SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Mitral Valve Repair Device
Device Trade Name:	PASCAL Precision Transcatheter Valve Repair System
Device Procode:	NKM
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P220003
Date of FDA Notice of Approval:	September 14, 2022

II. INDICATIONS FOR USE

The PASCAL Precision Transcatheter Valve Repair System (PASCAL Precision system) is indicated for the percutaneous reduction of significant, symptomatic mitral regurgitation (MR ≥ 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 MR.

III. CONTRAINDICATIONS

The PASCAL Precision system is contraindicated in patients with the following conditions:

- Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen
- Untreatable hypersensitivity or contraindication to nitinol alloys (nickel and titanium) or contrast media
- Active endocarditis of the mitral valve
- Rheumatic etiology for mitral regurgitation
- Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

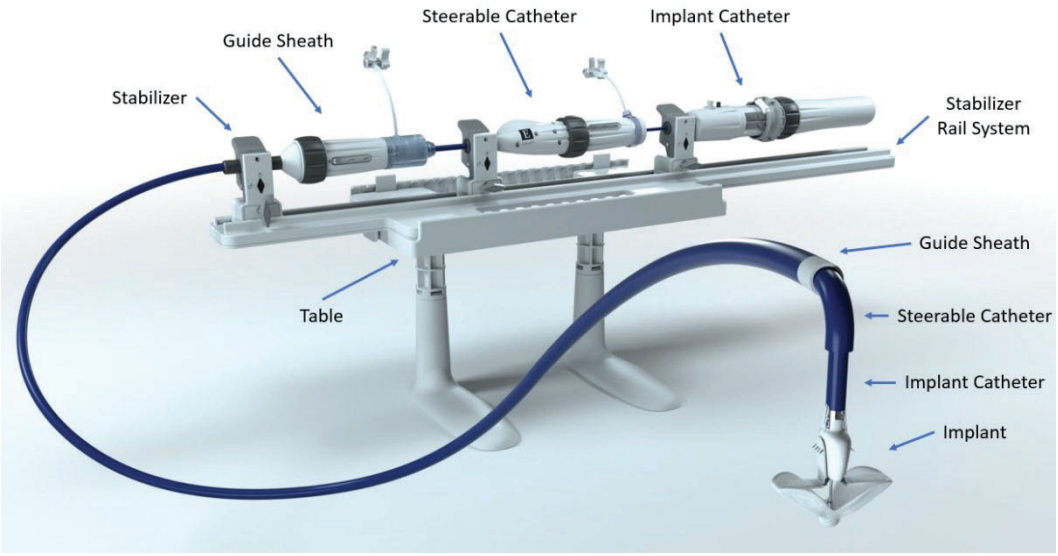
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PASCAL Precision system labeling.

V. DEVICE DESCRIPTION

The PASCAL Precision system (model 20000), as shown in Figure 1, comprises the PASCAL Precision implant system, the PASCAL Precision guide sheath, and various accessories.

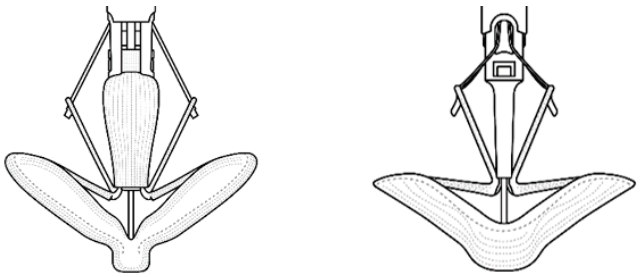
Figure 1: PASCAL Precision Transcatheter Valve Repair System



- **PASCAL Precision Implant System**

  The PASCAL Precision implant system consists of the steerable catheter (outermost catheter layer), and implant catheter (innermost catheter layer) delivery components, and the implant. The implant is available in two sizes, the PASCAL implant and the narrower profile PASCAL Ace implant, as shown in Figure 2. The implant is deployed and secured to the leaflets of the native mitral valve, acting as a gap filler in the regurgitant orifice. The primary components of the implant are the spacer, paddles, and clasps, which are constructed from nitinol and covered in polyethylene terephthalate (PET) cloth. The steerable catheter has a rotational control knob (flex knob) that actuates the flexion mechanism to navigate and position the implant to the target location. The implant catheter is attached to the implant by sutures and a threaded wire. It controls the deployment of the implant and is provided assembled within the steerable catheter.

Figure 2: PASCAL Implants



PASCAL PASCAL Ace

- **PASCAL Precision Guide Sheath**

  The PASCAL Precision guide sheath provides atrial access. It has a hydrophilic coating and a rotational control knob, which actuates the flexion mechanism to position the guide sheath. The implant system is inserted into the guide sheath. A peel away loader, as shown in Figure 3, is used to introduce the implant and steerable catheters through the guide sheath seals. The loader is included in both the implant system and guide sheath packaging for user convenience. The guide sheath packaging also includes an introducer component, as shown in Figure 4, which is compatible with a 0.035" guidewire.

Figure 3: Loader

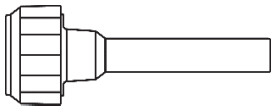
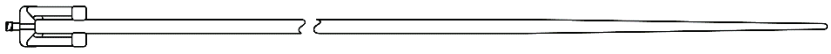


Figure 4: Introducer



- **Accessories**

  The PASCAL Precision system is used in conjunction with the PASCAL stabilizer rail system and the PASCAL table during a procedure. The stabilizer rail system is an optional, non-patient contacting, sterile, single-use accessory intended to aid with positioning and stabilization of the PASCAL Precision system during implantation procedures. The PASCAL table is used outside of the sterile field (beneath the sterile drape) to provide a stable platform for the implant system, guide sheath, and stabilizer rail system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of degenerative mitral regurgitation (DMR) in patients at prohibitive risk for mitral valve surgery, including medical therapy and treatment with other approved transcatheter edge-to-edge repair (TEER) therapy. 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 PASCAL Precision system is commercially available in the European Union and United Kingdom. The PASCAL Precision system implants (PASCAL and PASCAL Ace) are the same as those in the earlier generation PASCAL system (model 10000). The PASCAL system with the PASCAL implant is commercially available in the European Union, United Kingdom, Australia, Israel, Kuwait, and United Arab Emirates. The PASCAL system with the PASCAL Ace implant is commercially available in the European Union, United Kingdom, Australia, New Zealand, Israel, Kuwait, and Saudi Arabia. The PASCAL Precision system and the PASCAL system have 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 PASCAL Precision system:

- Death
- Abnormal laboratory values
- Allergic reaction to anesthetic, contrast, heparin, Nitinol
- Anemia or decreased hemoglobin (may require transfusion)
- Aneurysm or pseudoaneurysm
- Angina or chest pain
- Anaphylactic shock
- Arrhythmias – atrial (i.e., atrial fibrillation, Supraventricular tachycardia)
- Arrhythmias – ventricular (i.e., ventricular tachycardia, ventricular fibrillation)
- Arterio-venous fistula
- Atrial septal injury requiring intervention
- Bleeding
- Cardiac arrest
- Cardiac failure
- Cardiac injury, including perforation
- Cardiac tamponade/pericardial effusion
- Cardiogenic shock
- Chordal entanglement or rupture that may require intervention
- Coagulopathy, coagulation disorder, bleeding diathesis
- Conduction system injury which may require permanent pacemaker
- Deep vein thrombosis (DVT)
- Deterioration of native valve (e.g., leaflet tearing, retraction, thickening)
- Dislodgement of previously deployed implant
- Dyspnea
- Edema
- Electrolyte imbalance
- Emboli/embolization including air, particulate, calcific material, or thrombus
- Endocarditis
- Esophageal irritation
- Esophageal perforation or stricture
- Exercise intolerance or weakness
- Failure to retrieve any PASCAL Precision system components
- Fever
- Gastrointestinal bleeding or infarct
- Heart failure

- Hematoma
- Hemodynamic compromise
- Hemolysis
- Hemorrhage requiring transfusion or intervention
- Hypertension
- Hypotension
- Implant deterioration (wear, tear, fracture, or other)
- Implant embolization
- Implant malposition or failure to deliver to intended site
- Implant migration
- Implant thrombosis
- Infection
- Inflammation
- Left ventricular outflow tract (LVOT) obstruction
- Mesenteric ischemia
- Multi-system organ failure
- Myocardial infarction
- Native valve injury
- Native valve stenosis
- Nausea and/or vomiting
- Need for open surgery (conversion, emergent or non-emergent reoperation, explant)
- Nerve injury
- Neurological symptoms, including dyskinesia, without diagnosis of TIA or stroke
- Non-neurological thromboembolic event
- Pain
- Papillary muscle damage
- Paralysis
- PASCAL Precision system component(s) embolization
- Peripheral ischemia
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Pulmonary embolism
- Reaction to anti-platelet or anticoagulation agents
- Renal failure
- Renal insufficiency
- Respiratory compromise, respiratory failure, atelectasis, pneumonia – may require prolonged ventilation
- Retroperitoneal bleed
- Septal damage or perforation
- Septicemia, sepsis
- Skin burn, injury or tissue changes due to exposure to ionizing radiation
- Single leaflet device attachment (SLDA)
- Stroke
- Syncope
- Transient ischemic attack (TIA)
- Urinary tract infection and/or bleeding
- Valvular regurgitation
- Vascular injury or trauma, including dissection or occlusion
- Vessel spasm
- Ventricular wall damage or perforation
- Worsening native valve regurgitation / valvular insufficiency
- Worsening of heart failure
- Wound dehiscence, delayed or incomplete healing

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 PASCAL Precision system were performed in

accordance with ISO 5910:2018, *Cardiovascular implants and extracorporeal systems - Cardiac valve repair devices*.

1. **Biocompatibility**

Biocompatibility assessments were completed on the PASCAL Precision 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 biocompatibility test results for the PASCAL Precision system implants and delivery system components are summarized in Table 1 and Table 2, respectively.

Table 1: Summary of PASCAL Precision System Implants Biocompatibility Assessments

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method using human fibroblast cells	Non-cytotoxic
Sensitization	Guinea pig maximization test	Non-sensitizing
Irritation/ intracutaneous reactivity	Rabbit intracutaneous reactivity test	Non-irritating
Genotoxicity	Ames assay/bacterial reverse mutation test	Non-mutagenic
	Mouse lymphoma mutagenesis assay with confirmation	Non-clastogenic
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
	Complement activation test	No risk to activate complement
	Direct contact platelet and leukocyte count test	No impact on platelet and leukocyte counts
	In-vivo thrombogenicity with domestic pigs	No evidence of thrombosis or hemolysis after implantation for up to 20 weeks
Pyrogenicity	Rabbit pyrogen test –	Non-pyrogenic

Biological Effect Per ISO 10993-1	Test Method	Results
	materials mediated	
Acute systemic toxicity	Mouse systemic injection test	Not inducing significantly greater biological reactions than the control extracts
Implantation	90-day systemic toxicity in rabbits via intramuscular implantation	No microscopic evidence of cytotoxicity. No abnormalities were observed in any of the implant sites for the test article upon macroscopic gross tissue examination. The test article did not demonstrate any local or systemic signs of toxicity when implanted in rabbits for up to 90 days.
Physicochemical	Chemical characterization of volatile organic compounds, semi-volatile organic compounds, non-volatile organic compounds 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 PASCAL Precision System Steerable Catheter, Implant Catheter, and Guide Sheath Biocompatibility Assessments

Biological Effect Per ISO 10993-1	Test Method	Results
Cytotoxicity	Medium eluate method using L-929 mouse fibroblast cells	Non-cytotoxic
Sensitization	Guinea pig maximization test	Non-sensitizing
Irritation/intracutaneous reactivity	Rabbit intracutaneous reactivity test	Non-irritating
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
	Complement activation test	No risk to activate complement
	Platelet and leukocyte count test	No impact on platelet and leukocyte counts
	In-vivo thrombogenicity	No clinically significant risk

Biological Effect Per ISO 10993-1	Test Method	Results
	with domestic pigs	of thrombosis or thromboembolism
Pyrogenicity	Rabbit pyrogen test – materials mediated	Non-pyrogenic
Acute systemic toxicity	Mouse systemic injection test	Not inducing a significantly greater biological reaction than the control extracts

2. **Bench Testing**

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

Table 3: Summary of PASCAL Precision System Bench Testing

Test	Purpose	Results
PASCAL and PASCAL Ace Implants		
Finite element analysis	To determine mechanical stress/strain during device loading, deployment and cyclic loading. Results used to assess the fatigue life of the device.	No fracture of implant structural components predicted within a minimum of 600 million cycles under clinically representative challenging conditions.
Fatigue testing	To assess the fatigue resistance of the implants under cyclic loading for up to 600 million cycles.	No frame cracks or fractures were observed at minimum 10x magnification following 600 million cycles of fatigue testing.
Corrosion analysis (pitting, galvanic and fretting)	To assess pitting, galvanic and fretting corrosion resistance of the implant.	No pitting, galvanic or fretting corrosion observed.
Nickel leaching test	To evaluate the nickel leaching of the implant.	The release of nickel over time was well within acceptable limits.
MRI compatibility	To evaluate the magnetic resonance imaging (MRI) safety and compatibility of the implant and ensure that the implant is not affected by scanning at 1.5 Tesla and 3.0 Tesla field strengths.	The implants were determined to be Magnetic Resonance Conditional under the conditions listed in the device labeling.
PASCAL Precision Implant System		
Implant clasps fully close	To verify that implant clasps can fully close.	Delivery system performed as intended to close implant clasps.
Implant maximum paddle angle	To verify that implant paddle maximum opening angle is	Delivery system performed as intended to open implant

Test	Purpose	Results
	within prespecified angle.	paddles, met design requirements and acceptance criteria.
Implant retrieval force	To verify that the force to retrieve implant back into the guide sheath is within prespecified limits.	Force to retrieve met design requirements and acceptance criteria.
Implant system insertion force	To verify that force to advance the loader and implant system into guide sheath and through the length of the guide sheath is within prespecified limits.	Force to advance loader and implant system met design requirements and acceptance criteria.
Implant system torque tests	To verify that torque to turn, unscrew or release implant system components such as actuation knob, release cover, suture lock, actuation wire and release knob are within prespecified limits.	Force to torque various controls on the delivery system met design requirements and acceptance criteria.
Force to advance and retract implant system components (including sliders, steerable catheter and implant catheter)	To ensure that force to advance and retract the implant system and its components are within prespecified limits.	Force to advance and retract the device components met design requirements and acceptance criteria.
Suture tension to lift implant clasps	To verify that the suture tension to lift clasps are within prespecified limits.	Suture tension met design requirements and acceptance criteria.
Suture removal force	To verify that the force to remove sutures during implant deployment are within prespecified limits.	Suture removal force met design requirements and acceptance criteria.
Actuation wire release force	To verify that the actuation wire release force is within prespecified limits.	Actuation wire release force met design requirements and acceptance criteria.
Attachment finger wingspan measurement	To verify that the measurement of the wingspan of the implant catheter attachment fingers after implant release is within prespecified limits	Wingspan met design requirements and acceptance criteria.
PASCAL Precision Guide Sheath		
Guide sheath lubricity and integrity	To verify the frictional force from the guide sheath lubricity and to ensure guide sheath liner remains intact after implant system insertion and removal.	Frictional force and liner integrity met design requirements and acceptance criteria.

Test	Purpose	Results
Guide sheath hemostasis	To ensure the guide sheath maintains hemostasis.	Guide Sheath met design requirements and acceptance criteria.
Guide sheath flush port orientation	To verify that the guide sheath flex directions are oriented within the predetermined angle of flush tube.	Guide Sheath met design requirements and acceptance criteria.
Guide sheath air accumulation without aspiration	To verify that the volume of air within guide sheath prior to implant system insertion is within prespecified volume limits under clinically representative challenging pulsatile flow and wait period.	Guide sheath air volume met design requirements and acceptance criteria under simulated clinically representative challenging conditions.
Overall System		
Radiopacity tests	To test that the implant system, guide sheath and introducer have radiopaque features visible under imaging fluoroscopy.	All radiopaque features met design requirements for visibility under fluoroscopic imaging.
Functionality tests	To test that product functions as intended after predetermined ethylene oxide (EtO) sterilization, pre-conditioning, simulated distribution and shelf-life conditioning.	Delivery systems and accessories met design requirements and acceptance criteria for function in simulated use conditions.
Visual inspection	To test that product is free from physical defects and particulate.	Delivery systems and accessories met design requirements and acceptance criteria for visual inspection
Dimensional inspections	To verify implant system and guide sheath catheter diameters and working length are within prespecified tolerance limits.	Delivery systems and accessories met design requirements and acceptance criteria for dimensional inspection
Maximum extension height and distance	To verify that the implant system and guide sheath can extend and have an exposure distance that is within prespecified limits.	Delivery system components met design requirements and acceptance criteria.
Maximum actuation force (flexed and unflexed)	To verify the maximum actuation force for the implant system within the guide sheath under flexed and fully unflexed configurations	Delivery system components met design requirements and acceptance criteria.
System hemostasis	To ensure that the PASCAL Precision system maintains	Delivery system met design requirements and acceptance

Test	Purpose	Results
	hemostasis.	criteria.
Force to flex and flex angle	To verify that the force to flex and flex angles of the steerable catheter and guide sheath are within prespecified limits.	Delivery system components met design requirements and acceptance criteria.
Kink radius test	To verify that the guide sheath and implant system kink radius is within prespecified limits.	Delivery system components met design requirements and acceptance criteria.
Tensile tests	To verify guide sheath and implant system components meet the prespecified tensile strength limits.	Delivery system components and bonds met design requirements and acceptance criteria.
Torsion tests	To verify the implant system components meet torsional bond strength requirements.	Delivery system components and bonds met design requirements and acceptance criteria.
Air introduction	To verify that the PASCAL Precision system does not introduce air during device insertion or clinical maneuvers that could pose clinical risk.	Delivery systems met design requirements and acceptance criteria under simulated clinically representative challenging conditions.
Atrial pressure monitoring	To evaluate the pressure monitoring equivalency between the PASCAL Precision system and a 5F diagnostic pigtail catheter	The ability to measure atrial pressure was equivalent to the control device.
Particulate characterization	To evaluate and characterize the particulate and fiber counts of the PASCAL Precision system.	Particulate size and count were within established limits.

B. <u>Animal Studies</u>

The PASCAL Precision system underwent Good Laboratory Practice-compliant preclinical *in vivo* evaluations in a porcine model, as summarized below:

- *Acute study*: Three (3) sets of delivery components (implant system and guide sheath) were evaluated for acute thrombogenicity. Clinically significant moderate thrombus was discovered in the flushed contents of the implant catheter lumens of one test article, which was deemed unlikely to embolize based on its location. No clinically significant thromboembolism was observed in the target organs.

- *Chronic study*: A total of 12 PASCAL implants (3 at 30 days, 5 at 90 days, and 4 at 140 days) and 8 PASCAL Ace implants (4 at 90 days and 4 at 140 days) were evaluated for chronic safety and performance. The implants showed appropriate healing, with no structural damage or deterioration observed by gross and

histopathological assessment and no evidence of device embolization or other clinically significant device-related pathologies.

C. Sterilization

The PASCAL Precision system is sterilized via ethylene oxide (EtO) in accordance with EN ISO 11135-1:2014, *Sterilization of health care products – Ethylene oxide – Requirements for development, validation and routine control of a sterilization process for medical devices*. The validated EtO sterilization process demonstrated a minimum Sterility Assurance Level (SAL) of 10^{-6}.

D. Packaging and Shelf Life

The PASCAL Precision implant system and guide sheath are packaged separately. Each is secured to a high-density polyethylene (HDPE) card with preformed protective connectors and tunnels. The HDPE card is inserted into a Tyvek/poly pouch, which is sealed and inserted into a shelf carton and then a shipping carton. The PASCAL Precision system accessories are packaged in stand-alone shipper boxes and distributed separately from the rest of the system. The PASCAL table is packaged as a non-sterile product.

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

The shelf life is 1 year for the PASCAL Precision implant system and guide sheath and 2 years for the PASCAL stabilizer rail system, as demonstrated by packaging integrity and product functional testing on aged samples.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the PASCAL Precision system for patients with symptomatic DMR (≥3+) who are at prohibitive risk for mitral valve surgery under IDE G170166 (entitled the "CLASP IID trial"). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The main cohort of the CLASP IID trial was a prospective, multicenter, randomized, parallel-group study. Eligible patients were randomized (2:1) into two groups: PASCAL system and MitraClip system. The CLASP IID trial also had a single-arm side registry that enrolled eligible patients deemed inappropriate for randomization due to complex mitral valve anatomy deemed suitable for treatment with the PASCAL system, but not for the MitraClip

System.

The CLASP IID trial employed a Central Screening Committee (CSC) that ensured patient appropriateness for enrollment, an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues, a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint related events reported during the trial, and an echocardiographic core laboratory for independently analyzing all echocardiograms.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the CLASP IID trial was limited to patients who met the following inclusion criteria:

   - Eighteen (18) years of age or older.
   - Patient is able and willing to give informed consent and follow protocol procedures and comply with follow-up visit requirements.
   - Patient is determined to be at prohibitive risk for mitral valve surgery by the heart team.
   - Patient is determined to be a candidate for transcatheter mitral valve repair by the heart team for PASCAL, and for MitraClip (for randomized cohort only).
   - Patient must be deemed a candidate for transseptal catheterization by the site interventional operator.
   - Mitral regurgitation (3+ to 4+) as measured by the Echocardiographic Core Laboratory via transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE).
   - Suitable valve and regurgitant jet morphology.
   - Left ventricular ejection fraction (LVEF) > 20%.
   - Left ventricular end-diastolic diameter (LVEDD) < 80 mm by TTE.

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

   - Patient in whom a TEE is contraindicated or screening TEE is unsuccessful.
   - Mitral valve anatomy which may preclude proper PASCAL or MitraClip (for randomized cohort only) access, use and/or deployment or sufficient reduction in MR.
   - Echocardiographic evidence of intracardiac mass, thrombus, or vegetation. Chronic scarred thrombi may be considered for inclusion by the core laboratory.
   - Echocardiographic evidence of severe right ventricular dysfunction per core laboratory assessment
   - Patient with refractory heart failure requiring advanced intervention (i.e., left ventricular assist device, transplantation; American College of Cardiology/American Heart Association Stage D heart failure).
   - Clinically significant, untreated coronary artery disease.
   - Recent stroke.

- Other severe valve disorders requiring intervention or left ventricular outflow obstruction.
- Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis), 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.
- Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias.
- Any recent percutaneous coronary, carotid, endovascular intervention, carotid surgery, or cardiac surgery.
- Recent implant or revision of any rhythm management device (i.e., pacemaker, implantable cardioverter defibrillator [ICD], cardiac resynchronization therapy [CRT] with or without cardioverter-defibrillator).
- Tricuspid valve disease requiring surgery or severe tricuspid regurgitation.
- Any planned interventional cardiac procedure.
- Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
- Any prior mitral valve surgery or transcatheter mitral valve procedure (excluding chordal replacement or surgical annuloplasty repair).
- Active systemic infection, including active endocarditis.
- Active rheumatic heart disease or rheumatic etiology for MR.
- Severe aortic stenosis or regurgitation.
- Absence of CRT with a Class I indication criteria for biventricular pacing.
- Resting systolic blood pressure <90 or >160 mmHg after repeated measurements.
- Estimated pulmonary artery systolic pressure (PASP) > 70 mmHg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the catheterization laboratory is 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.
- Known history of untreated, severe carotid stenosis.
- History of deep vein thrombosis (DVT) or pulmonary embolism (PE).
- Presence of an occluded or thrombosed inferior vena cava (IVC) filter that would interfere with the delivery catheter, or presence of an ipsilateral deep vein thrombosis.
- Severe chronic obstructive pulmonary disease (COPD).
- Severe renal insufficiency with estimated glomerular filtration rate (eGFR) ≤ 25 ml/min or requiring chronic renal replacement therapy.
- Untreatable hypersensitivity or contraindication to any of the following: aspirin or clopidogrel or ticlopidine; heparin or bivalirudin, or warfarin; nitinol alloys (nickel and titanium); or contrast media.
- Pregnant or planning pregnancy within next 12 months. Note: Female patients of childbearing potential need to have a negative pregnancy test performed within 14 days prior to intervention and be adherent to an accepted method of contraception
- Concurrent medical condition with a life expectancy of less than 12 months in the judgment of the Investigator

- Patient is currently participating in another investigational biologic, drug or device clinical study where the primary study endpoint was not reached at time of enrollment
- Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship

2. Follow-up Schedule

The follow-up time points included day of implantation, discharge, 30 days, 6 months, 1 year, and annually thereafter to 5 years post procedure. Preoperative and post-operative assessments included physical assessments and medical history, laboratory measurements, imaging tests, and health surveys. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary safety endpoint was a composite of Major Adverse Events (MAEs) at 30 days, which included: cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding (defined as major bleeding or above), and non-elective mitral valve re-intervention (either percutaneous or surgical). The hypothesis for the primary safety endpoint of the randomized cohort was as follows:

$$H_0: P_{\text{PASCAL}}(T) - P_{\text{MitraClip}}(T) \geq 15\%$$
$$H_A: P_{\text{PASCAL}}(T) - P_{\text{MitraClip}}(T) < 15\%$$

where P_{PASCAL} and $P_{\text{MitraClip}}$ represent the proportions of patients with MAEs at 30 days in the PASCAL and MitraClip arms, respectively, and 15% is the non-inferiority margin.

The primary effectiveness endpoint was the proportion of patients with MR ≤ 2+ at 6 months as assessed by TTE by the Echocardiographic Core Laboratory. The hypothesis for the primary effectiveness endpoint of the randomized cohort was as follows:

$$H_0: P_{\text{PASCAL}}(T) - P_{\text{MitraClip}}(T) \leq -18\%$$
$$H_A: P_{\text{PASCAL}}(T) - P_{\text{MitraClip}}(T) > -18\%$$

where P_{PASCAL} and $P_{\text{MitraClip}}$ represent the proportions of patients with MR ≤ 2+ at 6 months in the PASCAL and MitraClip arms, respectively, and -18% is the non-inferiority margin.

Both the primary safety and the primary effectiveness hypotheses of the randomized cohort were to be tested at a one-sided significance level of 0.05. The registry cohort was to be analyzed descriptively.

Among the secondary endpoints, those to be evaluated at the 6-month or earlier follow-up time points included the following:

- Major adverse event rate at 6 months
- All-cause mortality at 30 days and 6 months
- Heart failure hospitalization at 30 days and 6 months
- New onset of permanent atrial fibrillation at 30 days
- Non-elective mitral valve re-intervention (either percutaneous or surgical) at 6 months
- Residual atrial septal defect (ASD) by Doppler at 30 days and 6 months
- Transfusion ≥ 2 units of whole blood or packed red blood cells through discharge
- Gastrointestinal complication requiring surgery at 30 days
- 6 Minute Walk Test (6MWT) at 30 days and 6 months
- Quality of life (QoL): Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-36, and EQ-5D-5L at 30 days and 6 months
- Total procedure time (pre-procedure prep time, procedure time, post-procedure time) through discharge
- Total length of stay at discharge

The planned sample size was 300 patients for the randomized cohort and 150 patients for the registry cohort. The randomized cohort employed a Bayesian adaptive design that would allow for three interim analyses by an unblinded independent statistician when 180, 210, and 240 patients, respectively, would have reached the 6-month follow-up. If the predictive probability of success for both the primary safety and effectiveness endpoints was to be greater than 96.5% in the first interim analysis, or greater than 95.0% in other interim analyses, an early win would be declared. However, even if an early win was to be declared in a planned interim analysis, the trial would continue the enrollment of 300 patients in the randomized cohort and all patients would continue to be followed for analyses of the secondary and additional endpoints.

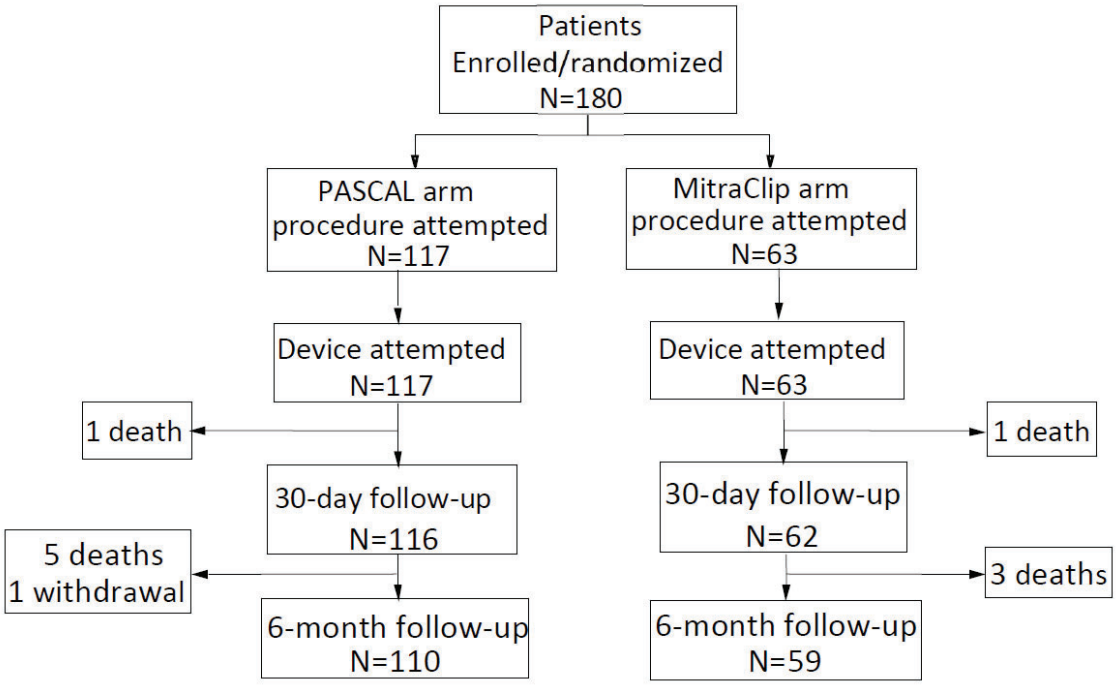
B. Accountability of PMA Cohort

The enrollment into the CLASP IID trial took place between November 2018 and December 2021. A total of 300 patients were enrolled in the randomized cohort and 98 patients in the registry cohort at 54 investigational sites in the U.S., Canada, and Germany.

The first planned interim analysis of the randomized cohort included 180 patients (117 in the PASCAL arm and 63 in the MitraClip arm) and reflected data collected through June 20, 2022. The results of this interim analysis are summarized herein and used to support the PMA approval decision.

The dispositions of the randomized patients at the time of the first planned interim analysis are detailed in Figure 5.

Figure 5: Patient Enrollment/Disposition (Randomized Cohort)



The analysis populations for the randomized cohort included: modified Intent-to-Treat (mITT) (safety) Population, mITT (effectiveness) Population, and As-Treated (AT) Population, as defined in Table 4. The primary safety and effectiveness analyses were performed on the mITT (safety) and mITT (effectiveness) populations, respectively.

Table 4: Analysis Populations (Randomized Cohort)

Analysis Population	Definition	Number of Patients	
		PASCAL	MitraClip
modified Intent-to-Treat (mITT) (safety)	All patients randomized to each treatment arm (i.e., ITT) who had the study procedure attempted (initiation of skin incision).	117	63
mITT (effectiveness)	All patients in the mITT (safety) population who had a study device attempted (insertion of the guide sheath or steerable guide into the femoral vein).	117	63
As-Treated (AT)	All patients in the mITT (effectiveness) population who had a study device attempted and implanted at the exit from procedure room.	116*	63

*One (1) patient had an aborted procedure due to inability to grasp leaflets.

At the time of database lock, of the randomized patients eligible for the 6-month visit, 94.5% in the PASCAL arm and 94.9% in the MitraClip arm completed the visit, as summarized in Table 5.

Table 5: Visit Compliance (Randomized Cohort) - mITT (Safety) Population

Visit Status	Randomized Cohort (N=180)			
	30 Days		6 Months	
	PASCAL (N=117)	MitraClip (N=63)	PASCAL (N=117)	MitraClip (N=63)
Ineligible for visit	1	1	7	4
Eligible for visit*	116	62	110	59
Follow-up visit completed†	98.3% (114/116)	100.0% (62/62)	94.5% (104/110)	94.9% (56/59)

*Patients were considered eligible if they completed the visit, or their visit windows were open and they were alive and had not exited the study prior to the window opening.
†Categorical variables: % (n/Total N)

In the registry cohort, a total of 98 patients underwent an index procedure with the PASCAL system, 92 of whom had the study device implanted and constituted the Implanted Population. Six (6) patients did not receive a study device due to inability to grasp leaflets (n=3), increased transmitral valve gradient (n=2) or insufficient MR reduction (n=1). The visit compliance of the registry patients implanted with a study device is shown in Table 6.

Table 6: Visit Compliance (Registry Cohort) – Implanted Population

Visit Status	Registry Cohort (N=92)	
	30 Days	6 Months
Ineligible for visit	1	6
Eligible for visit*	91	86
Follow-up visit completed†	96.7% (88/91)	90.7% (78/86)

*Patients were considered eligible if they completed the visit, or their visit windows were open and they were alive and had not exited the study prior to the window opening.
†Categorical variables: % (n/Total N)

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population in the randomized cohort are typical for a DMR study performed in the US, as shown in Table 7. The two treatment arms were well balanced, with no significant differences in patient demographics and baseline characteristics.

Table 7: Patient Demographics and Baseline Characteristics (Randomized Cohort) - mITT (Safety) Population

Demographics and Baseline Characteristics	Randomized Cohort Summary Statistics* (N=180)		p-value†
	PASCAL (N=117)	MitraClip (N=63)	
Age (years)	81.1 ± 6.87 (117)	81.2 ± 6.24 (63)	0.926
Sex at birth			
Male	66.7% (78/117)	68.3% (43/63)	0.869
Race			
Asian	4.3% (5/117)	1.6% (1/63)	0.598
Black or African American	2.6% (3/117)	3.2% (2/63)	
White	71.8% (84/117)	76.2% (48/63)	
Other	2.6% (3/117)	0.0% (0/63)	
Not available‡	18.8% (22/117)	19.0% (12/63)	
Body mass index (kg/m²)	25.9 ± 5.40 (117)	26.2 ± 4.82 (63)	0.499
New York Heart Association (NYHA) functional class			
Class I	0.9% (1/117)	0.0% (0/63)	0.573
Class II	38.5% (45/117)	38.1% (24/63)	
Class III	57.3% (67/117)	54.0% (34/63)	
Class IV	3.4% (4/117)	7.9% (5/63)	
Left ventricular ejection fraction (LVEF; %)	59.6 ± 8.68 (117)	58.3 ± 9.04 (63)	0.346
Society of Thoracic Surgeons (STS) score for mitral valve replacement (%)	5.7 ± 3.27 (117)	5.1 ± 2.58 (63)	0.437
STS score for mitral valve repair (%)	4.1 ± 2.82 (117)	3.6 ± 2.16 (63)	0.476
European System for Cardiac Operative Risk Evaluation (EuroSCORE) II (%)	3.9 ± 2.93 (117)	4.1 ± 3.09 (63)	0.736
Clinical frailty total score§			
≤ 3	17.9% (21/117)	15.9% (10/63)	0.837
> 3	82.1% (96/117)	84.1% (53/63)	
Cardiomyopathy	13.7% (16/117)	17.5% (11/63)	0.517
Coronary artery disease (≥ 50% stenosis)	39.3% (46/117)	39.7% (25/63)	1.000
Hypertension	83.8% (98/117)	90.5% (57/63)	0.263
Myocardial infarction	16.2% (19/117)	11.1% (7/63)	0.385
Stroke	7.7% (9/117)	1.6% (1/63)	0.169
Atrial fibrillation	57.3% (67/117)	60.3% (38/63)	0.752
Pacemaker/implantable cardioverter defibrillator	6.0% (7/117)	14.3% (9/63)	0.096
Percutaneous coronary intervention (PCI)/stent	23.1% (27/117)	22.2% (14/63)	1.000
Total number of open-heart surgeries (valve and coronary artery bypass graft)			

Demographics and Baseline Characteristics	Randomized Cohort Summary Statistics* (N=180)		p-value†
	PASCAL (N=117)	MitraClip (N=63)	
0	87.2% (102/117)	90.5% (57/63)	0.873
1	12.0% (14/117)	9.5% (6/63)	
2	0.9% (1/117)	0.0% (0/63)	
Chronic obstructive pulmonary disease (COPD)	17.1% (20/117)	19.0% (12/63)	0.838
Home oxygen use	5.1% (6/117)	4.8% (3/63)	1.000
Diabetes	16.2% (19/117)	23.8% (15/63)	0.235
Renal insufficiency or failure	35.0% (41/117)	42.9% (27/63)	0.335
Stage I (eGFR >=90)	0.0% (0/117)	0.0% (0/63)	-
Stage II (eGFR 60-89)	5.1% (6/117)	4.8% (3/63)	1.000
Stage III (eGFR 30-59)	28.2% (33/117)	36.5% (23/63)	0.311
Stage IV (eGFR 15-29)	1.7% (2/117)	1.6% (1/63)	1.000
Stage V (eGFR <15)	0.0% (0/117)	0.0% (0/63)	-
History of renal replacement therapy (e.g., dialysis)	0.9% (1/117)	0.0% (0/63)	1.000
COVID-19	0.9% (1/111)	1.7% (1/59)	1.000
Mitral regurgitation (MR) severity ≥ 3+ at baseline‖	100.0% (117/117)	100.0% (63/63)	-
Number of hospitalizations for heart failure in the last 12 months			
0	65.8% (77/117)	60.3% (38/63)	0.736
1	23.1% (27/117)	30.2% (19/63)	
2	7.7% (9/117)	7.9% (5/63)	
3	3.4% (4/117)	1.6% (1/63)	
Total number of days hospitalized for heart failure in the last 12 months (for those who had heart failure hospitalization)	8.6 ± 6.87 (38)	8.0 ± 6.73 (25)	0.678

*Categorical variables: % (n/Total N); continuous variables: Mean ± SD (n)
†p-value was based on Kruskal-Wallis test for continuous variables and Fisher's Exact test for categorical variables.
‡Race not collected for patients in Germany due to privacy regulations.
§A clinical frailty score of ≤ 3 was inclusive of "very fit," "well," and "managing well." A clinical frailty score of > 3 was inclusive of "vulnerable," "mildly frail," "moderately frail," "severely frail," "very severely frail," and "terminally ill."
‖Baseline MR severity was determined by transthoracic echocardiogram (TTE) for all patients except for 2 patients determined by transesophageal echocardiogram (TEE).

All patients in the PASCAL IID trial were required to be at prohibitive risk for surgical mitral valve repair or replacement per the local heart team. Reasons for prohibitive risk are summarized in Table 8 for the randomized cohort. The most common reason for prohibitive risk for both treatment arms was frailty as assessed by a cardiac surgeon using the Canadian

Study of Health and Aging (CSHA) Frailty Scale (84.6% in the PASCAL arm and 90.5% in the MitraClip arm).

Table 8: Reasons for Prohibitive Risk (Randomized Cohort) - mITT (Safety) Population

Prohibitive Risk Factors*	Summary Statistics†	
	PASCAL (N=117)	MitraClip (N=63)
Society of Thoracic Surgeons (STS) predicted mortality risk score for mitral valve replacement: ≥8%	21.4% (25/117)	14.3% (9/63)
STS predicted mortality risk score for mitral valve repair: ≥6%	17.9% (21/117)	9.5% (6/63)
Porcelain aorta or extensively calcified ascending aorta	1.7% (2/117)	0.0% (0/63)
Frailty (assessed by in-person cardiac surgeon consultation)	84.6% (99/117)	90.5% (57/63)
Hostile chest	6.0% (7/117)	6.3% (4/63)
Severe liver disease/cirrhosis (Model for End-Stage Liver Disease score >12)	0.0% (0/117)	1.6% (1/63)
Severe pulmonary hypertension (systolic pulmonary artery pressure > 2/3 systemic pressure)	2.6% (3/117)	4.8% (3/63)
Right ventricular dysfunction	0.9% (1/117)	1.6% (1/63)
Chemotherapy for malignancy	1.7% (2/117)	1.6% (1/63)
Immobility	11.1% (13/117)	12.7% (8/63)
Acquired immunodeficiency syndrome (AIDS)	0.0% (0/117)	0.0% (0/63)
High risk of aspiration	3.4% (4/117)	7.9% (5/63)
Internal mammary artery (IMA) at high risk of injury	1.7% (2/117)	0.0% (0/63)
Other	28.2% (33/117)	22.2% (14/63)

*At baseline, patients may present with more than one prohibitive risk factor.
†Categorical variables: % (n/Total N)

The demographics and baseline characteristics of the study population in the registry cohort are summarized in Table 9.

Table 9: Patient Demographics and Baseline Characteristics (Registry Cohort) - Implanted Population

Demographics and Baseline Characteristics	Registry Cohort Summary Statistics* (N=92)
Age (years)	81.4 ± 6.41 (92)
Sex at birth	
Male	62.0% (57/92)
Race	
Asian	3.3% (3/92)
Black or African American	4.3% (4/92)

Demographics and Baseline Characteristics	Registry Cohort Summary Statistics* (N=92)
White	72.8% (67/92)
Other	4.3% (4/92)
Not available†	15.2% (14/92)
Body mass index (kg/m²)	25.5 ± 4.43 (92)
New York Heart Association (NYHA) functional class	
Class I	3.3% (3/92)
Class II	28.3% (26/92)
Class III	64.1% (59/92)
Class IV	4.3% (4/92)
Left ventricular ejection fraction (LVEF; %)	58.7 ± 10.58 (92)
Society of Thoracic Surgeons (STS) score for mitral valve replacement (%)	6.6 ± 4.90 (92)
STS score for mitral valve repair (%)	4.6 ± 4.07 (92)
European System for Cardiac Operative Risk Evaluation (EuroSCORE) II (%)	5.0 ± 4.34 (92)
Clinical frailty total score‡	
≤ 3	17.4% (16/92)
> 3	82.6% (76/92)
Cardiomyopathy	19.6% (18/92)
Coronary artery disease (≥ 50% stenosis)	43.5% (40/92)
Hypertension	83.7% (77/92)
Myocardial infarction	16.3% (15/92)
Stroke	5.4% (5/92)
Atrial fibrillation	68.5% (63/92)
Pacemaker/implantable cardioverter defibrillator	16.3% (15/92)
Percutaneous coronary intervention (PCI)/stent	21.7% (20/92)
Total number of open-heart surgeries (valve and coronary artery bypass graft)	
0	81.5% (75/92)
1	17.4% (16/92)
2	1.1% (1/92)
Chronic obstructive pulmonary disease (COPD)	14.1% (13/92)
Home oxygen use	7.6% (7/92)
Diabetes	19.6% (18/92)
Renal insufficiency or failure	51.1% (47/92)
Stage I (eGFR >=90)	0.0% (0/92)
Stage II (eGFR 60-89)	5.4% (5/92)
Stage III (eGFR 30-59)	39.1% (36/92)
Stage IV (eGFR 15-29)	6.5% (6/92)
Stage V (eGFR <15)	0.0% (0/92)
History of renal replacement therapy (e.g., dialysis)	0.0% (0/92)
COVID-19	3.4% (3/89)

Demographics and Baseline Characteristics	Registry Cohort Summary Statistics* (N=92)
Mitral regurgitation (MR) severity ≥ 3+ at baseline§	100.0% (92/92)
Number of hospitalizations for heart failure in the last 12 months	
0	62.6% (57/91)
1	23.1% (21/91)
2	8.8% (8/91)
3	4.4% (4/91)
4	1.1% (1/91)
Total number of days hospitalized for heart failure in the last 12 months (for those who had heart failure hospitalization)	7.9 ± 8.49 (33)

*Categorical variables: % (n/Total N); continuous variables: Mean ± SD (n)
†Race not collected for patients in Germany due to privacy regulations.
‡A clinical frailty score of ≤ 3 was inclusive of "very fit," "well," and "managing well." A clinical frailty score of > 3 was inclusive of "vulnerable," "mildly frail," "moderately frail," "severely frail," "very severely frail," and "terminally ill."
§Baseline MR severity was determined by transthoracic echocardiogram (TTE) for all patients except for 2 patients determined by transesophageal echocardiogram (TEE).

The anatomical criteria of patients in the registry cohort that rendered the patients ineligible for randomization are summarized in Table 10. The most common anatomical complexity was the presence of two or more independent significant jets (42.4%), followed by evidence of severe bileaflet/multi-scallop prolapse involvement (17.4%), mitral valve orifice area <4.0 cm^2 (15.2%), and large flail gap (>10 mm) and/or flail width (>15 mm) (13.0%). A total of 83.7% of patients met 1 anatomical complexity criterion and 16.3% met 2 criteria.

Table 10: Anatomical Criteria (Registry Cohort) - Implanted Population

Anatomical Criteria	Summary Statistics* (N=92)
Presence of two or more independent significant jets	42.4% (39/92)
Evidence of severe bileaflet/multi-scallop prolapse involvement	17.4% (16/92)
Mitral valve orifice area <4.0 cm^2	15.2% (14/92)
Large flail gap (>10 mm) and/or large flail width (>15 mm)†	13.0% (12/92)
Presence of one significant jet in the commissural area	12.0% (11/92)
Presence of significant cleft or perforation in the grasping area	6.5% (6/92)
Leaflet mobility length <8 mm	4.3% (4/92)
Evidence of moderate to severe calcification in the grasping area	4.3% (4/92)
History of endocarditis and significant tissue defects in the leaflet†	1.1% (1/92)
Total number of anatomical criteria met	
1	83.7% (77/92)

Anatomical Criteria	Summary Statistics* (N=92)
2	16.3% (15/92)

*Categorical variables: % (n/Total N); patients can be counted in more than one anatomical criterion category.
†Anatomical criterion not pre-specified in the study protocol but identified by the Central Screening Committee as an anatomical criterion that made valve anatomy suitable for a PASCAL implant, but not for a MitraClip implant.

D. Safety and Effectiveness Results

This section summarizes the results of the first planned interim analysis of the randomized cohort, along with the results of the registry cohort. For brevity, only select results of the registry cohort are presented.

1. Primary Safety Endpoint

The primary safety endpoint results for the randomized cohort are presented in Table 11. The proportion of patients with MAEs at 30 days was 3.4% in the PASCAL arm and 4.8% in the MitraClip arm, with a rate difference (PASCAL - MitraClip) of -1.3%. Since the one-sided 95% upper confidence bound of the rate difference was 5.1%, which was lower than the pre-specified non-inferiority margin of 15%, the primary safety endpoint was met.

Table 11: MAEs at 30 Days (Randomized Cohort) - mITT (Safety) Population

Variable	PASCAL (N=117)		MitraClip (N=63)	
	No. Events	Patients* % (n/N)	No. Events	Patients % (n/N)
Composite major adverse events (MAEs)	5	3.4% (4/116)	3	4.8% (3/63)
Cardiovascular death	1	0.9% (1/116)	1	1.6% (1/63)
Stroke	0	0.0% (0/116)	0	0.0% (0/63)
Myocardial infarction	0	0.0% (0/116)	0	0.0% (0/63)
New need for renal replacement therapy	0	0.0% (0/116)	0	0.0% (0/63)
Severe bleeding	3	2.6% (3/116)	2	3.2% (2/63)
Non-elective mitral valve re-intervention	1	0.9% (1/116)	0	0.0% (0/63)
Composite rate difference (PASCAL - MitraClip)	-1.3%			
One-sided 95% upper confidence bound†	5.1%			
Non-inferiority margin	15.0%			
Non-inferiority test	Success			

*One (1) patient who was excluded from the denominator was not followed for at least 30 days and did not have an MAE at the time of the last follow-up.
†One-sided 95% upper confidence bound was based on unpooled Z test with continuity correction.

The primary safety endpoint results for the registry cohort are summarized in Table 12. The proportion of patients with MAEs at 30 days was 8.7%.

Table 12: MAEs at 30 Days (Registry Cohort) - Implanted Population

Variable	No. Events	Patients % (n/N)
Composite major adverse events (MAEs)	9	8.7% (8/92)
Cardiovascular death	1	1.1% (1/92)
Stroke	1	1.1% (1/92)
Myocardial infarction	1	1.1% (1/92)
New need for renal replacement therapy	1	1.1% (1/92)
Severe bleeding	4	4.3% (4/92)
Non-elective mitral valve re-intervention	1	1.1% (1/92)

2. Primary Effectiveness Endpoint

The primary effectiveness endpoint results for the randomized cohort are presented in Table 13. The proportion of patients with MR ≤2+ at 6 months was 96.5% in the PASCAL arm and 96.8% in the MitraClip arm. The rate difference between the PASCAL arm and the MitraClip arm was -0.3%, with a one-sided 95% lower confidence bound of -6.2%, which was greater than the pre-specified non-inferiority margin of -18%. Thus, the primary effectiveness endpoint was met.

Table 13: Proportion of Patients with MR ≤ 2+ at 6 Months (Randomized Cohort) - mITT (Effectiveness) Population

Variable	Randomized Cohort (N=180)	
	PASCAL (N=117)	MitraClip (N=63)
MR ≤ 2+; % (n/N)*	96.5% (110/114)	96.8% (60/62)
Rate difference (PASCAL - MitraClip)	-0.3%	
One-sided 95% lower confidence bound†	-6.2%	
Non-inferiority margin	-18.0%	
Non-inferiority test	Success	

*Of the 117 patients in the PASCAL mITT (effectiveness) population, data for 3 patients were unavailable for the primary effectiveness analysis, including 2 patients who died prior to reaching the 30-day follow-up and 1 patient who was missing their 30-day and 6-month follow-up due to residing outside of the U.S. at the time. Of the 63 patients in the MitraClip mITT (effectiveness) population, data for 1 patient were unavailable for the primary effectiveness analysis due to patient death prior to the 30-day follow-up.
†One-sided 95% lower confidence bound was based on unpooled Z test with continuity correction.

The primary effectiveness endpoint results for the registry cohort are presented in Table 14. The proportion of patients with MR ≤2+ at 6 months was 91.0%.

Table 14: Proportion of Patients with MR ≤ 2+ at 6 Months (Registry Cohort) - Implanted Population

Variable	Registry Cohort (N=92)
MR ≤ 2+; % (n/N)*	91.0% (81/89)

*Of the 92 patients in the Implanted Population of the registry cohort, data for 3 patients were unavailable for the primary effectiveness analysis, including 2 patients who died prior to completing the 30-day follow-up and 1 patient who missed the 30-day and 6-month follow-up visits (patient died on postoperative day 225).

3. Secondary Endpoints

Safety Endpoints

The results of various pre-defined secondary safety endpoints available at 30 days and 6 months are presented in Table 15 and Table 16 for the randomized cohort and registry cohort, respectively.

Table 15: Secondary Safety Endpoints (Randomized Cohort) - mITT (Safety) Population

Event	Rate*					
	Discharge		30 Days		6 Months	
	PASCAL (N=117)	MitraClip (N=63)	PASCAL (N=117)	MitraClip (N=63)	PASCAL (N=117)	MitraClip (N=63)
Major adverse events	-	-	-	-	6.1% (8, 7)	11.1% (9, 7)
All-cause mortality	-	-	1.7% (2, 2)	1.6% (1, 1)	5.1% (6, 6)	6.3% (4, 4)
Heart failure hospitalization	-	-	0% (0, 0)	1.6% (1, 1)	1.7% (3, 2)	3.2% (2, 2)
New onset of permanent atrial fibrillation	-	-	0% (0, 0)	0% (0, 0)	-	-
Non-elective mitral valve re-intervention (either percutaneous or surgical)	-	-	-	-	1.8% (2, 2)	1.6% (1, 1)
Residual atrial septal defect; % (n/Total N)	-	-	72.5% (50/69)	79.5% (31/39)	51.0% (26/51)	62.1% (18/29)
Transfusion of ≥2 units of whole blood or packed red blood cells; % (n/Total N)	0% (0/117)	1.6% (1/63)	-	-	-	-
Gastrointestinal	-	-	0% (0, 0)	0% (0, 0)	-	-

Event	Rate*					
	Discharge		30 Days		6 Months	
	PASCAL (N=117)	MitraClip (N=63)	PASCAL (N=117)	MitraClip (N=63)	PASCAL (N=117)	MitraClip (N=63)
complications requiring surgery						

*Kaplan-Meier rate (no. of events, no. of patients with the event), unless noted otherwise.

Table 16: Secondary Safety Endpoints (Registry Cohort) - Implanted Population

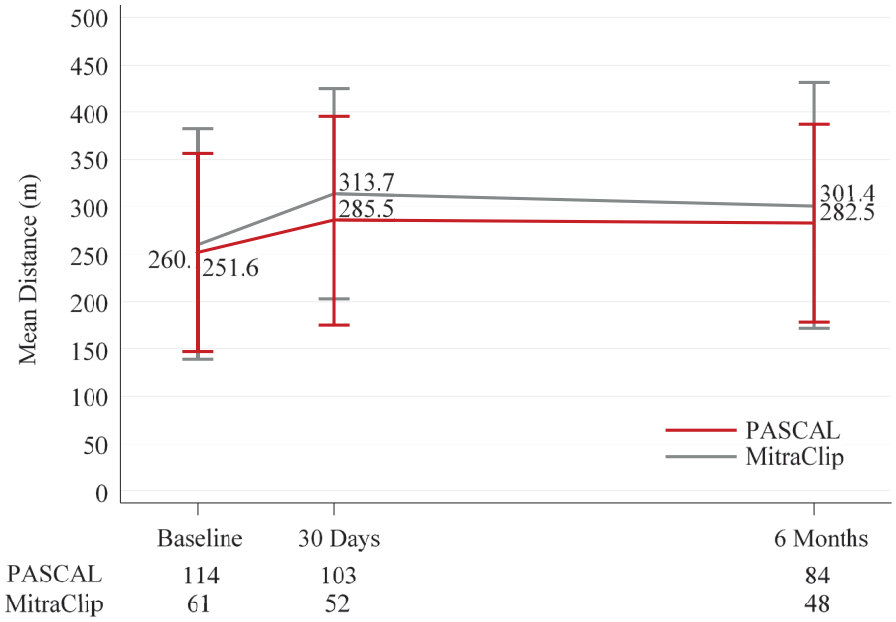
Event	Rate* (N=92)		
	Discharge	30 Days	6 Months
Major adverse events	-	-	12.0% (15, 11)
All-cause mortality	-	2.2% (2, 2)	6.5% (6, 6)
Heart failure hospitalization	-	5.5% (6, 5)	6.6% (9, 6)
New onset of permanent atrial fibrillation	-	0% (0, 0)	-
Non-elective mitral valve re-intervention (either percutaneous or surgical)	-	-	1.1% (1, 1)
Residual atrial septal defect; % (n/Total N)	-	80.6% (50/62)	73.7% (28/38)
Transfusion of ≥2 units of whole blood or packed red blood cells; % (n/Total N)	2.2% (2/92)	-	-
Gastrointestinal complications requiring surgery	-	0% (0, 0)	-

*Kaplan-Meier rate (no. of events, no. of patients with the event), unless noted otherwise.

6MWT Distance

The results for the 6MWT in the randomized cohort are presented in Figure 6. In the PASCAL arm, the mean 6MWT distance increased about 30 m at 30 days compared to baseline, which was sustained through 6 months. A generally similar trend was observed in the MitraClip arm, with an improvement of about 50 m at 30 days and 40 m at 6 months.

Figure 6: 6MWT Distance by Visit (Randomized Cohort) - mITT (Effectiveness) Population



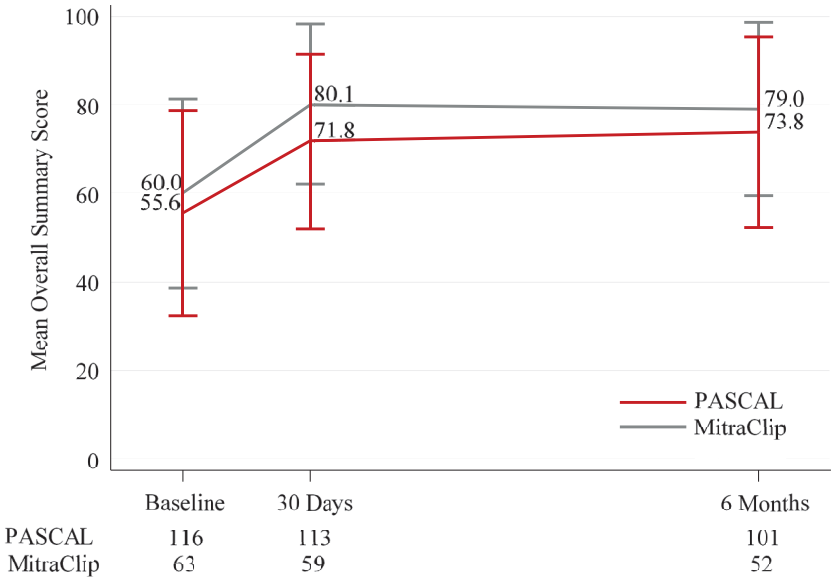
Note: The error bars represent standard deviations.

QoL

- KCCQ

The results for the KCCQ overall summary score are presented in Figure 7 for the randomized cohort. The mean score increased from 55.6 at baseline to 71.8 at 30 days and 73.8 at 6 months in the PASCAL arm and from 60.0 at baseline to 80.1 at 30 days and 79.0 at 6 months in the MitraClip arm.

Figure 7: KCCQ Overall Summary Score by Visit (Randomized Cohort) - mITT (Effectiveness) Population

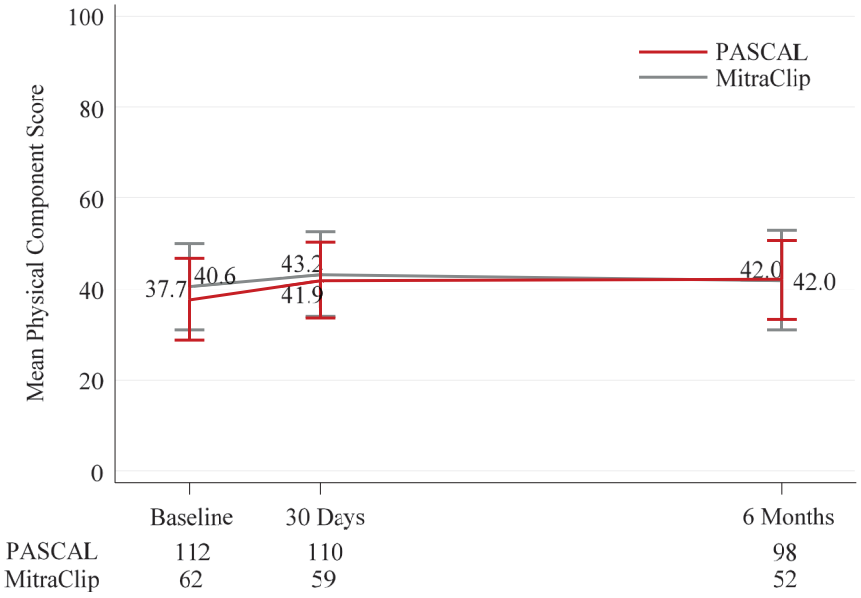


Note: The error bars represent standard deviations.

- SF-36

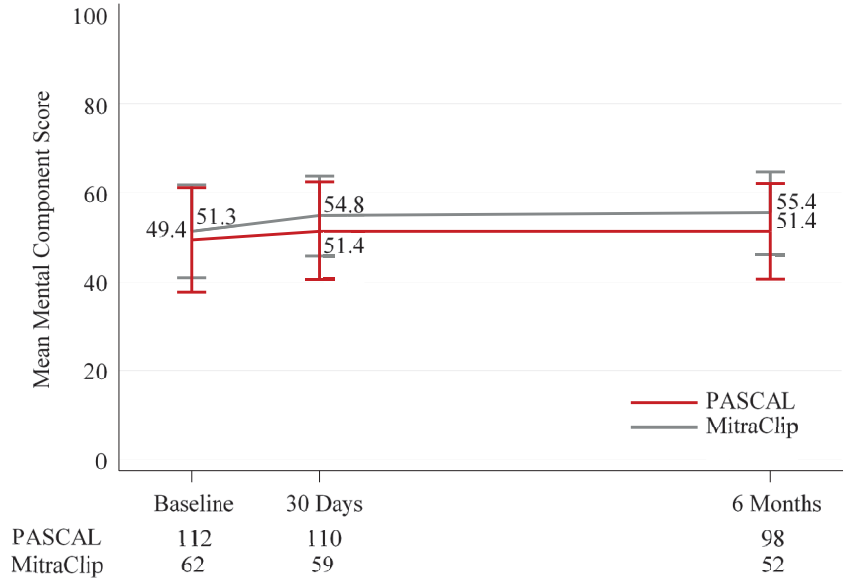
The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 8 and Figure 9, respectively, for the randomized cohort. In the two treatment arms, the mean SF-36 physical component scores increased about 1-4 points at 30 days and 6 months compared to the baseline; the corresponding mean SF-36 mental component scores increased about 2-4 points.

Figure 8: SF-36 Physical Component Summary Score by Visit (Randomized Cohort) - mITT (Effectiveness) Population



Note: The error bars represent standard deviations.

Figure 9: SF-36 Mental Component Summary Score by Visit (Randomized Cohort) - mITT (Effectiveness) Population

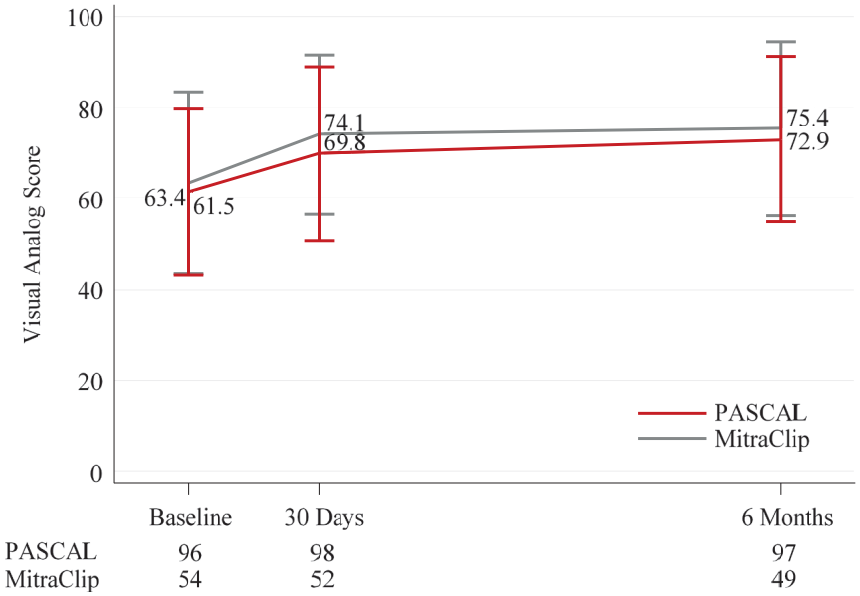


Note: The error bars represent standard deviations.

- EQ-5D-5L

The results for the EQ-5D-5L visual analog score (VAS) are presented in Figure 10 for the randomized cohort. The mean scores in the two treatment arms increased similarly in an approximate range of 8-12 points at 30 days and at 6 months compared to the baseline.

Figure 10: EQ-5D-5L Visual Analog Score by Visit (Randomized Cohort) - mITT (Effectiveness) Population



Note: The error bars represent standard deviations.

4. Adverse Events

The site-reported device- or procedure-related serious adverse events that occurred through 6 months in the randomized cohort are presented in Table 17.

Table 17: Site-Reported Device- or Procedure-related Serious Adverse Events (Randomized Cohort) - mITT (Safety) Population

Event	30 Days				6 Months			
	PASCAL (N=117)		MitraClip (N=63)		PASCAL (N=117)		MitraClip (N=63)	
	No. Events	Patients % (n/N)	No. Events	Patients % (n/N)	No. Events	Patients % (n/N)	No. Events	Patients % (n/N)
Acute kidney injury	1	0.9% (1/117)	0	0.0% (0/63)	1	0.9% (1/117)	0	0.0% (0/63)
Anemia	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)

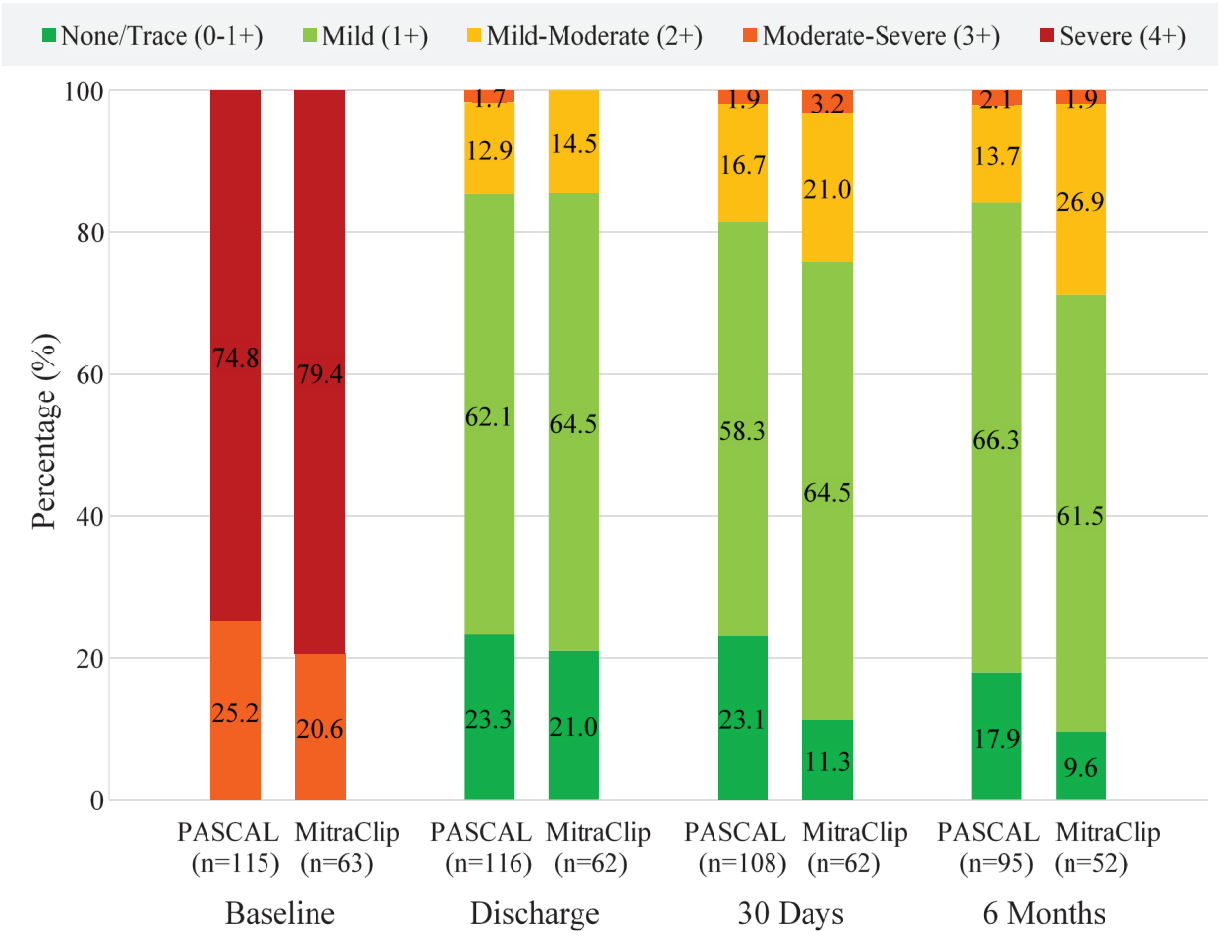
Event	30 Days				6 Months			
	PASCAL (N=117)		MitraClip (N=63)		PASCAL (N=117)		MitraClip (N=63)	
	No. Events	Patients % (n/N)	No. Events	Patients % (n/N)	No. Events	Patients % (n/N)	No. Events	Patients % (n/N)
Atrial fibrillation	2	1.7% (2/117)	0	0.0% (0/63)	2	1.7% (2/117)	0	0.0% (0/63)
Atrioventricular block second degree	1	0.9% (1/117)	0	0.0% (0/63)	1	0.9% (1/117)	0	0.0% (0/63)
Cardiac failure acute	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	2	3.2% (2/63)
Cardiac procedure complication	0	0.0% (0/117)	0	0.0% (0/63)	0	0.0% (0/117)	1	1.6% (1/63)
Cardiogenic shock	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)
Chest pain	1	0.9% (1/117)	0	0.0% (0/63)	1	0.9% (1/117)	0	0.0% (0/63)
Hypervolemia	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)
Hyponatremia	1	0.9% (1/117)	0	0.0% (0/63)	1	0.9% (1/117)	0	0.0% (0/63)
Hypotension	2	1.7% (2/117)	0	0.0% (0/63)	2	1.7% (2/117)	0	0.0% (0/63)
Leukocytosis	1	0.9% (1/117)	1	1.6% (1/63)	1	0.9% (1/117)	1	1.6% (1/63)
Lip injury	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)
Lower gastrointestinal hemorrhage	1	0.9% (1/117)	0	0.0% (0/63)	1	0.9% (1/117)	0	0.0% (0/63)
Mitral valve incompetence	2	1.7% (2/117)	2	3.2% (2/63)	3	2.6% (3/117)	2	3.2% (2/63)
Muscular weakness	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)
Septic shock	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)
Small intestinal obstruction	0	0.0% (0/117)	1	1.6% (1/63)	0	0.0% (0/117)	1	1.6% (1/63)
Vascular pseudoaneurysm	1	0.9% (1/117)	0	0.0% (0/63)	1	0.9% (1/117)	0	0.0% (0/63)

5. Other Study Observations

MR Severity Grade

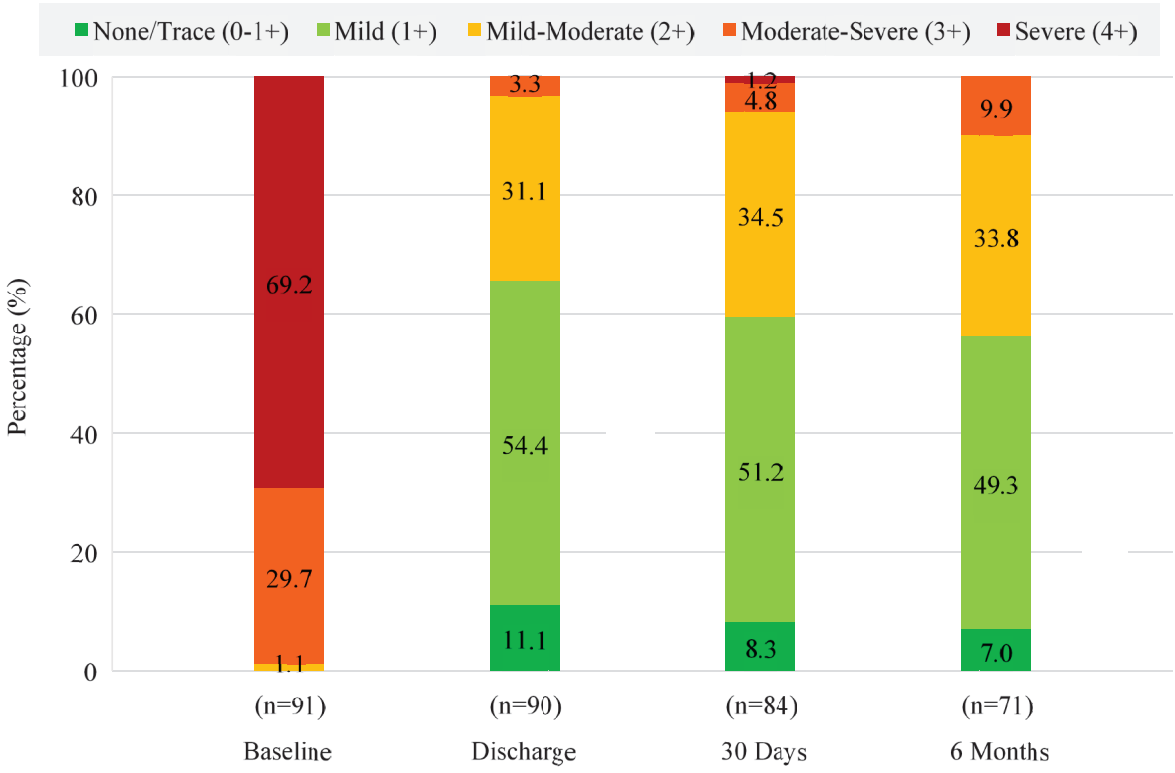
The MR severity grades by visit are presented in Figure 11 for the randomized cohort. The proportion of patients with MR ≥3+ decreased from 100% at baseline to 2.1% at 6 months in the PASCAL arm compared to 100% at baseline to 1.9% at 6 months in the MitraClip arm.

Figure 11: MR Severity Grade by Visit (Randomized Cohort) - mITT (Effectiveness) Population



The MR severity grades by visit, as measured by TTE, in the registry cohort are presented in Figure 12. At 6 months, only 9.9% of the patients had MR ≥3+ compared to 100% at baseline.

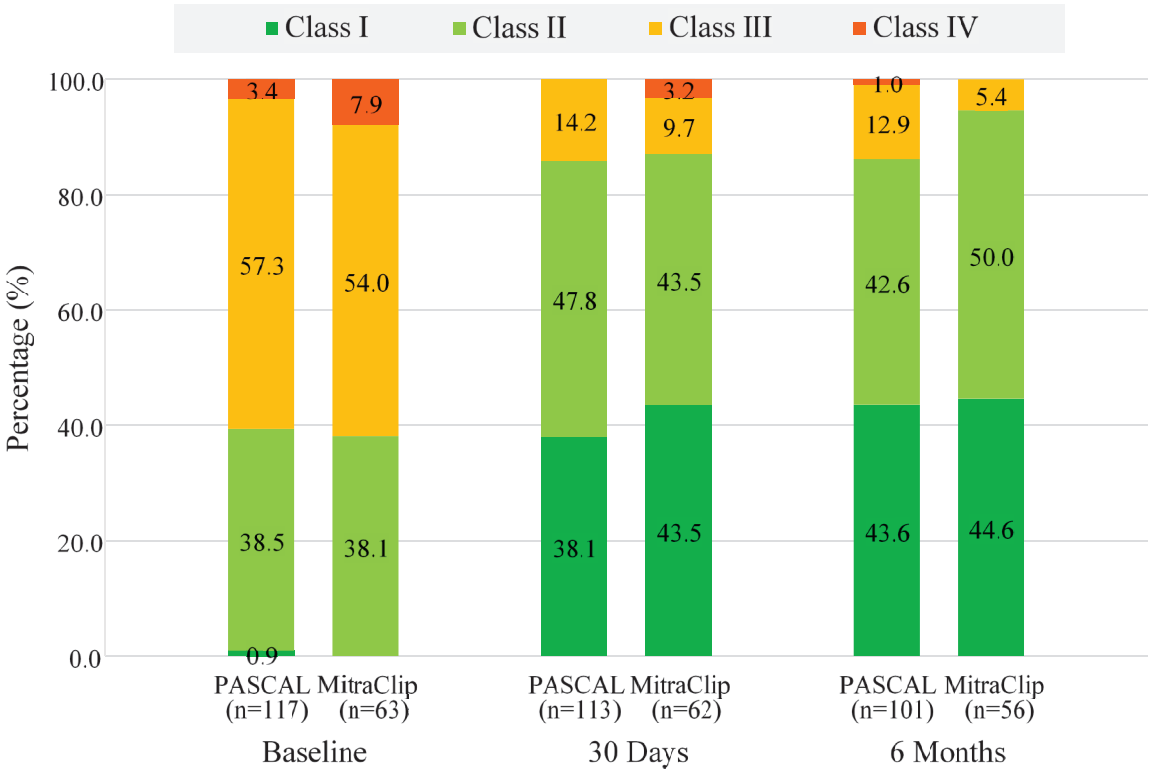
Figure 12: MR Severity Grade by Visit (Registry Cohort) - Implanted Population



NYHA Functional Class

The NYHA classifications by visit are presented in Figure 13 for the randomized cohort. At baseline, 60.7% of PASCAL patients and 61.9% of MitraClip patients were in NYHA class III/IV. The proportion of patients in NYHA class III/IV decreased to 13.9% in the PASCAL patients and 5.4% in the MitraClip patients at 6 months.

Figure 13: NYHA Class by Visit (Randomized Cohort)
mITT (Effectiveness) Population



Echocardiographic Parameters

Key echocardiographic parameters for the randomized cohort are summarized in Table 18.

Table 18: Echocardiographic Parameters by TTE (Randomized Cohort) - mITT (Effectiveness) Population

Parameter	Visit	Summary Statistic*	
		PASCAL (N=117)	MitraClip (N=63)
Left ventricular end-diastolic diameter (LVEDD; mm)	Baseline	57.1 ± 6.54 (117)	57.4 ± 6.50 (63)
	Discharge†	54.2 ± 6.72 (111)	56.0 ± 5.77 (59)
	30 days	53.2 ± 6.58 (108)	54.8 ± 6.43 (59)
	6 months	51.5 ± 8.02 (89)	53.5 ± 6.39 (50)
Left ventricular end-systolic diameter (LVESD; mm)	Baseline	38.3 ± 7.66 (116)	39.8 ± 7.83 (62)
	Discharge†	38.0 ± 7.62 (108)	40.3 ± 7.44 (58)
	30 days	37.3 ± 7.21 (106)	40.0 ± 9.80 (58)
	6 months	36.0 ± 7.25 (88)	37.4 ± 6.92 (49)
Ejection fraction (%)	Baseline	59.6 ± 8.68 (117)	58.3 ± 9.04 (63)
	Discharge†	57.1 ± 7.97 (116)	54.8 ± 8.98 (62)

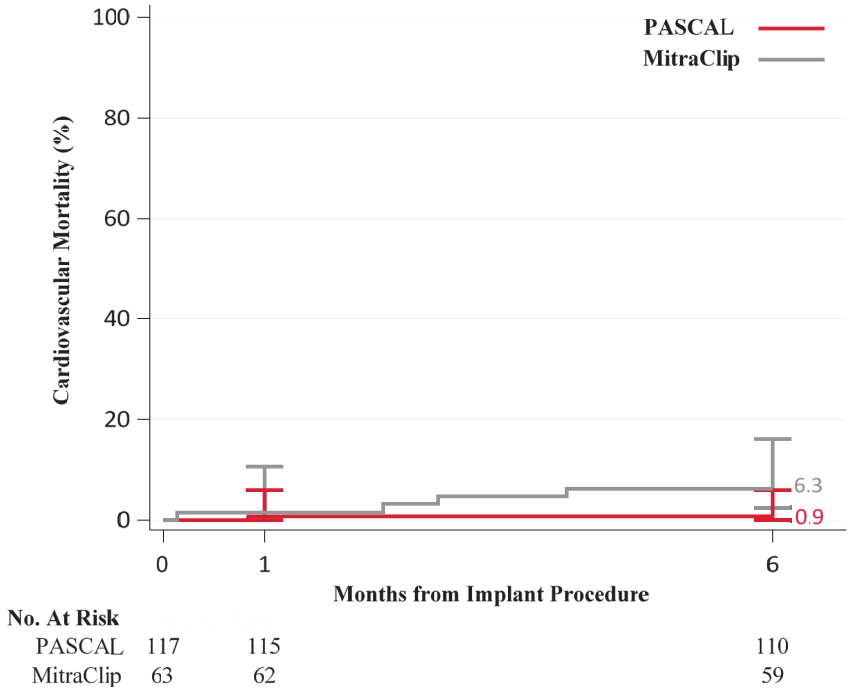
Parameter	Visit	Summary Statistic*	
		PASCAL (N=117)	MitraClip (N=63)
	30 days	57.7 ± 7.34 (108)	55.4 ± 8.27 (62)
	6 months	56.4 ± 7.71 (95)	55.8 ± 7.27 (52)
Transmitral antegrade mean gradient (mmHg)	Baseline	2.5 ± 1.14 (113)	2.4 ± 1.06 (59)
	Discharge†	3.8 ± 1.54 (115)	3.6 ± 1.36 (62)
	30 days	3.7 ± 1.67 (108)	3.6 ± 1.56 (62)
	6 months	3.7 ± 1.68 (92)	3.4 ± 1.33 (51)

*Continuous variables: Mean ± SD (n)
†Discharge or Day 7, whichever occurred first.

Cardiovascular Mortality

The Kaplan-Meier curves for cardiovascular mortality are shown in Figure 14 for the randomized cohort.

Figure 14: Cardiovascular Mortality Through 6 Months (Randomized Cohort) - mITT (Safety) Population



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Procedural Data

The general procedural data for the randomized cohort are summarized in Table 19.

Table 19: General Procedural Data (Randomized Cohort) - AT Population

Procedural Data	Summary Statistics*	
	PASCAL (N=116)	MitraClip (N=63)
General anesthesia	100.0% (116/116)	100.0% (63/63)
Implant rate†	100.0% (116/116)	100.0% (63/63)
Number of implanted devices	1.5 ± 0.57 (116) 1.0 (1.0, 3.0)	1.6 ± 0.68 (63) 2.0 (1.0, 3.0)
1	54.3% (63/116)	47.6% (30/63)
2	42.2% (49/116)	41.3% (26/63)
3	3.4% (4/116)	11.1% (7/63)
Total procedure time (min)‡	101.0 ± 49.42 (115) 88.0 (33.0, 357.0)	84.3 ± 37.14 (62) 79.0 (25.0, 174.0)
Device time (min)§	71.9 ± 45.27 (116) 59.5 (6.0, 232.0)	50.0 ± 31.72 (61) 41.0 (5.0, 144.0)
Fluoroscopy duration (min)	26.3 ± 15.99 (114) 23.0 (3.0, 79.0)	22.9 ± 14.39 (63) 20.0 (0.0, 75.0)
Total length of stay in days for the index hospitalization (from procedure date)	2.2 ± 2.82 (116) 1.0 (1.0, 20.0)	1.8 ± 1.45 (63) 1.0 (0.0, 7.0)

*Continuous variables: Mean ± SD (n); median (min, max).
Categorical variables: % (n/Total N).
†Implant rate: % of patients who had study device implanted, deployed as intended, and delivery system retrieved successfully.
‡Total procedure time: from procedure start time (femoral vein puncture/skin incision) to femoral vein access closure.
§Device time: from implant system insertion to removal.

6. Subgroup Analyses

The primary safety and primary effectiveness endpoints were examined by sex (male vs. female) and age (≤ 65 years vs. > 65 years; ≤ 80 years vs. > 80 years). There were no statistically significant interaction effects between treatment arms and sex or age for the primary safety or effectiveness outcome.

7. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 688 investigators of which none were full-time or part-time employees of the sponsor and 25 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 23
- 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)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems 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 randomized cohort of the CLASP IID trial, 96.5% of the PASCAL patients had an MR ≤2+ at 6 months, which was found to be statistically non-inferior to the proportion (96.8%) in the MitraClip patients within a non-inferiority margin of -18%. Thus, the primary effectiveness endpoint of the randomized trial was met. In the registry cohort, a high proportion (91.0%) of patients also had an MR ≤2+ at 6 months compared to none at baseline.

The reduction in MR contributed to improvement in patients' functional status, exercise capacity, and QoL, as evidenced by the NYHA class, 6MWT distance, and KCCQ measures. In the randomized PASCAL patients, the proportion of patients in NYHA class III or IV decreased from 60.7% at baseline to 13.9% at 6 months; the 6MWT distance increased by 30.9 m from baseline to 6 months; and the mean KCCQ summary score increased by 18.2 points within the same period. These results were generally comparable to those of the MitraClip patients.

B. Safety Conclusions

The risks of the device 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 and durability) and animal studies demonstrated that this device is suitable for long-term implant.

In the randomized cohort of the CLASP IID trial, 3.4% of the patients in the PASCAL arm experienced one or more MAEs at 30 days, which was found to be statistically non-inferior to the proportion (4.8%) in the MitraClip arm within a non-inferiority margin of 15%. Thus, the primary safety endpoint of the randomized trial was also met. The MAE rate in the registry cohort was 8.7% at 30 days. The most frequent MAE was severe bleeding.

C. Benefit-Risk Determination

The probable benefits of transcatheter mitral valve repair with the PASCAL Precision system in DMR patients include the reduction of MR and the resulting improvements in functional status, exercise capacity, and QoL.

The probable risks of the PASCAL Precision system include MAEs, such as cardiovascular death, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and non-elective mitral valve re-intervention.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for transcatheter mitral valve repair with the PASCAL Precision system.

In conclusion, given the available information above, the data support that for patients with significant, symptomatic DMR (≥ 3+) deemed at prohibitive risk for mitral valve surgery, the probable benefits of TEER with the PASCAL Precision system outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the PASCAL Precision system for the treatment of significant, symptomatic DMR (≥ 3+) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team.

XIII. CDRH DECISION

CDRH issued an approval order on September 14, 2022. The final clinical conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. **Continued Follow-up of the CLASP IID Trial Cohort**: The study will consist of all

living patients who were enrolled under the IDE. Patients will be followed according to the IDE clinical investigational plan. The objective of this study is to characterize the clinical outcomes annually through 5 years post-procedure. The safety and effectiveness endpoints include MAEs, all-cause mortality, non-elective mitral valve re-intervention (either percutaneous or surgical), stroke, transient ischemic attack (TIA), major vascular events, renal complications, residual ASD, MR grade, 6MWT distance, and QoL measures.

2. **Registry-Based Real-World Use Surveillance**: 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 surveillance occurs for commercial uses of the PASCAL Precision system for the DMR indication. The surveillance will be carried out to assess the real-world performance of the PASCAL Precision system and will involve all consecutive patients treated within the first 2 years that are entered into the TVT Registry (enrollment period). Patients will be followed through 5 years post procedure (follow-up duration). The clinical data through one (1) year will be collected through the TVT Registry. The follow-up data (including all-cause mortality, stroke, 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 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.