis or thromboembolism

Table 4. Summary of Commander M Delivery System Biocompatibility Assessments.

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method	Non-cytotoxic
Sensitization	Guinea pig maximization test	Non-sensitizing
Irritation/ Intracutaneous Reactivity	Rabbit intracutaneous reactivity test	Non-irritating

Biological Effect Per ISO 10993-1	Test Method	Results
Pyrogenicity	Rabbit pyrogen test – materials mediated	Non-pyrogenic
Acute systemic toxicity	Mouse systemic injection test	Not inducing significantly greater biological reactions than the control extracts
Hemocompatibility	*In vitro* hemolysis (indirect contact)	Non-hemolytic
	In vitro hemolysis (direct contact)	Non-hemolytic
	Complement activation test	No risk to activate complement
	In vivo thrombogenicity with domestic pigs	No clinically significant risk of thrombosis or thromboembolism

2. Bench Testing

A summary of the bench testing results is summarized in Table 5.

Table 5. Summary of SAPIEN M3 Transcatheter Mitral Valve Replacement System Bench Testing.

Test	Purpose	Results
SAPIEN M3 Transcatheter Heart Valve		
Corrosion resistance	To evaluate the corrosion resistance of the SAPIEN M3 valve frame in accordance with ASTM F2129.	Met prespecified corrosion resistance acceptance criteria.
Frame fatigue testing	To assess the fatigue resistance of the SAPIEN M3 valve frames under cyclic loading for up to 600 million cycles.	No fractures observed at minimum 10x magnification following 600 million cycles of fatigue testing.
Crush resistance	To characterize the crush resistance of the SAPIEN M3 valve frame from opposing lateral force after reaching final diameter.	Resisted permanent deformation and generated acceptable crush resistance forces.
Radial Strength	To characterize radial strength and stiffness of the SAPIEN M3 valve frame	Met prespecified minimum radial strength.

Test	Purpose	Results
Valve expansion and foreshortening	To evaluate the relationship of the SAPIEN M3 valve length and diameter during expansion.	Demonstrated to have acceptable expansion dimensions.
Migration testing	To assess the resistance of the SAPIEN M3 valve to migration that would compromise hemodynamic performance or result in embolization.	No migration or embolization
Magnetic resistance imaging (MRI) compatibility	To evaluate MRI safety and compatibility of the SAPIEN M3 valve and ensure that the SAPIEN M3 valve is not affected by scanning at 1.5 Tesla and 3.0 Tesla field strengths.	SAPIEN M3 valve can be labeled “MR Conditional.”
Hydrodynamic assessment	To determine the hydrodynamic performance of the SAPIEN M3 valve in terms of effective orifice area and regurgitation under mitral cardiac conditions.	Met prespecified minimum hydrodynamic performances.
Flow visualization	To qualitatively investigate flow characteristics of the SAPIEN M3 valve under mitral conditions.	Exhibited similar flow as the reference valve.
Particle image velocimetry	To assess quantitatively the flow fields and hemolytic potential downstream of the SAPIEN M3 valve.	Exhibited similar flow characteristics to the commercial reference valve.
Bernoulli relationship	To verify whether the Bernoulli relationship applies to clinical pressure drop measurements.	Exhibited similar pressure drop and Bernoulli coefficient values to the commercial reference valve.
Accelerated wear testing	To assess SAPIEN M3 valve durability to 200 million cycles.	Met minimum prespecified hydrodynamic performance specifications and no abnormal wear patterns observed.

Test	Purpose	Results
Dynamic failure mode testing	To characterize potential failure modes affecting the durability of the SAPIEN M3 valve.	Demonstrated a gradual degradation failure mode consistent with the commercial reference valve.
Finite element analysis	To determine mechanical strain during SAPIEN M3 valve loading, deployment and cyclic loading. Results used to assess the fatigue life of the device.	No fracture of SAPIEN M3 valve structural components predicted within a minimum of 600 million cycles under clinically representative challenging conditions.
SAPIEN M3 Dock		
Magnetic resistance imaging (MRI) compatibility	To evaluate MRI safety and compatibility of the SAPIEN M3 dock and ensure that the SAPIEN M3 dock is not affected by scanning at 1.5 Tesla and 3.0 Tesla field strengths	SAPIEN M3 dock can be labeled “MR Conditional.”
Corrosion resistance	To evaluate the corrosion resistance of the SAPIEN M3 dock in accordance with ASTM F2129.	Met prespecified corrosion resistance acceptance criteria.
Dock fatigue testing	To assess the fatigue resistance of the SAPIEN M3 dock under cyclic loading for up to 600-million cycles.	No fractures observed at minimum 10x magnification following 600 million cycles of fatigue testing.
Finite element analysis	To determine mechanical strain during dock loading, deployment and cyclic loading. Results used to assess the fatigue life of the device.	No fracture of SAPIEN M3 dock structural components predicted within a minimum of 600 million cycles under clinically representative challenging conditions.
SAPIEN M3 Dock Steerable Catheter		
Dimensional inspections	To verify system level dimensions to ensure product meets specifications.	Met design requirements and acceptance criteria.
Radiopacity	To verify that the SAPIEN M3 dock steerable catheter tip, marker bands and pull rings are visible under fluoroscopy.	Visible under fluoroscopy.

Test	Purpose	Results
Tensile verification	To verify that tensile strength of bonds meets pre-defined specifications	Met design requirements and acceptance criteria.
Visual inspection	To verify that the external surface of catheter working length is free from defects.	Met design requirements and acceptance criteria.
Hemostasis	To verify that the steerable catheter maintains hemostasis while inside the guide sheath.	Met design requirements and acceptance criteria.
Hydrophilic coating characterization	To evaluate and characterize the lubricity and integrity of the hydrophilic coating after simulated use.	Lubricity and particulate sizes and counts within established limits.
Simulated use	To simulate the use of the SAPIEN M3 dock steerable catheter with the SAPIEN M3 dock in a clinical setting, including flushing, tracking, kink resistance, and SAPIEN M3 dock deployment and retrieval.	Met design requirements and acceptance criteria.
Edwards 23F Guide Sheath		
Dimensional inspections	To verify system level dimensions to ensure product meets specifications.	Met design requirements and acceptance criteria.
Radiopacity	To verify that the tip of the guide sheath is visible under fluoroscopy.	Visible under fluoroscopy.
Tensile verification	To verify that tensile strength of bonds meets pre-defined specifications	Met design requirements and acceptance criteria.
Visual inspection	To verify that the external surface of the guide sheath working length is free from defects.	Met design requirements and acceptance criteria.
Hemostasis	To verify that hemostasis is maintained with a guidewire and other devices inside the guide sheath and without any devices present.	Met design requirements and acceptance criteria.

Test	Purpose	Results
Hydrophilic coating characterization	To evaluate and characterize the lubricity and integrity of the hydrophilic coating after simulated use.	Lubricity and particulate sizes and counts within established limits.
Simulated use	To simulate the use of the guide sheath with the SAPIEN M3 transcatheter mitral valve replacement system in a clinical procedure, including flushing, tracking, kink resistance, and insertion and removal forces.	Met design requirements and acceptance criteria.
Commander M Delivery System		
Dimensional inspections	To verify system level dimensions to ensure product meets specifications.	Met design requirements and acceptance criteria.
Radiopacity	To verify that flex tip, marker bands, and balloon shaft are visible under fluoroscopy.	Visible under fluoroscopy.
Balloon performance	Verification that the Commander M delivery system balloon functions as intended when subjected to the following testing: inflation/deflation, inflation pressure, burst pressure, balloon fatigue, deployed balloon dimensional inspection	Met design requirements and acceptance criteria.
Tensile verification	To verify that tensile strength of bonds meets pre-defined specifications	Met design requirements and acceptance criteria.
Visual inspection	To verify that the external surface of catheter working length is free from defects.	Met design requirements and acceptance criteria.
Hemostasis	To verify that the Commander M delivery system maintains hemostasis while inside the guide sheath and with the loader.	Met design requirements and acceptance criteria.

Test	Purpose	Results
Simulated use	To simulate the use of the Commander M delivery system with the SAPIEN M3 transcatheter mitral valve replacement system in a clinical setting, including flushing, tracking, kink resistance, and SAPIEN M3 valve deployment.	Met design requirements and acceptance criteria.
SAPIEN M3 Crimper		
Dimensional inspections	To verify system level dimensions to ensure product meets specifications.	Met design requirements and acceptance criteria.
Visual inspection	To verify that the external surface of the SAPIEN M3 crimper is free from defects.	Met design requirements and acceptance criteria.
Simulated use	To verify the ability of the SAPIEN M3 crimper to reliably crimp the SAPIEN M3 valve onto the Commander M delivery system.	Met design requirements and acceptance criteria.

3. Sterilization

The SAPIEN M3 valve is sterilized via terminal liquid sterilization (TLS) in accordance with ISO 14160:2020, *Sterilization of health care products -- Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives*. The validated TLS sterilization process demonstrated a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The SAPIEN M3 dock steerable catheter, Edwards 23F guide sheath, Commander M delivery system, and SAPIEN M3 crimper are sterilized via ethylene oxide (EO) in accordance with EN ISO 11135-1:2014+A1:2018, *Sterilization of health care products – Ethylene oxide – Requirements for development, validation and routine control of a sterilization process for medical devices*. The validated EO sterilization process demonstrated a minimum Sterility assurance level of 10^{-6}.

4. Packaging and Shelf-Life

The SAPIEN M3 valve is stored in a jar filled with a sterile glutaraldehyde solution, which is sealed with an integrated gasket lid to form the primary sterile barrier. The jar is contained within the inner packaging assembly and inserted into a shelf carton to complete the protective packaging system for the SAPIEN M3 valve.

The SAPIEN M3 dock steerable catheter and Edwards 23F guide sheath are secured to a Polyethylene Terephthalate Glycol (PETG) tray with a retainer. The PETG tray is inserted into a Tyvek pouch, which is sealed and inserted into a shelf carton and then a shipping box.

The Commander M delivery system is secured to a high-density polyethylene (HDPE) card with preformed protective connectors and tubes. The HDPE card is inserted into a Tyvek pouch, which is sealed and inserted into a shelf carton and then a shipping box.

The SAPIEN M3 crimper is secured to a PETG tray with an HDPE retainer. The PETG tray is sealed with a Tyvek lid and inserted into a shelf carton and then a shipping box.

The packaging validation for the sterile components of the SAPIEN M3 system was conducted per EN ISO 11607-1:2020, *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems*, and EN ISO 11607-2:2020, *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes*. The packaging validation demonstrated that the packaging system was able to maintain a sterile barrier after exposure to temperature, distribution conditioning, and aging.

The shelf life for the SAPIEN M3 valve is 3 years, as demonstrated by packaging integrity and product functional testing on aged samples.

The shelf life for all remaining sterile components of the SAPIEN M3 system (SAPIEN M3 dock, SAPIEN M3 dock steerable catheter, Commander M delivery system, and SAPIEN M3 crimper) and the Edwards 23F guide sheath is 2 years, as demonstrated by packaging integrity and product functional testing on aged samples.

B. Animal Studies

The SAPIEN M3 system underwent Good Laboratory Practice-compliant preclinical *in vivo* evaluations in an ovine model (chronic study) and porcine model (acute study), as summarized in Table 6.

Table 6. Summary of SAPIEN M3 Transcatheter Mitral Valve Replacement System Animal Studies.

Chronic 140-day (20 week) Study	
Sample size / animal model	12 adult sheep
Test articles	12 SAPIEN M3 valves, 12 SAPIEN M3 docks.
Technique	The study animals were implanted with the SAPIEN M3 dock and valve in the mitral position via transfemoral, transseptal approach through the Edwards 23F guide sheath utilizing the SAPIEN M3 dock steerable catheter and Commander M delivery system.

Objective	To evaluate the chronic *in vivo* safety of the valve with respect to the following items: – adverse clinical events – device performance – systemic toxicity
Results	Ten (10) of the twelve (12) study animals survived to their 140 day endpoint and passed all protocol requirements. One animal died on Day 68 during anesthetic recovery from the scheduled echography assessment. One animal was electively sacrificed on Day 71 for ethical reasons concerning severe dyspnea and non-response to diuretic treatment.
Conclusion	All the implants showed appropriate healing, no structural damage or deterioration, or any evidence of device embolization, migration or any other clinically significant device-related events under gross and histopathological assessment.
Acute Study	
Sample size / animal model	3 adult pigs
Test articles	3 Edwards 23F guide sheaths, 3 SAPIEN M3 dock steerable catheters, 3 Commander M delivery systems.
Technique	The SAPIEN M3 dock steerable catheter was advanced through the Edwards 23F guide sheath using a transseptal approach and the SAPIEN M3 dock was implanted. The SAPIEN M3 dock steerable catheter was removed and the Commander M delivery system was advanced to the implant site, inflated and deflated, then removed through the Edwards 23F guide sheath, according to the Instructions for Use.
Objective	To evaluate the acute *in vivo* safety of the SAPIEN M3 transcatheter mitral valve replacement system with respect to hemocompatibility (thrombogenicity).
Results	Activated clotting time (ACT) levels were maintained between 250 and 400 seconds throughout the procedures. No clinically significant thrombus or clinically significant thromboembolism was observed in the test articles as compared to the control articles following a clinically relevant dwell time.
Conclusion	There were no clinically significant signs of thrombus caused by the Edwards 23F guide sheath, SAPIEN M3 dock steerable catheter, or Commander M delivery system.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of transcatheter mitral valve replacement (TMVR) with the SAPIEN M3 system in patients with symptomatic moderate-to-severe or severe MR and those with mitral valve dysfunction due to severe MAC who are deemed unsuitable for surgery or TEER therapy under IDE G170152 (entitled the "ENCIRCLE" study). The ENCIRCLE study included three cohorts, namely, Main Cohort, MAC Registry, and Failed TEER Registry. Data from the Main Cohort and MAC Registry were the basis for the PMA approval decision. A summary of the Main Cohort and MAC Registry clinical study is presented below.

The ENCIRCLE study utilized: an independent Case Review Board, which reviewed cases submitted by the investigational sites to determine if the patients being considered were appropriate candidates for the study; an Echocardiography Core Laboratory, which reviewed echocardiography images acquired at baseline and follow-up visits; a Computed Tomography (CT) Core Laboratory, which reviewed CT images acquired at baseline; an independent Data Safety Monitoring Board (DSMB), which was instructed to notify the applicant of any safety or compliance issues; and a Clinical Events Committee (CEC), which was responsible for adjudicating endpoint-related events reported during the study.

X.1. Summary of the Main Cohort

A. Study Design

The ENCIRCLE study Main Cohort was a prospective, single-arm, multicenter study. Patients in the Main Cohort were enrolled between June 9, 2020, and October 10, 2023. The database for this PMA application reflected data collected through February 3, 2025, and included 299 patients treated at 56 investigational sites in the US, Australia, Canada, Israel, Netherlands, and the United Kingdom.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ENCIRCLE study Main Cohort was limited to patients who met the following inclusion criteria:

   - 18 years of age or older
   - MR ≥3+ as assessed by the Echocardiography Core Laboratory
   - New York Heart Association (NYHA) functional class ≥ II
   - Per the Heart Team, commercially available surgical or transcatheter treatment options are deemed unsuitable due to clinical, anatomic, or technical considerations.
   - Patient's heart failure management has been optimized based on patient characteristics and applicable guidelines, and stable for at least 30 days prior to enrollment.
     Note: Patients who require significant changes to heart failure medication after enrollment but prior to the procedure must re-stabilize for 30 days to be eligible.

- The patient or patient's legal representative has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent.

Patients were not permitted to enroll in the ENCIRCLE study Main Cohort if they met any of the following exclusion criteria:

- Mitral/cardiac anatomy that would preclude appropriate delivery and deployment of the dock or valve, including but not limited to:
  - Annular dimensions that could potentially increase the risk of paravalvular leak (as assessed by the CT Core Laboratory)
  - Commissural jet or lateral commissural flail/prolapse that could potentially increase the risk of paravalvular leak
  - Medial commissural flail or prolapse
  - Calcification that would interfere with the SAPIEN M3 transcatheter mitral valve replacement system during delivery or after implantation; if potential for interference is uncertain, see MAC Registry
  - Interatrial septum or left atrium not suitable for transcatheter trans-septal access
  - Left ventricular end diastolic diameter (LVEDD) ≥75 mm as assessed by the Echocardiography Core Laboratory
  - Sub-valvular anatomy that is unsuitable for dock encircling as assessed by the CT Core Laboratory
  - Significant risk of left ventricular outflow tract (LVOT) obstruction as assessed by the CT core laboratory
- Inappropriate anatomy for femoral introduction and delivery of the SAPIEN M3 dock and valve
- Presence of any device that will contact or interfere with the SAPIEN M3 transcatheter mitral valve replacement system during delivery or after implantation
- Left ventricular ejection fraction (LVEF) <25% as assessed by the Echocardiography Core Laboratory
- Severe right ventricular dysfunction as assessed by the Echocardiography Core Laboratory
- Need for aortic, tricuspid, or pulmonic valve intervention within the next 12 months
- History of heart transplant
- Cardiac imaging evidence of intracardiac mass, thrombus, or vegetation
- Active bacterial endocarditis within 180 days of the procedure
- Hemodynamic instability requiring inotropic or mechanical support within 30 days of the procedure.
- Myocardial infarction (MI) within 30 days of the procedure
- Clinically significant untreated coronary artery disease (CAD) requiring revascularization
- Any percutaneous cardiovascular intervention, cardiovascular surgery, or carotid surgery within 30 days of the procedure.
- Stroke or transient ischemic attack within 90 days of the procedure
- Irreversible, severe pulmonary hypertension (e.g., pulmonary artery systolic pressure ≥2/3 systemic pressure)

- Chronic obstructive pulmonary disease (COPD) requiring home oxygen therapy or chronic outpatient oral steroid use
- Renal insufficiency (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or receiving renal replacement therapy
- Liver disease (cirrhosis of the liver [Child-Pugh class B or C])
- Planned surgery within the next 12 months
- Inability to tolerate or a medical condition precluding treatment with antithrombotic (antiplatelet, anticoagulant) therapy, including heparin administration during the procedure
- Active infection requiring current antibiotic therapy (if temporary illness, patient may be a candidate 2 weeks after discontinuation of antibiotics)
- Active SARS-CoV-2 infection (Coronavirus-19 [COVID-19]) or previously diagnosed with COVID-19 with sequelae that could confound endpoint assessments (as assessed by the Case Review Board)
- Leukopenia (White Blood Cells (WBC) <3000 cells/μL), anemia (Hemoglobin (Hgb) <9 g/dL), thrombocytopenia (platelet <50,000 cells/μL), history of bleeding diathesis or coagulopathy, or hypercoagulable states
- Refusal of blood products
- Female who is pregnant or lactating
- Estimated life expectancy <12 months due to non-cardiac conditions
- Participating in another investigational drug or device study that has not reached its primary endpoint
- Patient considered to be part of a vulnerable population

2. Follow-up Schedule

Follow-up time points included discharge, 30 days, 6 months, and annually through 5-years post-procedure. Preoperative and post-operative assessments included physical assessment, laboratory measurements, imaging tests, as well as health status and quality of life (QoL) questionnaires. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Endpoint

The primary endpoint was a non-hierarchical composite of all-cause death and heart failure rehospitalization at 1year. Heart failure rehospitalization was defined as hospitalization for symptoms, signs and/or laboratory evidence of worsening heart failure; and administration of intravenous or mechanical heart failure therapies.

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

$$H_0: \pi \geq 45\%$$
$$H_A: \pi < 45\%$$

where π is the true event rate at 1 year and 45% was a performance goal. The Kaplan-Meier analysis was used to estimate the event rate, the 95% confidence interval was computed using Greenwood's formula, and the p-value was calculated using the Wald Test with Greenwood's formula. An initial sample size of 250 patients was estimated to provide at least 85% power to reject the null hypothesis at a one-sided significance level of 2.5%. The study incorporated a pre-planned interim analysis for sample size re-estimation, with the potential to increase the sample size to a maximum of 600 patients. During the interim analysis the enrollment was allowed to continue.

Secondary Endpoints

Once the primary endpoint was met, testing for statistical significance was performed on 4 pre-specified non-hierarchical hypothesis-driven secondary endpoints at 1 year compared to baseline, as listed in Table 7. To keep the overall type I error of 0.05, the Hochberg method was applied for multiplicity adjustment.

Table 7. List of Hypothesis-Driven Secondary Endpoints.

No.	Secondary Endpoint	Null and Alternative Hypotheses	Statistical Test*
1	Improvement in MR severity at 1 year over baseline	H_0: $p = 0.5$ H_1: $p > 0.5$	Sign test
2	Improvement in NYHA class at 1 year over baseline	H_0: $p = 0.5$ H_1: $p > 0.5$	Sign test
3	Improvement in KCCQ summary score at 1 year over baseline	H_0: $\mu_D \leq 0$ H_1: $\mu_D > 0$	Paired *t*-test
4	Improvement in LVEDVi at 1 year over baseline	H_0: $\mu_D \geq 0$ H_1: $\mu_D < 0$	Paired *t*-test

MR: mitral regurgitation; NYHA: New York Heart Association; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDVi: left ventricular end-diastolic volume index; H_0: null hypothesis; H_1: alternative hypothesis

*The Hochberg method was applied for multiplicity adjustment to keep the overall type I error of 0.05.

Descriptive Endpoints

Key descriptive endpoints included the following:

- KCCQ overall summary score
- EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire visual analog score
- NYHA functional class
- 6-minute walk test distance (6MWT) distance
- Proportion of patients with MR ≤1+

B. Patient Accountability

At the time of database lock, a total of 299 patients out of 1171 patients enrolled for screening had the procedure started (All-Treated [AT] Population) in the Main Cohort and 287 patients had the study valve implanted (Valve Implant [VI] Population). The most common reason for screening failure was mitral/cardiac anatomy that precluded appropriate delivery and deployment of the dock or valve. Patient accountability through 1 year is summarized in Figure 7.

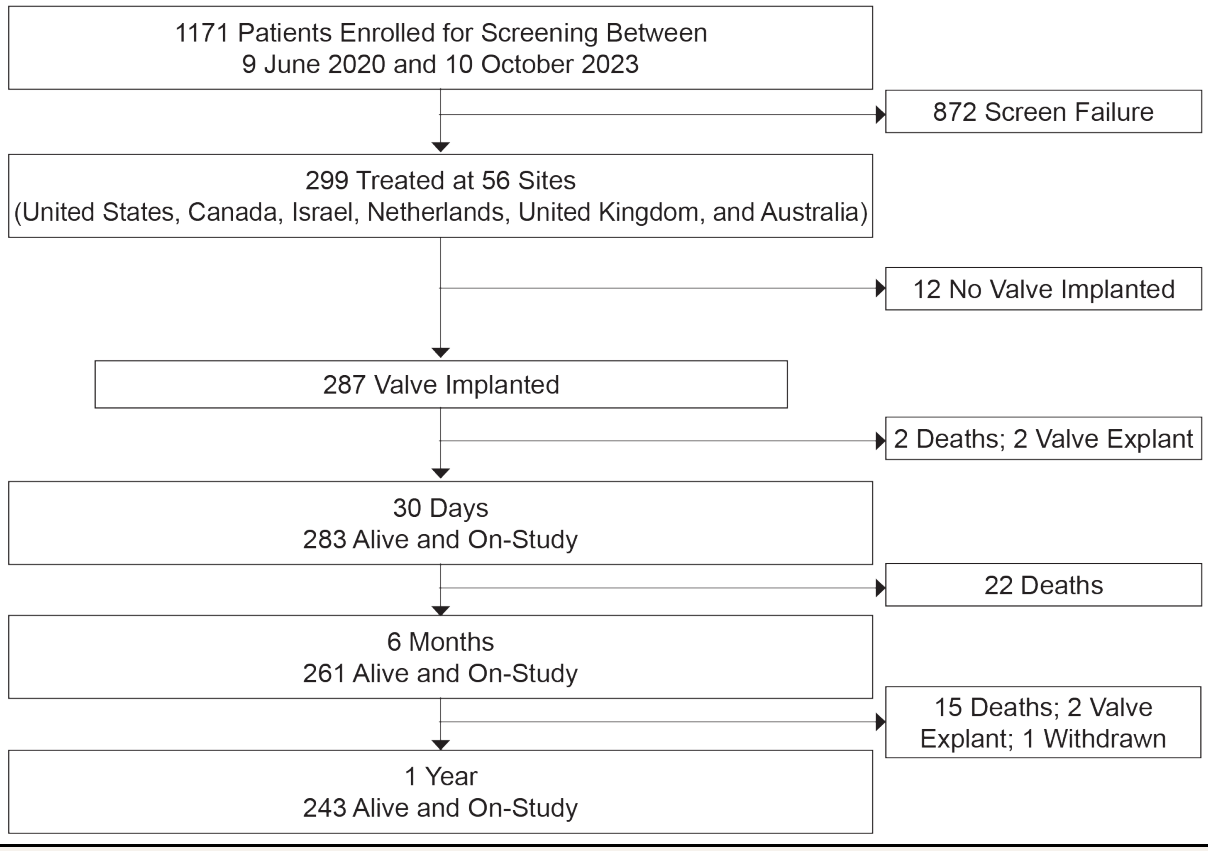

Figure 7. Patient Accountability Through 1 Year – Main Cohort.

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population for the Main Cohort are presented in Table 8, which are typical for a TMVR device study performed in the U.S.

Table 8. Patient Demographics and Baseline Characteristics - Main Cohort (AT Population).

Demographics and Baseline Characteristics	Summary Statistics*
Age - years	75.5 ± 9.35 (299)

Demographics and Baseline Characteristics	Summary Statistics*
Sex	
Male	50.8% (152/299)
Female	49.2% (147/299)
Hispanic or Latino Ethnicity	3.7% (11/299)
Race	
American Indian or Alaska Native	1.0% (3/299)
Asian	2.3% (7/299)
Black or African American	9.0% (27/299)
Native Hawaiian or Other Pacific Islander	0.3% (1/299)
White	75.9% (227/299)
Other	3.0% (9/299)
Unknown	8.4% (25/299)
Society of Thoracic Surgeons (STS) score for mitral valve replacement	6.6 ± 4.09 (299)
Society of Thoracic Surgeons (STS) score for mitral valve repair	5.0 ± 4.14 (299)
New York Heart Association (NYHA) class	
I	0.0% (0/299)
II	28.8% (86/299)
III	67.9% (203/299)
IV	3.3% (10/299)
Chronic kidney disease	41.1% (123/299)
Previous myocardial infarction	30.1% (90/299)
Prior aortic valve intervention	15.7% (47/299)
Prior mitral valve intervention	8.7% (26/298)
Aortic valve disease	41.1% (123/299)
Pulmonic valve disease	15.7% (47/299)
Tricuspid valve disease	63.2% (189/299)
Rheumatic heart disease	4.3% (13/299)
Prior coronary artery bypass grafting (CABG)	30.4% (91/299)
Prior percutaneous coronary intervention (PCI)	35.5% (106/299)
Prior stroke	11.7% (35/299)
Peripheral vascular disease (PVD)	15.1% (45/299)
Atrial fibrillation	69.9% (209/299)
Permanent pacemaker or defibrillator	35.8% (107/299)

Demographics and Baseline Characteristics	Summary Statistics*
Cardiac ablation	15.5% (46/297)
Echocardiographic findings (core laboratory transthoracic echocardiogram)	
Mitral valve mean gradient (mmHg)	3.4 ± 1.97 (284)
Left ventricular ejection fraction (LVEF) (%)	48.4 ± 11.96 (299)
Left ventricular end diastolic diameter (cm)	5.5 ± 0.76 (298)
Left ventricular end diastolic volume (mL)	143.7 ± 53.48 (294)
Left ventricular end systolic volume (mL)	76.5 ± 40.33 (294)
Mitral regurgitation etiology	
Primary (degenerative)	35.4% (105/297)
Secondary (functional ventricular)	53.9% (160/297)
Secondary (functional atrial)	4.4% (13/297)
Mixed (functional and degenerative)	6.4% (19/297)
Total mitral regurgitation (MR) degree†	
≤2+	0.0% (0/299)
3+	52.2% (156/299)
4+	47.8% (143/299)
Presence of mitral annular calcification (MAC)	24.4% (73/299)

*Continuous measures - mean ± SD (n); categorical measures - % (no./total no.).
†Baseline MR is based on the worse case between transesophageal echocardiogram and transthoracic echocardiogram.

D. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 9 and Figure 8. The composite rate of all-cause death and heart failure rehospitalization at 1 year was 25.2%, with a one-sided 97.5% upper confidence bound of 30.6%, which is less than the performance goal of 45% ($p<0.001$). Therefore, the primary endpoint was met.

Table 9. Primary Endpoint Analysis - Main Cohort (AT Population).

Event	Event Rate*	95% CI†	Performance Goal	P-value‡	Primary Endpoint Status
All-cause death or heart failure rehospitalization at 1 year	25.2% (73)	[20.6%, 30.6%]	45%	<0.001	Endpoint met
All-cause death	13.9% (40)	[10.4%, 18.5%]	-	-	-
Heart failure rehospitalization	16.7% (47)	[12.8%, 21.6%]	-	-	-

CI: confidence interval.
*Kaplan-Meier estimate % (no. of patients with the event).
†CI was calculated based on a one-sided significance level of 0.025 using Greenwood's formula.
‡The p-value was calculated using the Wald Test with Greenwood's formula.

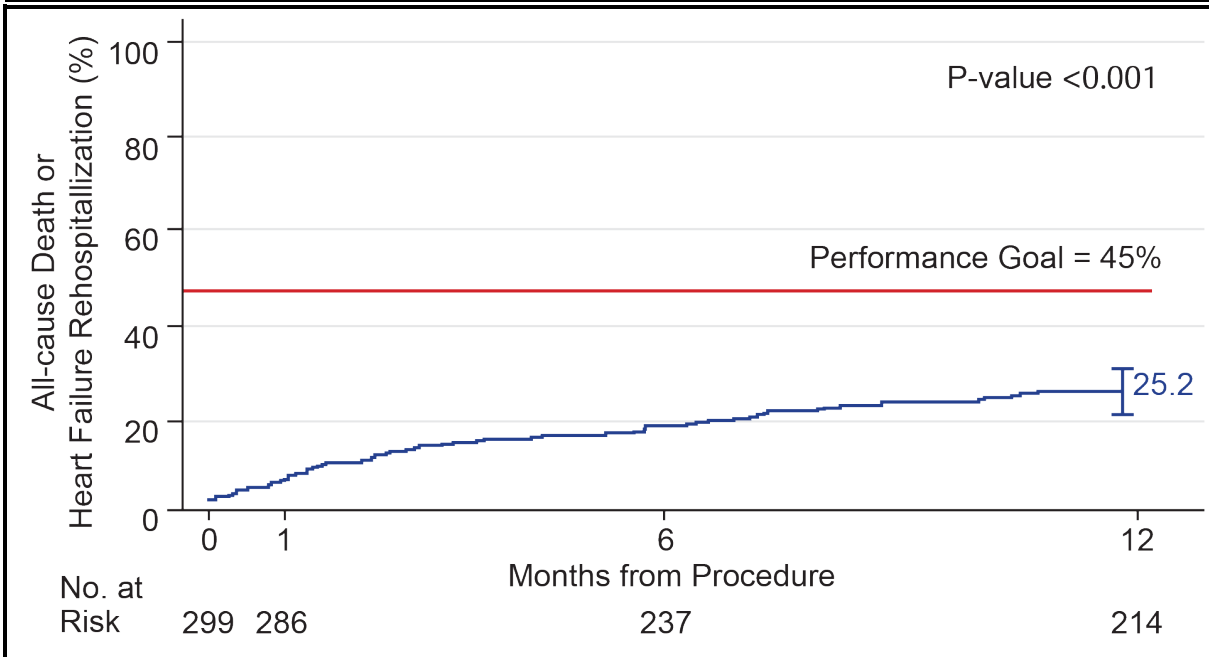

Figure 8. Kaplan-Meier Curve for All-Cause Death or Heart Failure Rehospitalization Through 1 Year – Main Cohort (AT Population).

The times to first event for each of the primary endpoint components are shown in Figure 9 and Figure 10.

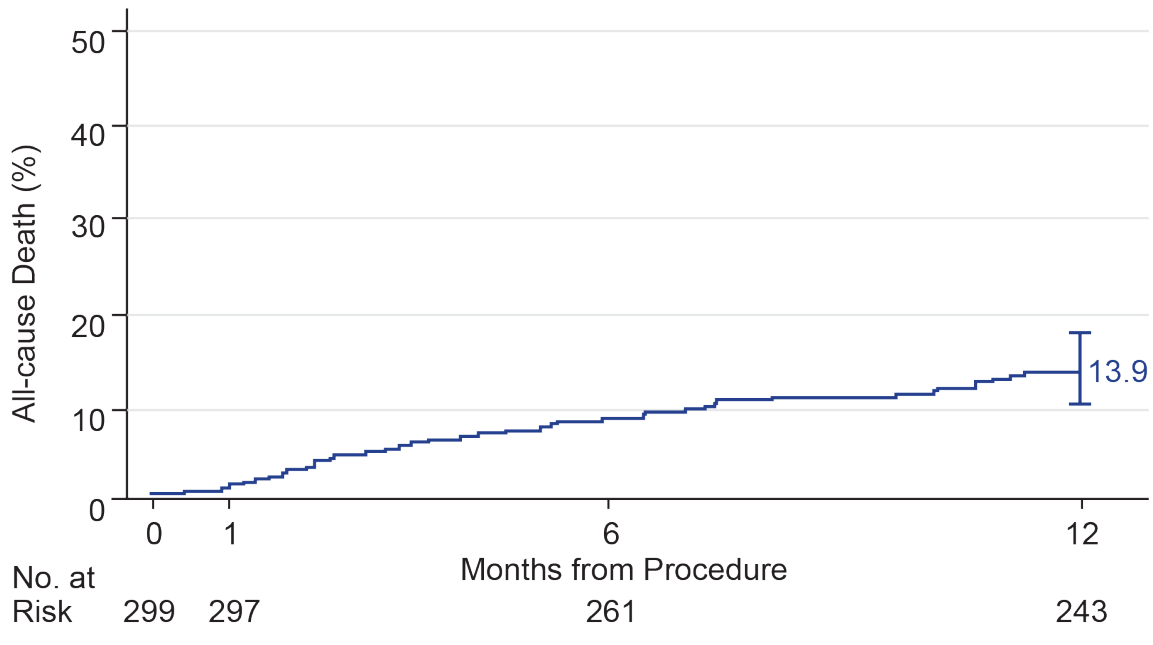

Figure 9. All-Cause Death Through 1 Year – Main Cohort (AT Population).

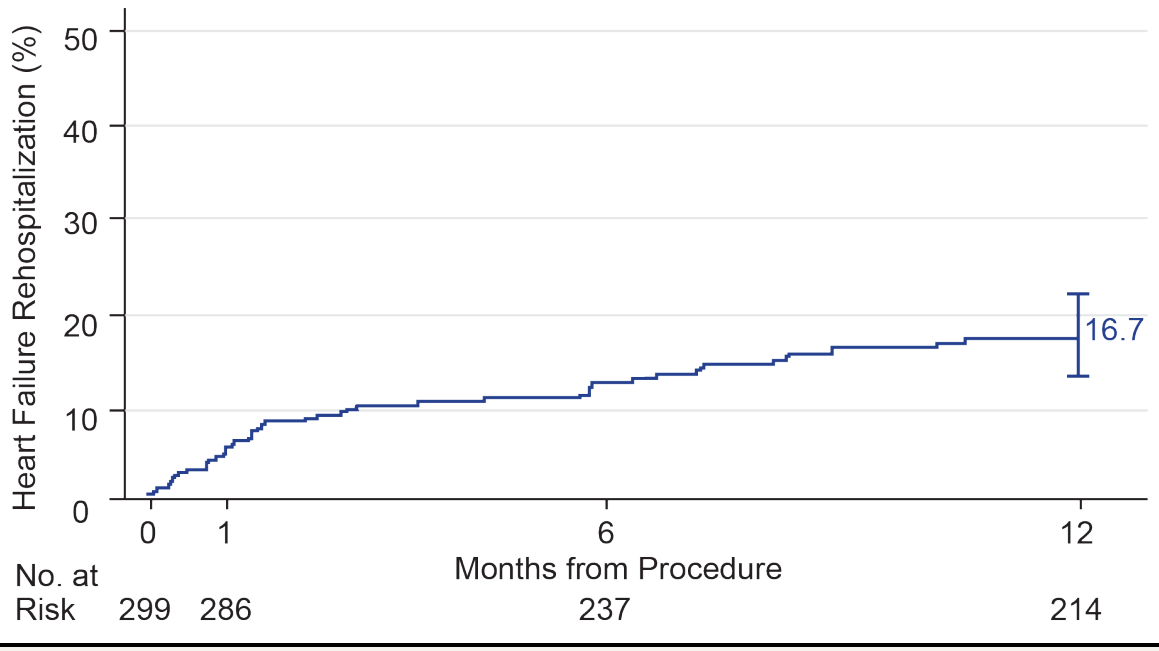

Figure 10. Heart Failure Rehospitalization Through 1 Year – Main Cohort (AT Population).

2. Secondary Endpoints

Since the primary endpoint was met, paired analyses from baseline for the four prespecified non-hierarchical hypothesis-driven secondary endpoints were tested for statistical significance. All four secondary endpoints were met, as presented in Table 10.

Table 10. Results of Secondary Endpoints - Main Cohort (VI Population).

No.	Endpoint	Summary Statistics*	P-value	Test Result
1	Improvement in MR severity at 1 year over baseline	100.0% (232/232)	<0.001†	Pass
2	Improvement in NYHA class at 1 year over baseline	73.4% (171/233)	<0.001†	Pass
3	Improvement in KCCQ summary score at 1 year over baseline	18.4 ± 1.68 (229)	<0.001‡	Pass
4	Improvement in LVEDVi at 1 year over baseline (mL/m^2)	-4.7 ± 1.39 (208)	<0.001‡	Pass

MR: mitral regurgitation; NYHA: New York Heart Association; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDVi: left ventricular end-diastolic volume index.
*Categorical measures - % (no. / total no.); continuous measures - mean ± SE (n).
†P-value was from sign test.
‡P-value was from paired t-test.
The Hochberg procedure was used for multiplicity adjustment to control family-wise type I error.

3. Descriptive Endpoints

KCCQ

The KCCQ overall summary scores by visit are presented in Figure 11. The mean score increased from 57.0 at baseline to 75.0 at 1 year post-procedure.

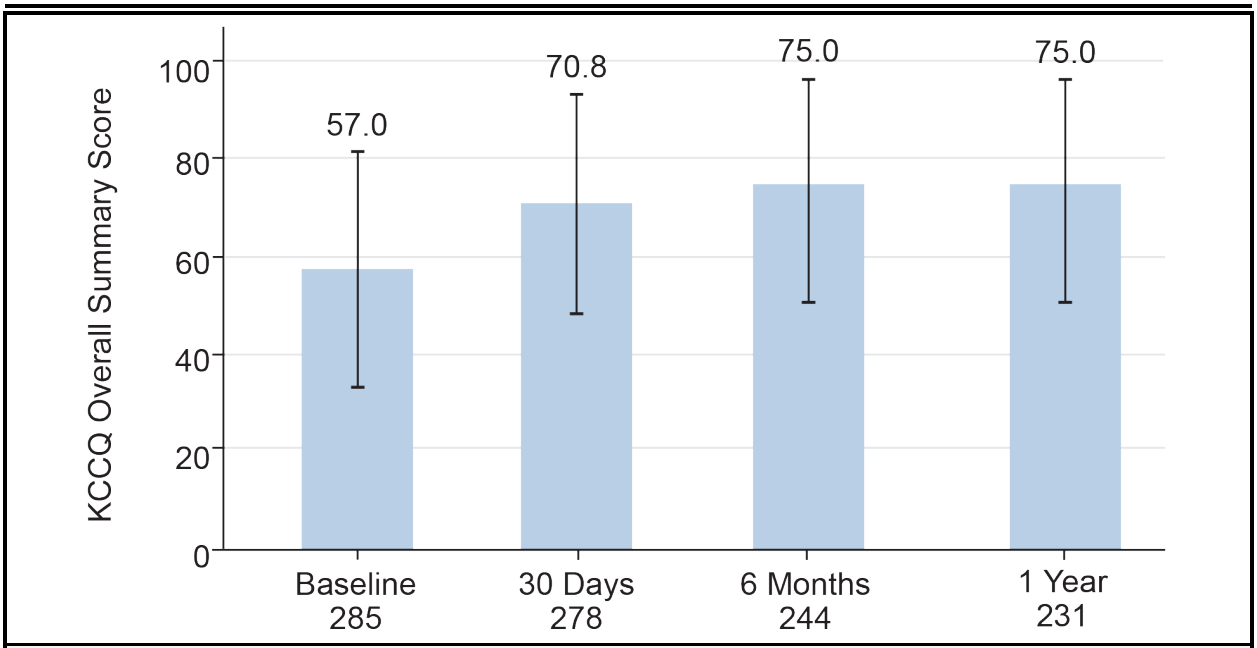

Figure 11. KCCQ Overall Summary Score by Visit – Main Cohort (VI Population). The error bars represent standard deviations.

EQ-5D-5L

The results for the EQ-5D-5L visual analog score (VAS) are presented in Figure 12. The mean score was 64.8 at baseline and 73.5 at 1 year post-procedure.

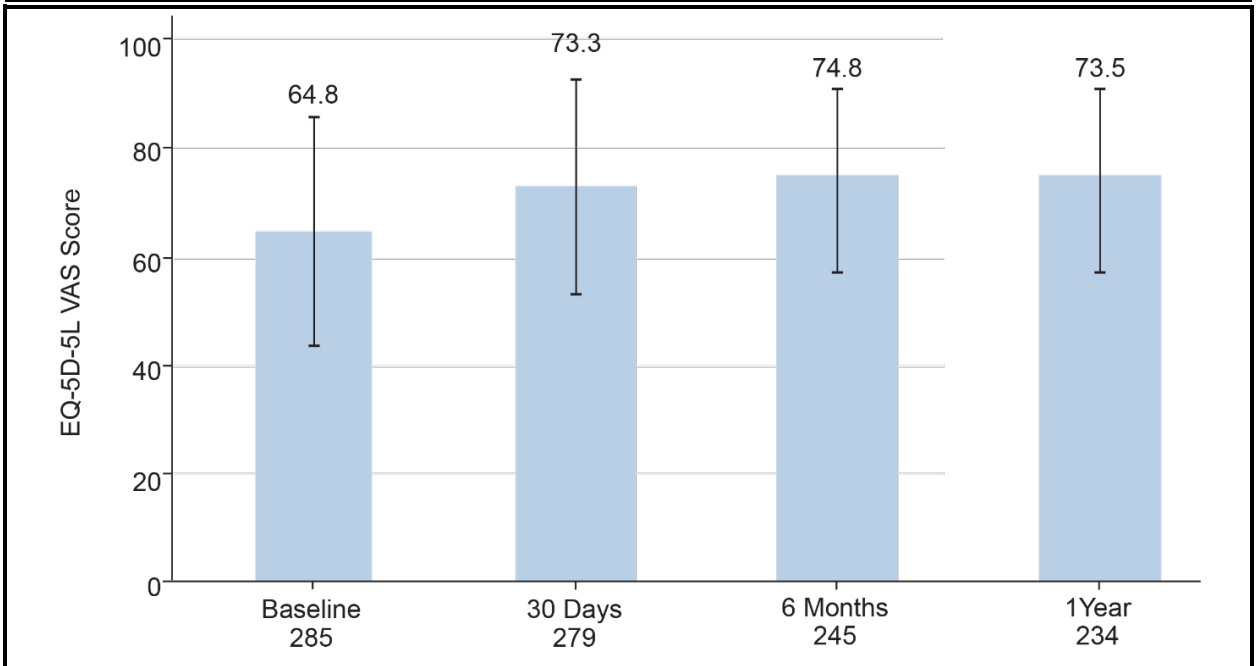

Figure 12. EQ-5D-5L Visual Analog Score by Visit – Main Cohort (VI Population). The error bars represent standard deviations.

NYHA Functional Class

The NYHA classifications by visit are presented in Figure 13. At 1 year post-procedure, 87.9% of patients were in NYHA class I/II compared to 28.6% at baseline.

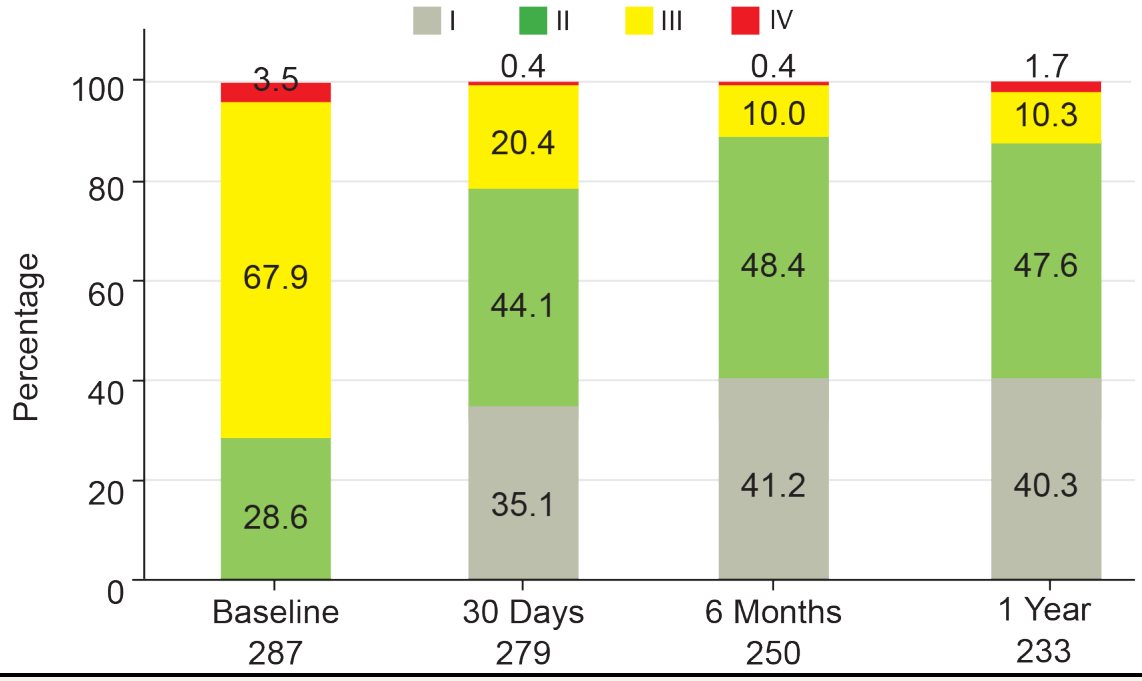

Figure 13. NYHA Functional Class by Visit – Main Cohort (VI Population).

6MWT Distance

The results for the 6MWT distance are presented in Figure 14. The mean walk distance increased from 239.6 meters at baseline to 259.4 meters at 1 year post-procedure.

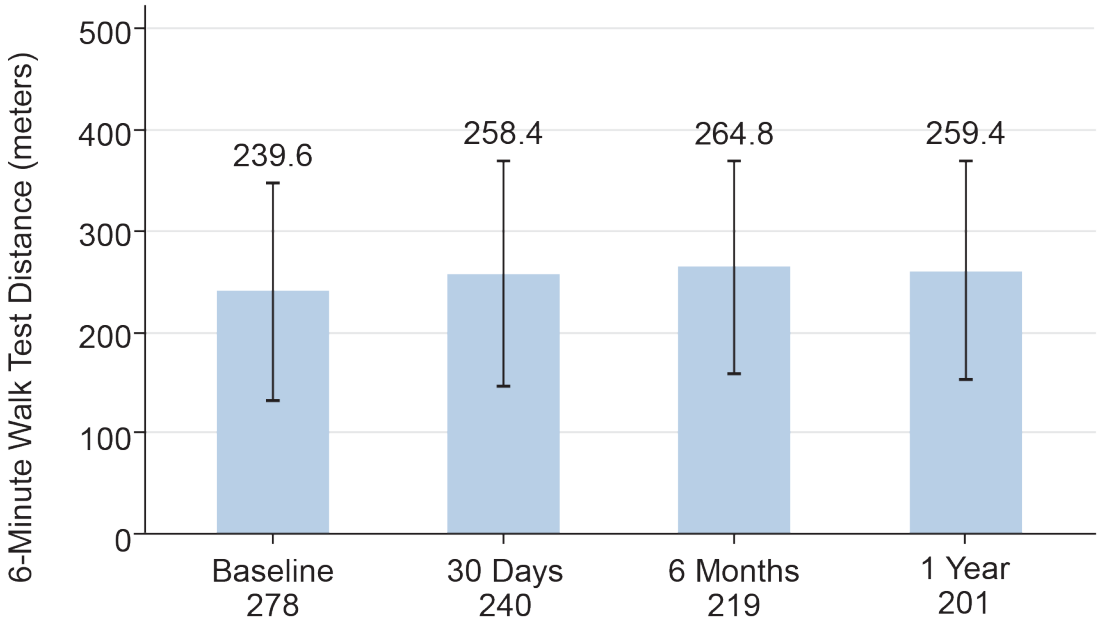

Figure 14. 6MWT Distance by Visit – Main Cohort (VI Population). The error bars represent standard deviations.

MR Severity

MR severity by visit is shown in Figure 15. MR reduction to ≤1+ was achieved in 95.7% of patients at 1 year.

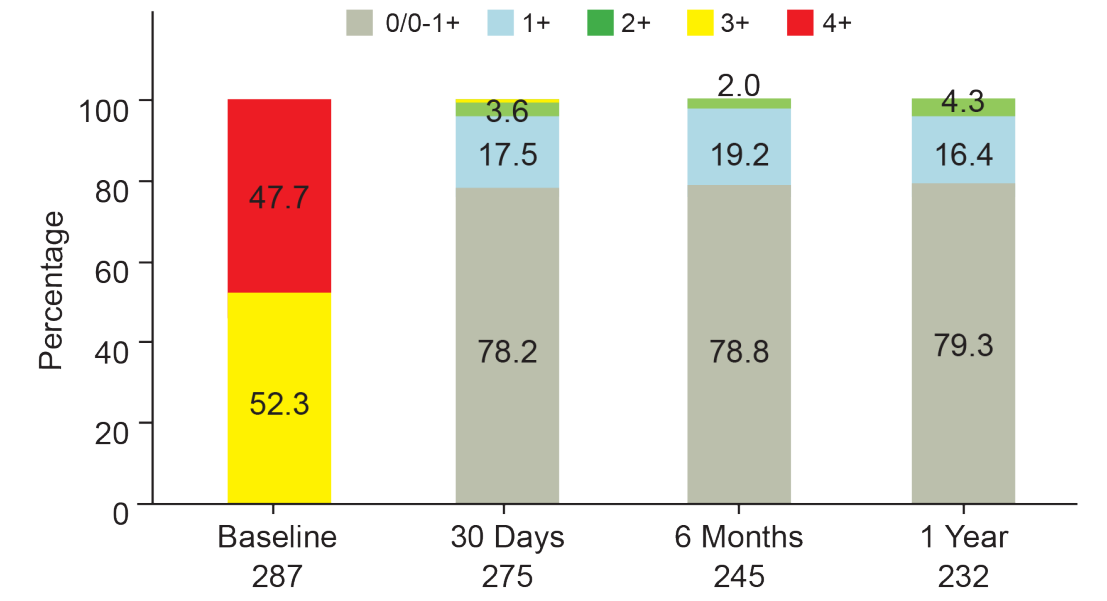

Figure 15. MR Severity by Visit – Main Cohort (VI Population). The worst case between transesophageal echocardiogram and transthoracic echocardiogram results was used as the baseline and transthoracic echocardiogram results were used for all other visits.

4. Adverse Events

The Kaplan-Meier estimates of CEC-adjudicated serious adverse events and other adverse events of clinical interest through 1 year are presented in Table 11.

Table 11. CEC-Adjudicated Adverse Events Through 1 Year - Main Cohort (AT Population).

Event	Kaplan-Meier Estimate*		
	30 Days	6 Months	1 Year
All-cause death	0.7% (2, 2)	8.7% (25, 25)	13.9% (40, 40)
Cardiovascular	0.7% (2, 2)	6.3% (18, 18)	8.9% (25, 25)
Non-cardiovascular	0.0% (0, 0)	2.5% (7, 7)	5.6% (15, 15)
Heart failure rehospitalization	4.0% (13, 12)	12.2% (43, 35)	16.7% (63, 47)
All stroke	2.7% (8, 8)	6.3% (18, 18)	9.3% (29, 26)
Disabling	1.7% (5, 5)	2.4% (7, 7)	3.9% (13, 11)
Non-disabling	1.0% (3, 3)	3.9% (11, 11)	5.5% (16, 15)
Acute kidney injury Stage 2	0.7% (2, 2)	---	---
Acute kidney injury Stage 3	2.3% (7, 7)	---	---
New-onset atrial fibrillation	7.9% (7, 7)	11.5% (10, 10)	11.5% (10, 10)
New permanent pacemaker implantation	2.6% (5, 5)	4.9% (9, 9)	5.5% (10, 10)
Life-threatening bleeding	3.7% (11, 11)	3.7% (11, 11)	6.8% (19, 19)
Fatal bleeding	0.0% (0, 0)	0.8% (2, 2)	1.1% (3, 3)
Hemolysis†	3.0% (9, 9)	3.7% (11, 11)	3.7% (11, 11)
Hemolytic anemia‡	4.3% (13, 13)	7.1% (21, 21)	7.1% (21, 21)
Valve thrombosis§	4.4% (13, 13)	9.3% (27, 27)	12.9% (36, 36)
Clinically significant leaflet thrombosis	2.3% (7, 7)	5.5% (16, 16)	6.7% (19, 19)
Dock fracture	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Dock migration	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Valve embolization	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Valve fracture	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Valve migration	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Clinically significant TMVR-related LVOT obstruction	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Mitral valve reintervention‖	2.3% (8, 7)	4.5% (14, 13)	6.4% (19, 18)
Balloon mitral valvuloplasty	0.0% (0, 0)	0.0% (0, 0)	0.4% (1, 1)
Percutaneous paravalvular leak closure	1.3% (5, 4)	3.1% (10, 9)	3.5% (11, 10)
Surgical mitral valve replacement	0.7% (2, 2)	0.7% (2, 2)	1.5% (4, 4)
Valve in valve	0.0% (0, 0)	0.4% (1, 1)	1.2% (3, 3)

Event	Kaplan-Meier Estimate*		
	30 Days	6 Months	1 Year
Other	0.3% (1, 1)	0.3% (1, 1)	0.3% (1, 1)
Myocardial infarction	0.7% (2, 2)	1.8% (5, 5)	1.8% (5, 5)
Transient ischemic attack (TIA)	0.7% (2, 2)	1.0% (3, 3)	2.2% (6, 6)
Study device related endocarditis	0.0% (0, 0)	0.7% (2, 2)	1.1% (3, 3)
Major vascular complication	0.7% (2, 2)	0.7% (2, 2)	0.7% (2, 2)
Major access site complication	2.3% (7, 7)	4.1% (12, 12)	4.9% (14, 14)
Atrial septal defect	2.3% (7, 7)	4.1% (12, 12)	4.9% (14, 14)
Major cardiac structure complication	2.3% (7, 7)	2.7% (8, 8)	2.7% (8, 8)

TMVR: transcatheter mitral valve replacement; LVOT: left ventricular outflow obstruction.
*Kaplan-Meier estimate – % (no. events, no. of patients with the event).
†Hemolysis: the presence of a paravalvular leak on echocardiogram plus acute decrease in haptoglobin levels and/or increase in serum lactate dehydrogenase (LDH) levels and/or standard blood examinations supporting hemolysis with associated anemia and diagnosis of hemolysis due to prosthetic valve, not requiring transfusion.
‡Hemolytic anemia: hemolysis requiring transfusion or intervention (or need for intervention) on the mitral valve.
§Inadequate anticoagulation (no anticoagulation, gap in treatment, or subtherapeutic) appeared to be a factor in the occurrence of device thrombosis regardless of the type of anticoagulation prescribed. The observed valve thrombosis rate at 1 year was 7.0% in patients with adequate anticoagulation and 20.9% in those with inadequate anticoagulation.
‖Only interventions after procedure.

5. Subgroup Analyses

The primary endpoint results by gender and by MR etiology are presented in Table 12 and Table 13, respectively. The results were consistent when analyzed by gender and MR etiology.

Table 12. Primary Endpoint Analysis by Gender – Main Cohort (AT Population).

Event	Summary Statistics*	
	Male (N=152)	Female (N=147)
All-cause death or heart failure rehospitalization at 1 year	25.2% (37)	25.2% (36)
All-cause death	14.5% (21)	13.4% (19)

Event	Summary Statistics*	
	Male (N=152)	Female (N=147)
Heart failure rehospitalization	16.9% (24)	16.4% (23)

*Kaplan-Meier estimate % (no. of patients with the event).

Table 13. Primary Endpoint Analysis by MR Etiology – Main Cohort (AT Population).

Event	Summary Statistics*	
	Primary MR (N=105)	Secondary MR (N=160)
All-cause death or heart failure rehospitalization at 1 year	26.3% (26)	25.5% (40)
All-cause death	15.3% (15)	12.9% (20)
Heart failure rehospitalization	17.8% (17)	17.1% (26)

MR: mitral regurgitation.
*Kaplan-Meier estimate % (no. of patients with the event).

The primary endpoint result by race is shown in Table 14.

Table 14. Primary Endpoint Result by Race – Main Cohort (AT Population).

Race	All-cause Death or Heart Failure Rehospitalization at 1 Year* (N=299)
White or Caucasian	55/227
Black or African American	9/27
Native Hawaiian or Other Pacific Islander	0/1
Asian	1/7
American Indian or Alaskan Native	0/3
Other	4/9
Unknown	4/25

*no. of patients with events/total no. patients in the subgroup.

6. Other Study Observations

Procedural Information

The procedural data are presented in Table 15.

Table 15. Procedure Data - Main Cohort (AT Population).	
Variable	**Summary Statistics***
Procedure time (min)†	127.0 ± 47.13 (293)
Total fluoroscopy time (min)	51.9 ± 24.61 (297)
Dock deployment time (min)‡	65.9 ± 35.04 (291)
Multiple valve implant	0.0% (0/287)
Percutaneous paravalvular leak closure	5.0% (15/299)
Procedure aborted	4.0% (12/299)
Conversion to surgery	0.0% (0/287)

*Continuous measures - mean ± SD (n); categorical measures - % (no./total no.).
†Defined as the time from femoral vein access to guide sheath removal.
‡Defined as the time from steerable catheter insertion to removal.

Index Hospitalization

The index hospitalization information is presented in Table 16.

Table 16. Index Hospitalization Information - Main Cohort (VI Population).	
Variable	**Summary Statistics***
Index hospitalization stay (days)†	2.9 ± 3.55 (286)
Intensive care stay (days)	0.7 ± 1.47 (286)
In-hospital death	0.3% (1/287)

*Continuous measures - mean ± SD (total no.); categorical measures – % (no./total no.).
†Index hospitalization stay excludes in-hospital deaths.

Additional Echocardiographic Data

Additional echocardiographic data through 1 year are presented in Table 17, which show a generally positive trend in left ventricular remodeling.

Table 17. Additional Echocardiographic Data - Main Cohort (VI Population).				
Parameter	**Summary Statistics***			
	Baseline	**30 Days**	**6 Months**	**1 Year**
LV end diastolic volume index (mL/m^2)	75.0 ± 24.94 (282)	70.2 ± 24.33 (254)	71.5 ± 24.53 (221)	70.6 ± 26.69 (213)
LV end diastolic diameter (cm)	5.5 ± 0.04 (286)	5.3 ± 0.05 (261)	5.4 ± 0.05 (232)	5.3 ± 0.05 (228)

LV ejection fraction (%)	48.4 ± 11.95 (287)	38.7 ± 11.56 (276)	40.5 ± 12.32 (246)	41.3 ± 12.16 (235)
LV end diastolic volume (mL)	143.4 ± 53.71 (282)	133.6 ± 52.96 (254)	136.8 ± 53.40 (221)	135.6 ± 56.17 (213)
LV end systolic volume (mL)	76.7 ± 40.82 (282)	84.5 ± 43.85 (252)	84.7 ± 46.26 (216)	83.6 ± 48.55 (207)
Transmitral antegrade mean gradient (mmHg)	3.4 ± 1.96 (272)	5.4 ± 2.11 (274)	5.3 ± 2.28 (246)	5.5 ± 2.22 (233)
Stroke volume index (mL/m^2)	28.8 ± 8.73 (278)	35.9 ± 13.65 (268)	37.1 ± 14.22 (241)	37.8 ± 14.87 (227)
Cardiac output index ($L/min/m^2$)	2.1 ± 0.60 (278)	2.5 ± 0.86 (268)	2.5 ± 0.88 (241)	2.5 ± 0.90 (227)

LV: left ventricular.
*Continuous measures - mean ± SD (n).

Correlation Between KCCQ and Other Outcomes

Post hoc analyses were performed to explore the correlation between KCCQ overall summary score change from baseline and heart failure rehospitalization, NYHA functional class, MR severity, and 6MWT distance. The results are shown in Figure 16 through Figure 19, which show a correlation between higher KCCQ overall summary score and absence of heart failure hospitalization, lower NYHA functional class, lower grade of MR severity, and larger improvement in 6MWT distance at 1 year.

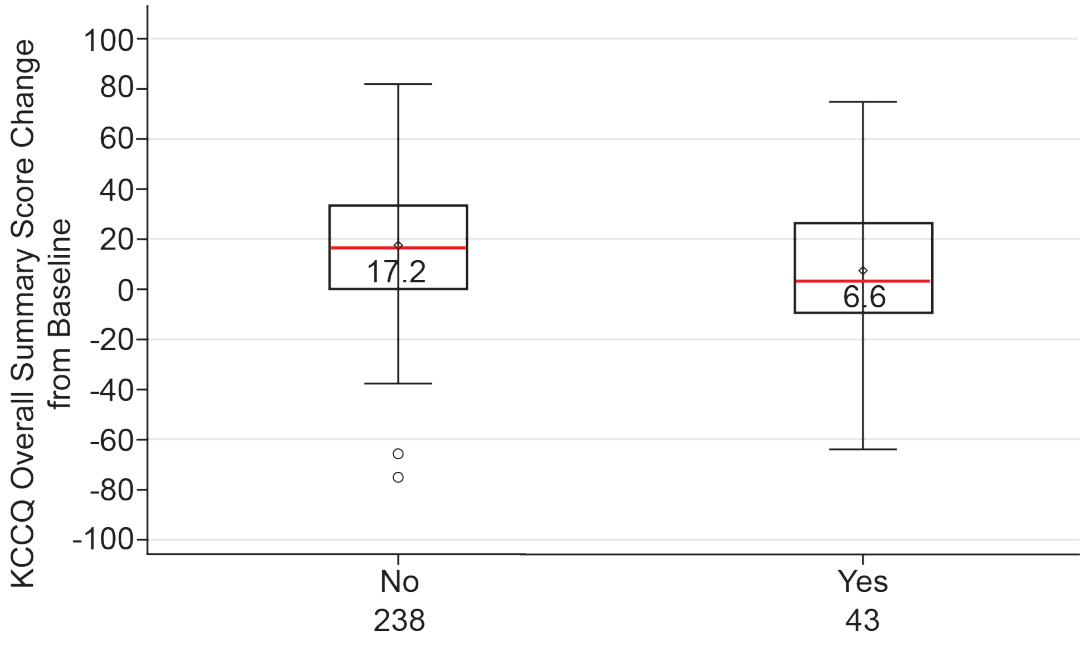

Figure 16. KCCQ Overall Summary Score vs. Heart Failure Rehospitalization at 1 Year – Main Cohort (AT Population).

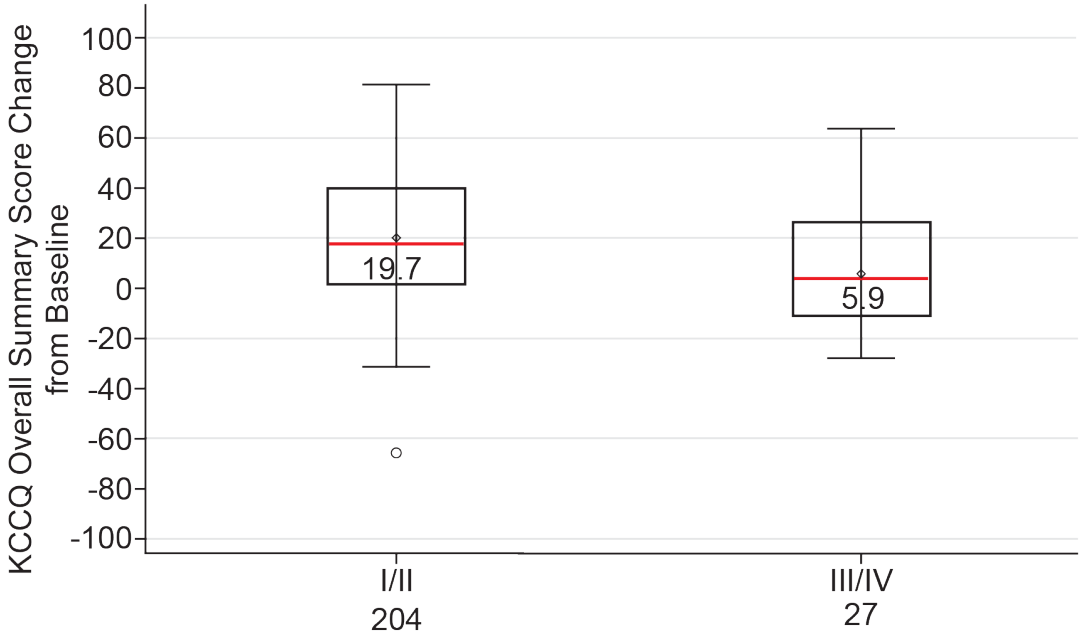

Figure 17. KCCQ Overall Summary Score vs. NYHA Functional Class at 1 Year – Main Cohort (AT Population).

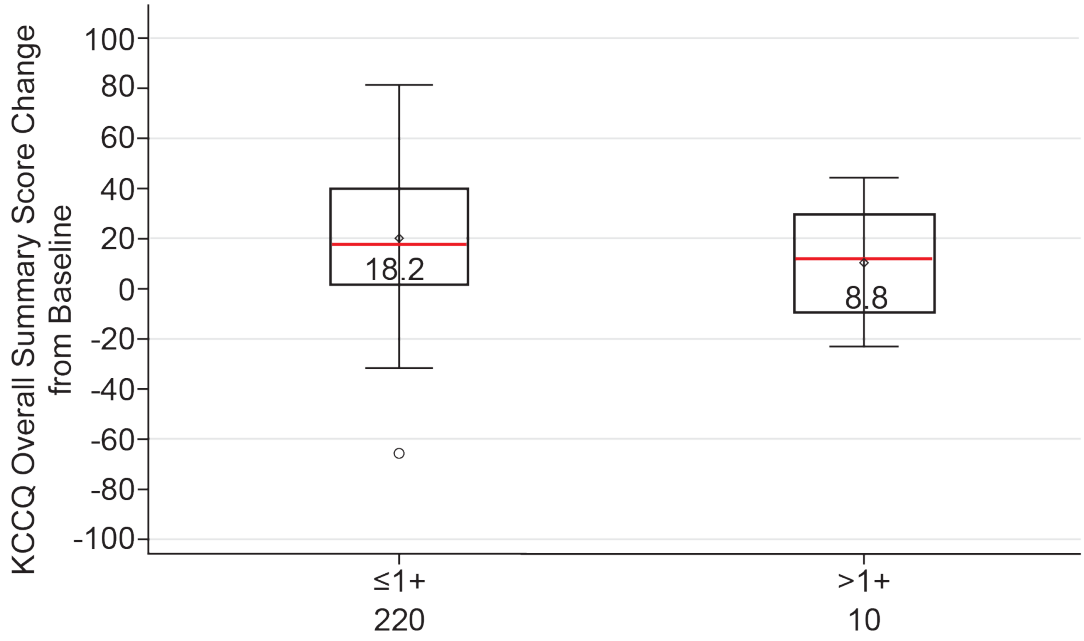

Figure 18. KCCQ Overall Summary Score vs. MR Severity at 1 Year – Main Cohort (AT Population).

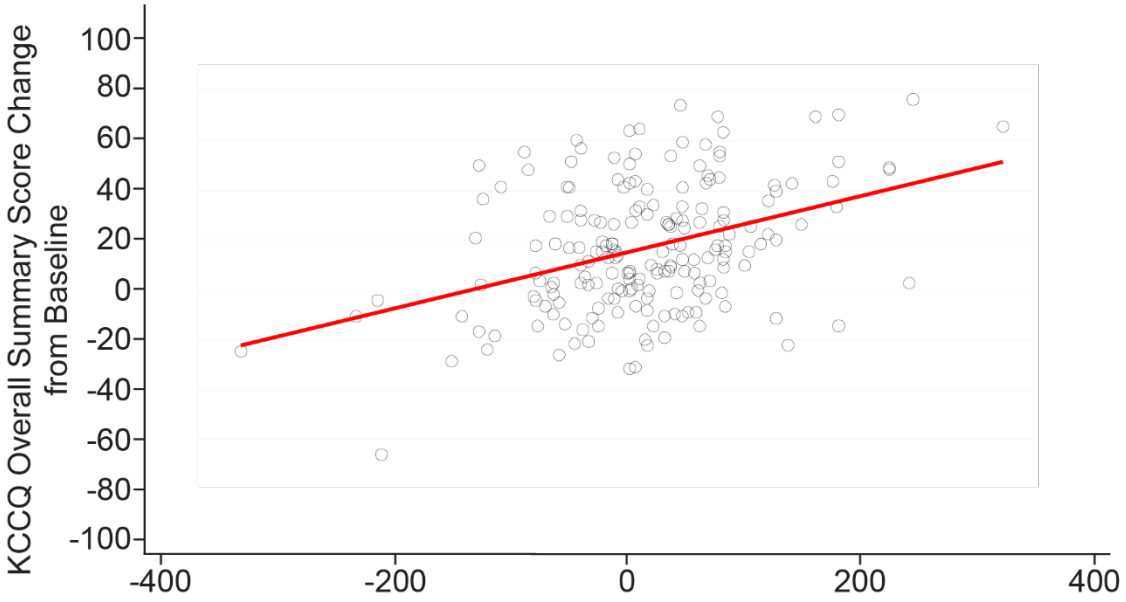

Figure 19. KCCQ Overall Summary Score vs. 6MWT Distance Change at 1 Year – Main Cohort (AT Population).

7. Pediatric Extrapolation

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

X.2. Summary of the MAC Registry

A. Study Design

The ENCIRCLE study MAC Registry was a prospective, single-arm, multicenter study. Patients in the MAC Registry were enrolled between January 20, 2022, and March 21, 2024. The database for this PMA application reflected data collected through February 3, 2025, and included 100 patients treated at 36 investigational sites in the US, Australia, Canada, Netherlands, and the United Kingdom.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the MAC Registry was limited to patients who met the same inclusion criteria as in the Main Cohort, with the exception of the following modified inclusion criterion:

   – MR ≥3+ (if the impact of the calcification on delivery and implantation of the SAPIEN M3 system is uncertain), moderate MR and moderate mitral stenosis (MS), or severe MS as assessed by the Echocardiography Core Laboratory

Patients were not permitted to enroll in the MAC Registry if they met any of the Main Cohort exclusion criteria.

2. Follow-up Schedule

   The follow-up schedule for patients in the MAC Registry was identical to that in the Main Cohort.

3. Clinical Endpoints

   The clinical endpoints for the MAC Registry were the same as those for the Main Cohort. However, no hypothesis testing was performed; only descriptive statistics was performed.

B. Patient Accountability

At the time of database lock, a total of 100 patients of 364 patients enrolled for screening had the procedure started (AT Population) in the MAC Registry and 93 patients had the study valve implanted (VI Population). Patient accountability through 1 year is summarized in Figure 20.

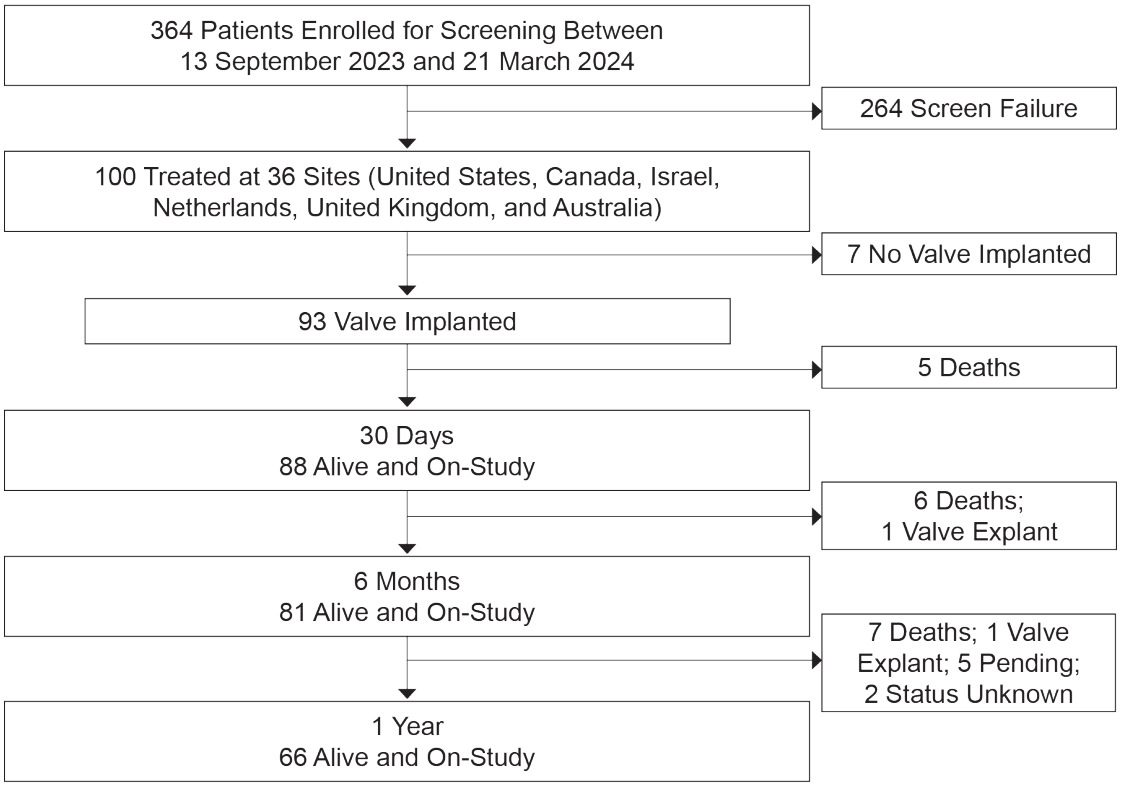

Figure 20. Patient Accountability Through 1 Year – MAC Registry.

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population for the MAC Registry are presented in Table 18, which are typical for a TMVR device study in patients with severe MAC performed in the U.S.

Table 18. Patient Demographics and Baseline Characteristics – MAC Registry (AT Population).

Demographics and Baseline Characteristics	Summary Statistics*
Age - years	76.1 ± 9.22 (100)
Sex	
Male	51.0% (51/100)
Female	49.0% (49/100)
Hispanic or Latino Ethnicity	3.0% (3/100)
Race	
American Indian or Alaska Native	0.0% (0/100)
Asian	2.0% (2/100)
Black or African American	1.0% (1/100)
Native Hawaiian or Other Pacific Islander	0.0% (0/100)
White	85.0% (85/100)
Other	2.0% (2/100)
Unknown	10.0% (10/100)
Society of Thoracic Surgeons (STS) score for mitral valve replacement	8.4 ± 4.90 (100)
Society of Thoracic Surgeons (STS) score for mitral valve repair	6.0 ± 5.45 (100)
New York Heart Association (NYHA) class	
I	0.0% (0/100)
II	27.0% (27/100)
III	69.0% (69/100)
IV	4.0% (4/100)
Chronic kidney disease	42.0% (42/100)
Previous myocardial infarction	25.0% (25/100)
Prior aortic valve intervention	48.0% (48/100)
Prior mitral valve intervention	3.0% (3/100)
Aortic valve disease	71.0% (71/100)
Pulmonic valve disease	11.0% (11/100)
Tricuspid valve disease	69.0% (69/100)

Demographics and Baseline Characteristics	Summary Statistics*
Rheumatic heart disease	7.0% (7/100)
Prior coronary artery bypass grafting (CABG)	28.0% (28/100)
Prior percutaneous coronary intervention (PCI)	38.0% (38/100)
Prior stroke	14.0% (14/100)
Peripheral vascular disease (PVD)	17.0% (17/100)
Atrial fibrillation	66.0% (66/100)
Permanent pacemaker or defibrillator	38.0% (38/100)
Cardiac ablation	18.0% (18/100)
Echocardiographic findings (core laboratory transthoracic echocardiogram)	
Mitral valve mean gradient (mmHg)	6.1 ± 3.27 (100)
Left ventricular ejection fraction (LVEF) (%)	54.6 ± 10.53 (100)
Left ventricular end diastolic diameter (cm)	4.9 ± 0.66 (100)
Left ventricular end diastolic volume (mL)	112.2 ± 44.30 (97)
Left ventricular end systolic volume (mL)	52.0 ± 27.77 (97)
Mitral regurgitation etiology	
Primary (degenerative)	77.0% (77/100)
Secondary (functional ventricular)	15.0% (15/100)
Secondary (functional atrial)	0.0% (0/100)
Mixed (functional and degenerative)	8.0% (8/100)
Total mitral regurgitation (MR) degree†	
≥3+	71.0% (71/100)
=2+	19.0% (19/100)
=1+ with severe stenosis	10.0% (10/100)
Presence of mitral annular calcification (MAC)	98.0% (98/100)

*Continuous measures - mean ± SD (n); categorical measures - % (no./total no.).
†Baseline MR is based on the worse case between transesophageal echocardiogram and transthoracic echocardiogram.

The CT Core Laboratory conducted calcium evaluation to characterize the calcium morphology at each of the six mitral segments (A1, A2, and A3 for the anterior annulus and leaflet, and P1, P2, and P3 for the posterior annulus leaflet). The results are presented in Table 19.

Table 19. Annular and Leaflet Calcifications - MAC Registry (AT Population).	
Calcium Characteristics	**Summary Statistics***
Annular calcifications	
A1	
Grade	
None	40.0% (40/100)
Mild	15.0% (15/100)
Moderate	23.0% (23/100)
Severe	22.0% (22/100)
Spur	34.0% (34/100)
A2	
Grade	
None	66.0% (66/100)
Mild	8.0% (8/100)
Moderate	11.0% (11/100)
Severe	15.0% (15/100)
Spur	39.0% (39/100)
A3	
Grade	
None	37.0% (37/100)
Mild	19.0% (19/100)
Moderate	19.0% (19/100)
Severe	25.0% (25/100)
Spur	40.0% (40/100)
P1	
Grade	
None	23.0% (23/100)
Mild	16.0% (16/100)
Moderate	26.0% (26/100)
Severe	35.0% (35/100)
Spur	9.0% (9/100)
P2	
Grade	
None	13.0% (13/100)

Calcium Characteristics	Summary Statistics*
Mild	13.0% (13/100)
Moderate	22.0% (22/100)
Severe	52.0% (52/100)
Spur	20.0% (20/100)
P3	
Grade	
None	19.0% (19/100)
Mild	14.0% (14/100)
Moderate	20.0% (20/100)
Severe	47.0% (47/100)
Spur	15.0% (15/100)
Leaflet calcifications	
A1	
None	48.0% (48/100)
Mild	13.0% (13/100)
Pronounced	39.0% (39/100)
A2	
None	49.0% (49/100)
Mild	5.0% (5/100)
Pronounced	46.0% (46/100)
A3	
None	39.0% (39/100)
Mild	14.0% (14/100)
Pronounced	47.0% (47/100)
P1	
None	69.0% (69/100)
Mild	19.0% (19/100)
Pronounced	12.0% (12/100)
P2	
None	48.0% (48/100)
Mild	25.0% (25/100)
Pronounced	27.0% (27/100)
P3	
None	61.0% (61/100)

Calcium Characteristics	Summary Statistics*
Mild	16.0% (16/100)
Pronounced	23.0% (23/100)

*Categorical measures - % (no./total no.).

D. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 20 and Figure 21. The composite rate of all-cause death and heart failure rehospitalization at 1 year was 34.1%.

Table 20. Primary Endpoint Analysis – MAC Registry (AT Population).

Event	Summary Statistics*
All-cause death or heart failure rehospitalization at 1 year	34.1% (32)
All-cause death	21.7% (20)
Heart failure rehospitalization	19.6% (17)

*Kaplan-Meier estimate % (no. of patients with the event).

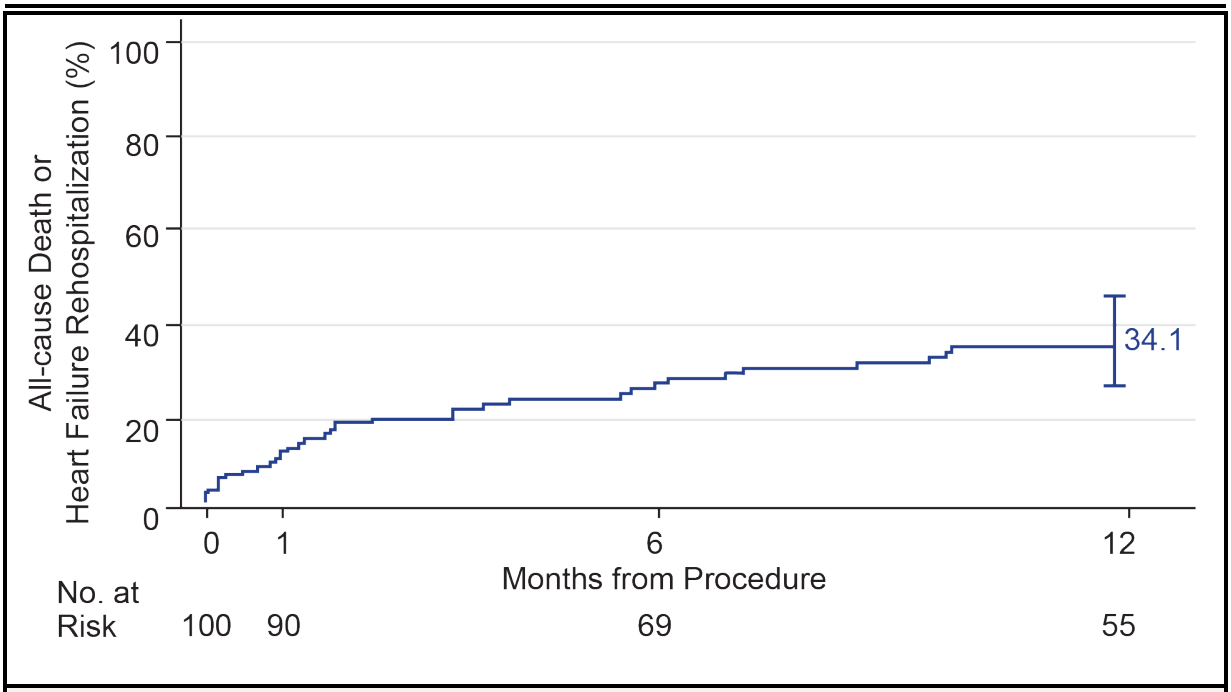

Figure 21. Kaplan-Meier Curve for All-Cause Death or Heart Failure Rehospitalization Through 1 Year – MAC Registry (AT Population).

The times to first event for each of the primary endpoint components are shown in Figure 22 and Figure 23.

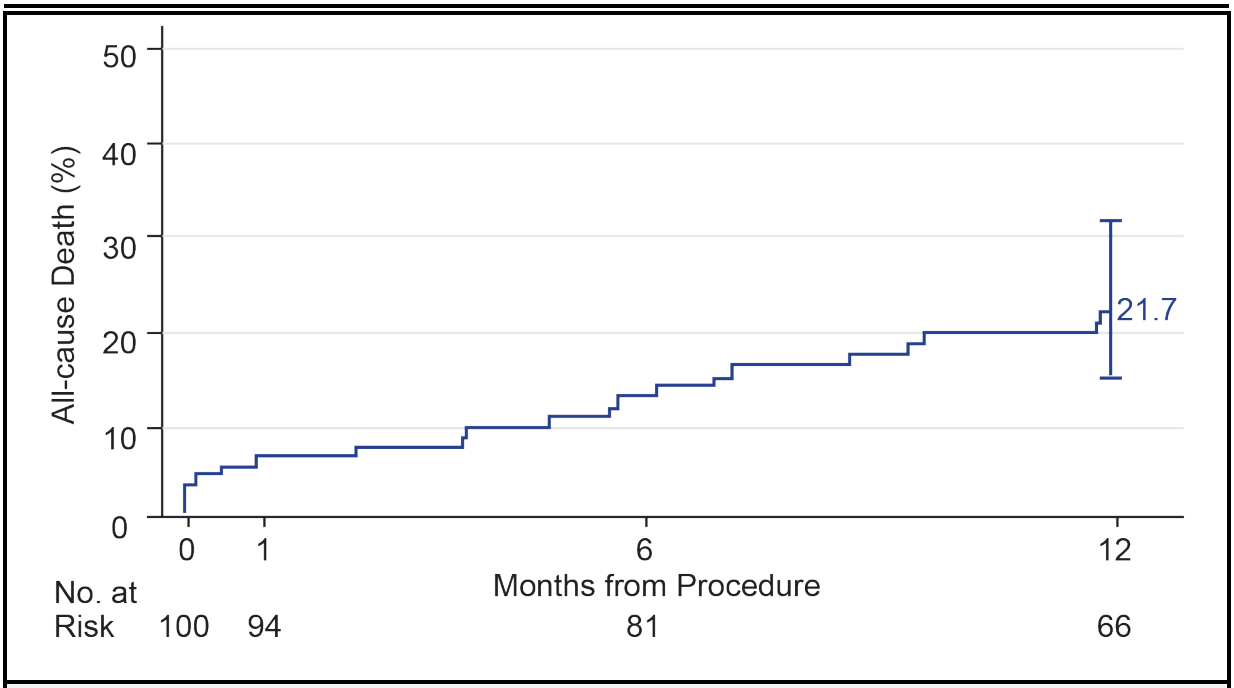

Figure 22. All-Cause Death Through 1 Year – MAC Registry (AT Population).

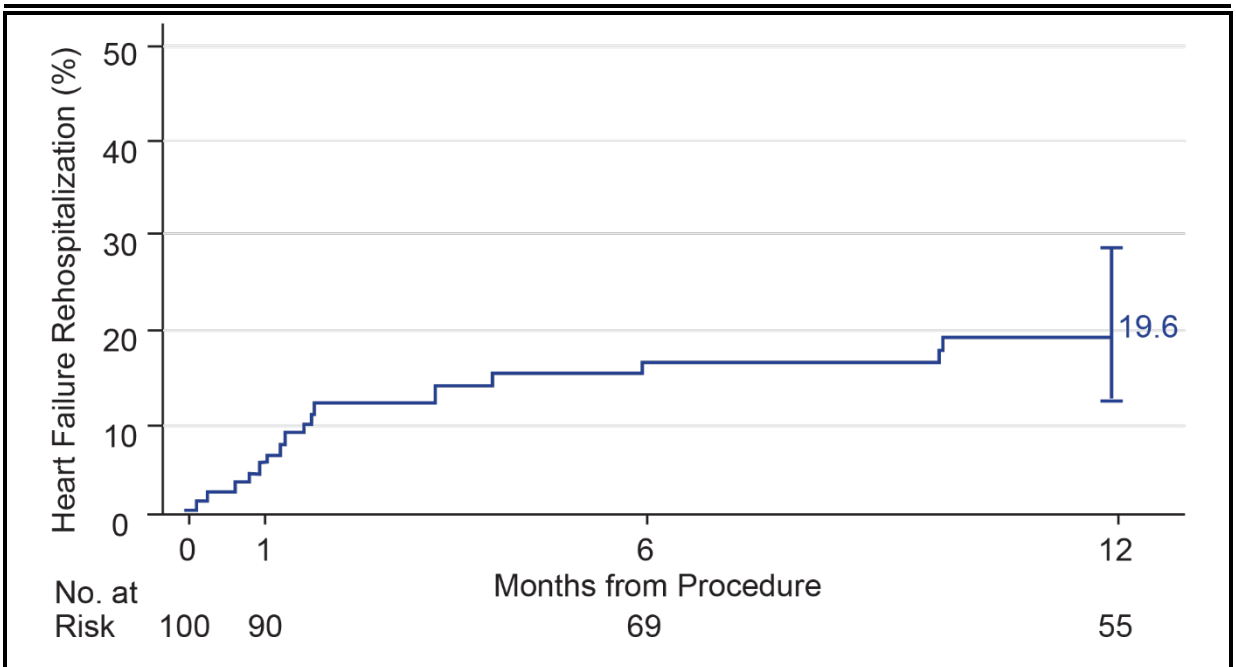

Figure 23. Heart Failure Rehospitalization Through 1 Year – MAC Registry (AT Population).

2. Secondary Endpoints

The paired results of the four secondary endpoints are presented in Table 21.

Table 21. Results of Secondary Endpoints – MAC Registry (VI Population).

No.	Endpoint	Summary Statistics*
1	Improvement in MR severity at 1 year over baseline	96.3% (52/54)
2	Improvement in NYHA class at 1 year over baseline	65.5% (38/58)
3	Improvement in KCCQ summary score at 1 year over baseline	19.7 ± 2.87 (61)
4	Improvement in LVEDVi at 1 year over baseline (mL/m^2)	-2.7 ± 2.53 (48)

MR: mitral regurgitation; NYHA: New York Heart Association; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDVi: left ventricular end-diastolic volume index.
*Categorical measures - % (no. / total no.); continuous measures - mean ± SE (n). All results were from paired analyses.

3. Descriptive Endpoints

KCCQ

The KCCQ overall summary scores by visit are presented in Figure 24. The mean score increased from 52.9 at baseline to 72.6 at 1 year post-procedure.

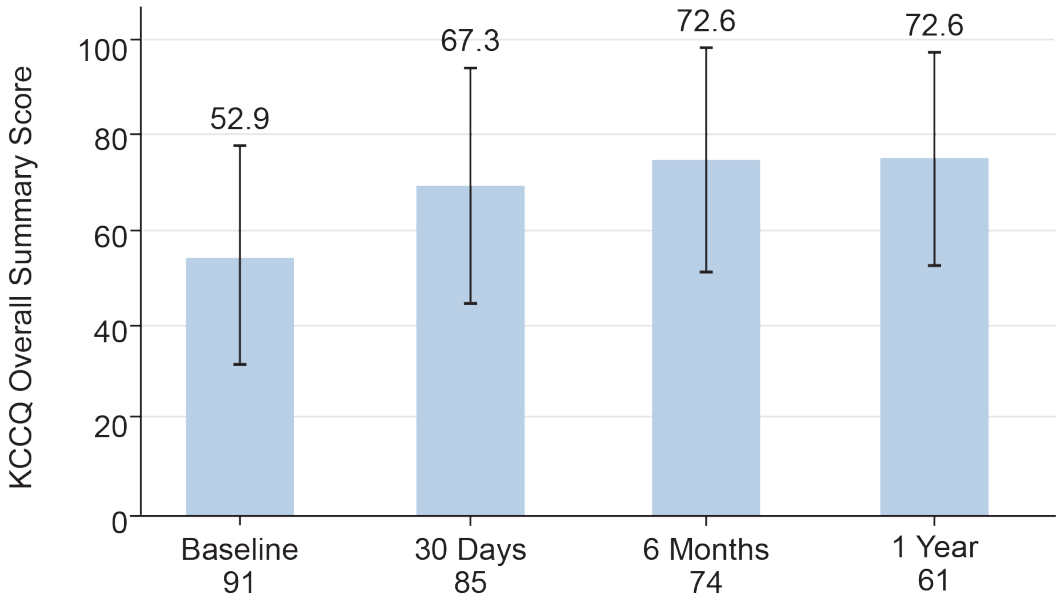

Figure 24. KCCQ Overall Summary Score by Visit – MAC Registry (VI Population). The error bars represent standard deviations.

EQ-5D-5L

The results for the EQ-5D-5L VAS are presented in Figure 25. The mean score was 60.7 at baseline and 72.4 at 1 year post-procedure.

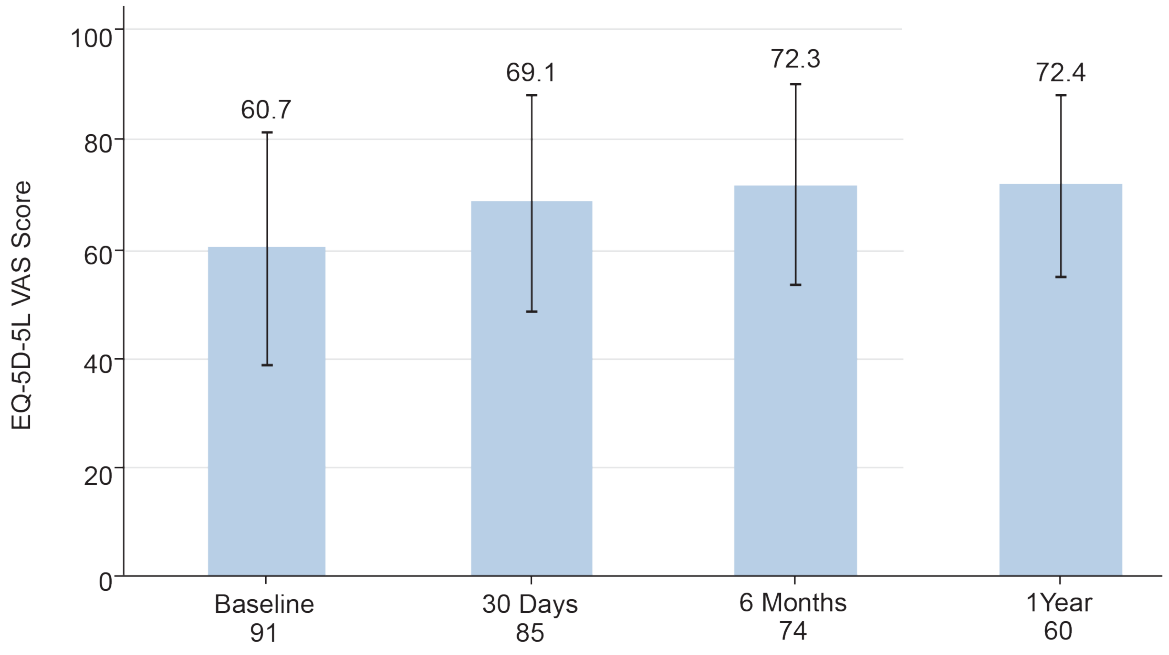

Figure 25. EQ-5D-5L Visual Analog Score by Visit – MAC Registry (VI Population). The error bars represent standard deviations.

NYHA Functional Class

The NYHA classifications by visit are presented in Figure 26. At 1 year post-procedure, 87.9% of patients were in NYHA class I/II compared to 26.9% at baseline.

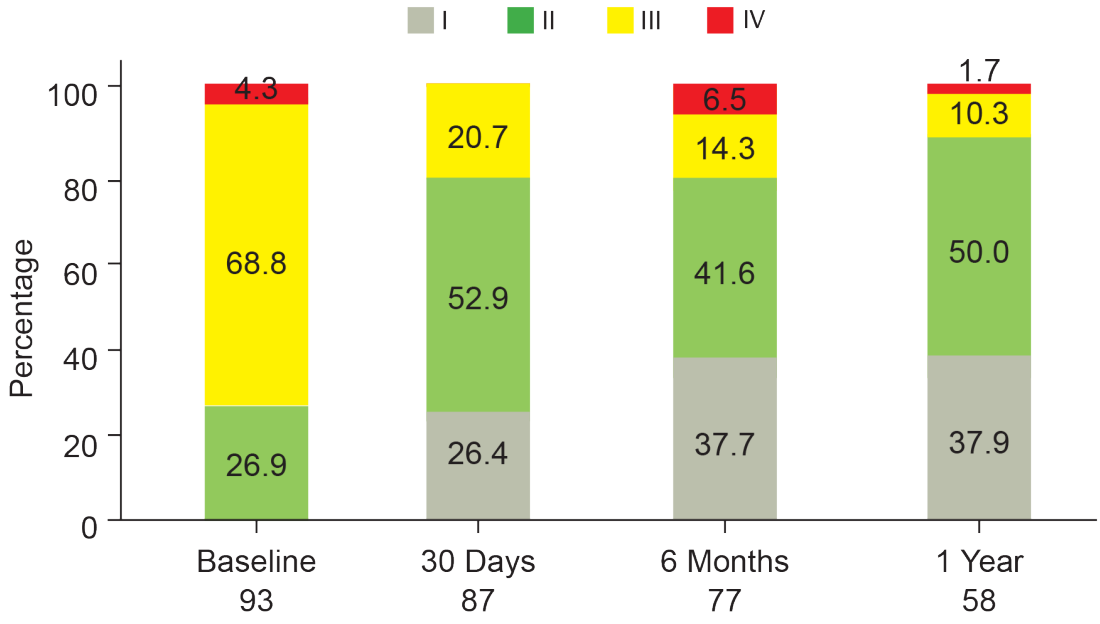

Figure 26. NYHA Functional Class by Visit – MAC Registry (VI Population).

6MWT Distance

The results for the 6MWT distance are presented in Figure 27. The mean walk distance increased from 230.7 meters at baseline to 284.1 meters at 1 year post-procedure.

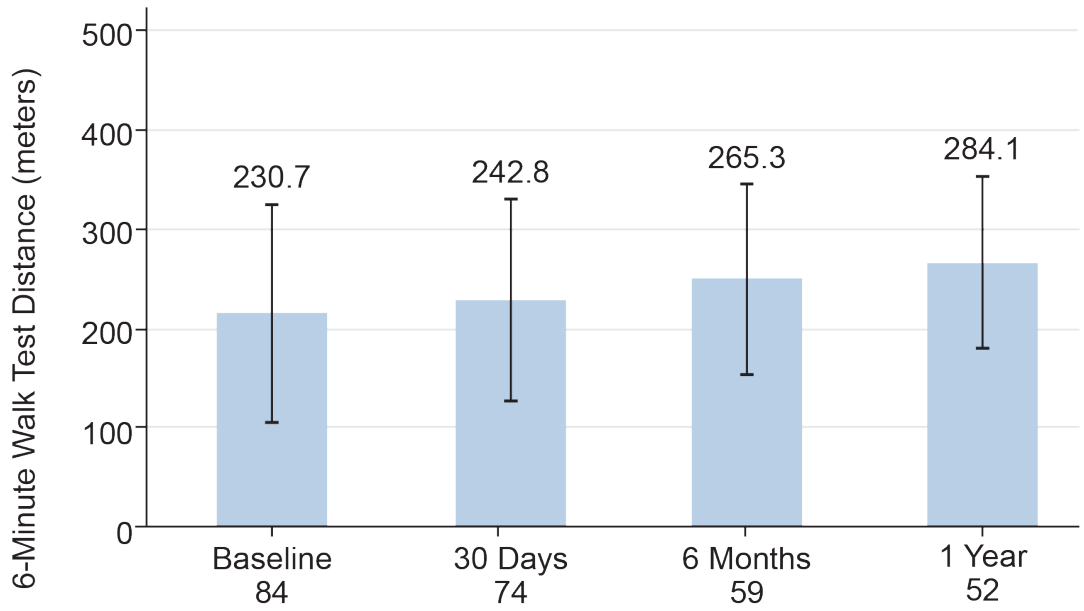

Figure 27. 6MWT Distance by Visit – MAC Registry (VI Population). The error bars represent standard deviations.

MR severity

MR severity by visit is shown in Figure 28. MR reduction to ≤1+ was achieved in 98.2% of patients at 1 year.

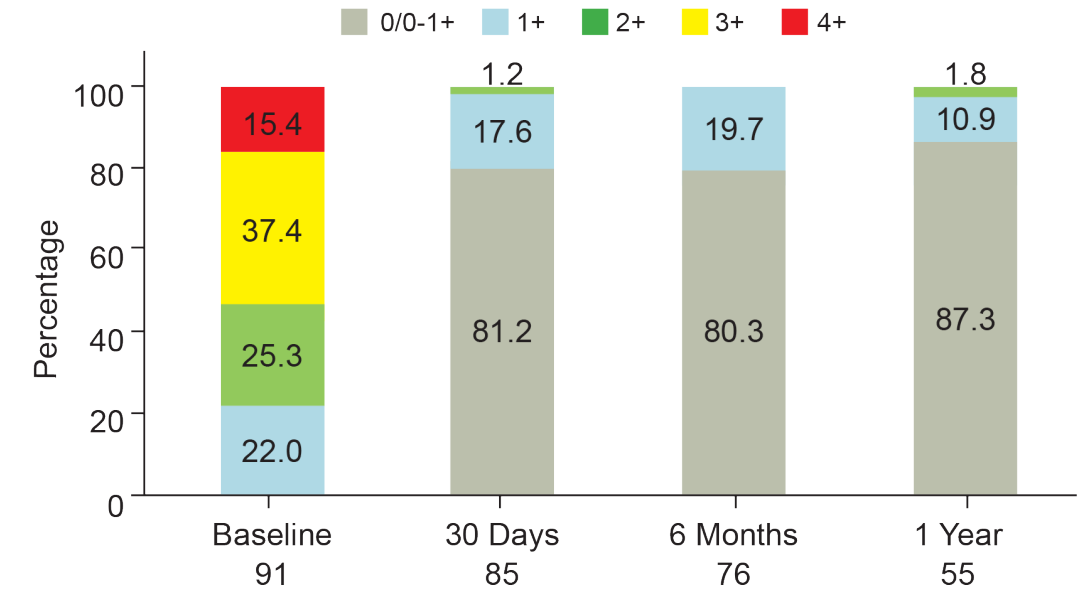

Figure 28. MR Severity by Visit – MAC Registry (VI Population). The worst case between transesophageal echocardiogram and transthoracic echocardiogram results was used as the baseline and transthoracic echocardiogram results were used for all other visits.

4. Adverse Events

The Kaplan-Meier estimates of CEC-adjudicated serious adverse events and other adverse events of clinical interest through 1 year are presented in Table 22.

Table 22. CEC-Adjudicated Adverse Events Through 1 Year – MAC Registry (AT Population).

Event	Kaplan-Meier Estimate*		
	30 Days	6 Months	1 Year
All-cause death	6.0% (6, 6)	12.4% (12, 12)	21.7% (20, 20)
Cardiovascular	6.0% (6, 6)	8.2% (8, 8)	15.6% (14, 14)
Non-cardiovascular	0.0% (0, 0)	4.6% (4, 4)	7.2% (6, 6)
Heart failure rehospitalization	5.2% (5, 5)	15.5% (17, 14)	19.6% (25, 17)
All stroke	1.0% (1, 1)	1.0% (1, 1)	7.8% (7, 6)
Disabling	0.0% (0, 0)	0.0% (0, 0)	5.5% (5, 4)
Non-disabling	1.0% (1, 1)	1.0% (1, 1)	2.3% (2, 2)
Acute kidney injury Stage 2	3.1% (3, 3)	---	---
Acute kidney injury Stage 3	1.0% (1, 1)	---	---
New-onset atrial fibrillation	12.1% (4, 4)	21.7% (7, 7)	21.7% (7, 7)
New permanent pacemaker implantation	6.6% (4, 4)	6.6% (4, 4)	11.6% (6, 6)
Life-threatening bleeding	7.0% (8, 7)	10.3% (11, 10)	11.6% (12, 11)
Fatal bleeding	2.0% (2, 2)	3.2% (3, 3)	4.6% (4, 4)
Hemolysis†	4.0% (4, 4)	4.0% (4, 4)	4.0% (4, 4)
Hemolytic anemia‡	9.2% (9, 9)	9.2% (9, 9)	9.2% (9, 9)
Valve thrombosis	1.0% (1, 1)	4.4% (4, 4)	5.8% (5, 5)
Clinically significant leaflet thrombosis§	1.0% (1, 1)	1.0% (1, 1)	2.5% (2, 2)
Dock fracture	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Dock migration	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Valve embolization	1.0% (1, 1)	1.0% (1, 1)	1.0% (1, 1)
Valve fracture	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Valve migration	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Clinically significant TMVR-related LVOT obstruction	1.0% (1, 1)	1.0% (1, 1)	5.0% (4, 4)
Mitral valve reintervention‖	3.1% (3, 3)	8.8% (8, 8)	11.6% (10, 10)
Balloon mitral valvuloplasty	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Percutaneous paravalvular leak closure	3.1% (3, 3)	7.7% (7, 7)	9.0% (8, 8)
Surgical mitral valve replacement	0.0% (0, 0)	1.1% (1, 1)	2.6% (2, 2)
Valve in valve	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)

Event	Kaplan-Meier Estimate*		
	30 Days	6 Months	1 Year
Other	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	2.1% (2, 2)	3.2% (3, 3)	4.6% (4, 4)
Transient ischemic attack (TIA)	0.0% (0, 0)	1.1% (1, 1)	1.1% (1, 1)
Study device related endocarditis	1.1% (1, 1)	1.1% (1, 1)	1.1% (1, 1)
Major vascular complication	2.0% (2, 2)	2.0% (2, 2)	2.0% (2, 2)
Major access site complication	5.0% (5, 5)	7.3% (7, 7)	7.3% (7, 7)
Atrial septal defect	5.0% (5, 5)	7.3% (7, 7)	7.3% (7, 7)
Major cardiac structure complication	7.0% (7, 7)	9.2% (9, 9)	9.2% (9, 9)

TMVR: transcatheter mitral valve replacement; LVOT: left ventricular outflow obstruction.
[†]Hemolysis: the presence of a paravalvular leak on echocardiogram plus acute decrease in haptoglobin levels and/or increase in serum lactate dehydrogenase (LDH) levels and/or standard blood examinations supporting hemolysis with associated anemia and diagnosis of hemolysis due to prosthetic valve, not requiring transfusion.
[‡]Hemolytic anemia: hemolysis requiring transfusion or intervention (or need for intervention) on the mitral valve.
[§]Inadequate anticoagulation (no anticoagulation, gap in treatment, or subtherapeutic) appeared to be a factor in the occurrence of device thrombosis regardless of the type of anticoagulation prescribed.
[‖]Only interventions after procedure.

5. Subgroup Analyses

The primary endpoint results by gender are presented in Table 23. Kaplan–Meier estimates of all-cause death at 1 year were higher in female patients (38.3%) compared with male patients (6.3%). *Post hoc* analyses on demographics and baseline characteristics revealed no clear predictors for the higher observed mortality rate in female patients than that in male patients. The majority of the deaths were adjudicated by the CEC to be unrelated to the procedure or device.

Table 23. Primary Endpoint Result by Gender – MAC Registry (AT Population).		
Event	**Summary Statistics***	
	Male (N=51)	**Female (N=49)**
All-cause death or heart failure rehospitalization at 1 year	26.8% (13)	41.7% (19)
All-cause death	6.3% (3)	38.3% (17)
Heart failure rehospitalization	21.0% (10)	18.1% (7)

*Kaplan-Meier estimate % (no. of patients with the event).

The primary endpoint result by race is shown in Table 24.

Table 24. Primary Endpoint Result by Race – MAC Registry (AT Population).	
Race	**All-cause Death or Heart Failure Rehospitalization at 1 Year* (N=100)**
White or Caucasian	30/85
Black or African American	0/1
Native Hawaiian or Other Pacific Islander	0/0
Asian	0/2
American Indian or Alaskan Native	0/0
Other	0/2
Unknown	2/10

*no. of patients with events/total no. patients in the subgroup.

6. Other Study Observations

Procedural Information

The procedural data are presented in Table 25.

Table 25. Procedure Data – MAC Registry (AT Population).	
Variable	**Summary Statistics***
Procedure time (min)†	127.1 ± 49.85 (98)
Total fluoroscopy time (min)	57.4 ± 32.14 (100)
Dock deployment time (min)‡	70.5 ± 36.74 (97)
Multiple valve implant	3.0% (3/100)

Variable	Summary Statistics*
Percutaneous paravalvular leak closure	12.0% (12/100)
Procedure aborted	7.0% (7/100)
Conversion to surgery	1.0% (1/100)

*Continuous measures - mean ± SD (n); categorical measures - % (no./total no.).
†Defined as the time from femoral vein access to guide sheath removal.
‡Defined as the time from steerable catheter insertion to removal.

Index Hospitalization

The index hospitalization information is presented in Table 26.

Table 26. Index Hospitalization Information – MAC Registry (VI Population).

Variable	Summary Statistics*
Index hospitalization stay (days)†	3.0 ± 3.38 (88)
Intensive care stay (days)	0.5 ± 1.30 (88)
In-hospital death	5.4% (5/93)

*Continuous measures - mean ± SD (total no.); categorical measures – % (no./total no.).
†Index hospitalization stay excludes in-hospital deaths.

Additional Echocardiographic Data

Additional echocardiographic data through 1 year are presented in Table 27, which show improved hemodynamics.

Table 27. Additional Echocardiographic Data – MAC Registry (VI Population).

Parameter	Summary Statistics*			
	Baseline	30 Days	6 Months	1 Year
LV end diastolic volume index (mL/m^2)	57.6 ± 22.20 (91)	56.6 ± 18.89 (79)	57.1 ± 18.51 (63)	57.8 ± 17.45 (48)
LV end diastolic diameter (cm)	5.0 ± 0.07 (93)	4.9 ± 0.07 (80)	4.9 ± 0.08 (73)	5.0 ± 0.09 (51)
LV ejection fraction (%)	54.7 ± 10.43 (93)	46.5 ± 10.67 (86)	46.2 ± 10.07 (76)	48.9 ± 10.22 (56)
LV end diastolic volume (mL)	111.5 ± 44.47 (91)	110.3 ± 38.92 (79)	111.4 ± 37.11 (63)	116.8 ± 37.49 (48)
LV end systolic volume (mL)	51.8 ± 28.13 (91)	59.7 ± 28.80 (74)	60.5 ± 28.89 (59)	59.7 ± 27.13 (46)

Transmitral antegrade mean gradient (mmHg)	6.0 ± 3.24 (93)	5.6 ± 1.76 (85)	5.4 ± 1.68 (75)	5.6 ± 2.20 (56)
Stroke volume index (mL/m^2)	27.7 ± 8.23 (88)	36.2 ± 14.69 (82)	34.7 ± 10.11 (71)	35.5 ± 12.43 (50)
Cardiac output index ($L/min/m^2$)	2.0 ± 0.58 (88)	2.7 ± 1.12 (82)	2.5 ± 0.71 (71)	2.5 ± 0.74 (50)

LV: left ventricular.
*Continuous measures - mean ± SD (n).

7. Pediatric Extrapolation

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

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation. The ENCIRCLE trial involved 352 investigators, of which none were full-time or part-time employees of the sponsor and 54 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f), as described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 54
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: 1

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

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

In accordance with the provisions of section 515(c)(3) 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the Main Cohort, the Kaplan-Meier estimate for the composite rate of all-cause death and heart failure rehospitalization at 1 year was 25.2%, with a one-sided 97.5% upper confidence bound of 30.6%, which met the performance goal of 45% ($p<0.001$). MR reduction to ≤1+ was achieved in 95.7% of patients at 1 year. The reduction translated into favorable left ventricular remodeling, with a significant reduction in LVEDVi at 1 year and improved hemodynamics, including increased stroke volume and cardiac index. Clinically significant benefits in functional and health status were seen in patients, as evidenced by more patients in NYHA class I/II (87.9%) compared to baseline (28.6%). The mean KCCQ overall summary score increased by 18.0 points at 1 year compared to baseline. The EQ-5D-5L VAS score improved by 8.7 points at 1 year compared to baseline.

In the MAC Registry, the Kaplan-Meier estimate for the composite rate of all-cause death and heart failure rehospitalization at 1 year was 34.1%. MR was successfully reduced to ≤1+ in 98.2% of patients at 1 year. Patients experienced improved hemodynamics through 1 year, including increased stroke volume and cardiac index. Clinically significant benefits in functional and health status were manifested by more patients in NYHA class I/II (87.9%) and a 19.7-point increase in the mean KCCQ overall summary score at 1 year compared to baseline. The EQ-5D-5L VAS score improved by 11.7 points at 1 year compared to baseline.

B. Safety Conclusions

The risks of the SAPIEN M3 system are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that this device is suitable for long-term implant.

The valve implantation success rate was high, with the procedure being aborted in 4.0% and 7.0% of the cases in the Main Cohort and MAC Registry, respectively. The CEC adjudicated severe adverse events at 30 days included all-cause death (0.7% in the Main Cohort and 6.0% in the MAC Registry), all stroke (2.7% and 1.0%), new-onset atrial fibrillation (7.9% and 12.1%), life-threatening bleeding (3.7% and 7.0%) and clinically significant leaflet thrombosis (2.3% and 1.0%).

C. Benefit-Risk Determination

The probable benefits of TMVR with the SAPIEN M3 system include improved hemodynamics and improved health and functional statuses as measured by KCCQ and NYHA functional class, respectively.

The probable risks of TMVR with the SAPIEN M3 system include death, stroke, new-onset atrial fibrillation, life-threatening bleeding, and clinically significant leaflet thrombosis.

1. Patient Perspectives

   Patient perspectives considered during the review included patient reported outcomes as measured by KCCQ and EQ-5D-5L.

In conclusion, given the available information above, the data support that for patients with symptomatic moderate-to-severe or severe MR and those with symptomatic mitral valve dysfunction associated with MAC, who are deemed unsuitable for surgery or TEER therapy, the probable benefits of TMVR with the SAPIEN M3 system outweigh the probable risks.

D. Overall Conclusion

The data in this application supports the reasonable assurance of safety and effectiveness of the SAPIEN M3 system in patients with symptomatic moderate-to-severe or severe MR and those with symptomatic mitral valve dysfunction associated with MAC who are deemed unsuitable for surgery or TEER therapy by a multidisciplinary heart team.

XIV. CDRH DECISION

CDRH issued an approval order on December 22, 2025. The final conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. **Continued Follow-up of ENCIRCLE Premarket Cohort**: The study will consist of all living patients who were enrolled under the IDE, including those enrolled in the continued access protocol (CAP) investigation. The objective of this study is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints include all-cause death, all stroke, heart failure rehospitalization, mitral valve reintervention, 6MWT distance, KCCQ score, EQ-5D-5L score, NYHA functional class, and echocardiographic endpoints.

2. **Registry-Based Real-World Use Surveillance**: The surveillance will be carried out to assess the real-world performance of the SAPIEN M3 system. It will consist of two cohorts, namely, patients treated for symptomatic moderate-to-severe or severe MR (Cohort A) and patients treated for symptomatic mitral valve dysfunction associated with MAC (Cohort B) that are entered into the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry. Cohort A will involve all consecutive patients treated in the first 2 years following device approval or a total of 500 consecutively treated patients, whichever is greater (Cohort A enrollment period). Cohort B will involve all consecutive patients treated in the first 2 years following device approval or a total of 200 consecutively treated patients, whichever is greater (Cohort B enrollment period). Data collection in Cohort A will continue for under-enrolled racial and ethnic groups until each group has enrolled a minimum number of patients as specified: Black/African American, 50; Asian, 50, American Indian/Alaskan Native, 25, Native Hawaiian/Pacific Islander, 25; and Hispanic or Latino

ethnicity, 50. All patients will be followed through 5 years post-procedure (Cohort A and Cohort B follow-up period). The clinical data through one (1) year will be collected through the TVT Registry. The follow-up data (including all-cause death, stroke, mitral valve reintervention, and heart failure rehospitalizations) from year 2 through year 5 post-procedure will be obtained through linking the TVT Registry data with the Centers for Medicare and Medicaid Services (CMS) claims database.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.