MitraClip Post-Approval Study (MitraClip PAS) Summary

1.0 INTRODUCTION

The EVEREST I, EVEREST II and REALISM clinical studies have evaluated the MitraClip device in patients diagnosed with mitral regurgitation (MR). The clinical data from these trials have demonstrated that the MitraClip device and the procedure is safe. The MitraClip device has also been shown to effectively reduce MR, improve left ventricular function, and improve clinical outcomes, as evidenced by improvements in NYHA Functional Class and improvements in Quality of Life in patients with significant MR.

EVEREST I Feasibility Study	Evaluated the safety of the MitraClip device
EVEREST II Randomized Clinical Trial	Compared the safety and effectiveness of the MitraClip device to conventional open-heart surgical mitral valve repair
EVEREST II High Risk Registry	Evaluated the safety and effectiveness of the MitraClip device in high risk surgical candidates
EVEREST II REALISM Continued Access Registry	Evaluating the safety and effectiveness of the MitraClip device in high risk and non-high risk patients

Follow-up on patients enrolled in the EVEREST I and EVEREST II clinical trials, including REALISM, is ongoing, and will continue through 5 years.

2.0 OBJECTIVES

The purpose of the MitraClip PAS is to collect data on the MitraClip device when used by a broad group of physicians in a commercial use setting. These data will be used to support the following objectives:

1. To confirm the long-term safety and effectiveness of the MitraClip device in the commercial use setting.
2. To confirm that the MitraClip device can be used safely by implanting physicians with varying levels of experience
3. To identify any low-frequency or unanticipated MitraClip device-related adverse events that may occur in a commercial setting.

3.0 ENDPOINTS

Two co-primary endpoints and a secondary endpoint have been developed for the MitraClip PAS to evaluate long-term safety and effectiveness of the MitraClip device:

3.1 Primary Safety Endpoint

The primary safety endpoint is a composite of death and stroke through 12 months

3.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is mitral valve surgery through 24 months

3.3 Secondary Safety Endpoints

A composite of all-cause death, stroke (major and minor), myocardial infarction (MI), and non-elective cardiovascular (CV) surgery for device related complications in the Device group at 30 days will be used as a secondary measure of safety.

4.0 CLINICAL PROTOCOL

4.1 Trial Design and Scope

MitraClip PAS is a prospective, non-randomized, single arm, multicenter, post-approval study evaluating the MitraClip device for the treatment of moderate-to-severe or severe MR in patients deemed too high risk to undergo mitral valve surgery, as defined in the labeling for the MitraClip device. The study will be composed of two separate arms corresponding to functional MR (FMR) patients and degenerative MR patients (DMR), and all analyses will be performed for each arm separately. Patients who undergo the MitraClip procedure will complete follow-up through 5 years. Reporting of adverse events will occur annually through 5 years. Abbott Vascular will work in collaboration with Society of Thoracic Surgeons (STS) and American College of Cardiology (ACC) societies to conduct this post-approval study.

4.2 Enrollment and Sample Size

Enrollment in the DMR arm will begin upon market approval of the MitraClip System in the US. Enrollment in the FMR arm will commence after the COAPT IDE trial is fully enrolled. Each arm will enroll 1200 patients, for a total study size of 2400 patients.

All patients who are eligible for the MitraClip device in the US (per approved labeling) and who may undergo the MitraClip procedure in the US will be consecutively enrolled into the MitraClip PAS.

4.3 Patient Selection

Patients will be included or excluded from enrollment in the PAS based on the labeling which will reflect the population approved for treatment with the MitraClip device. Two cardiothoracic surgeons, one of whom has at least 25 mitral valve repair experience in the prior year, must agree that the patient is too high risk for mitral valve surgery before s/he can be included in the study. The PAS is assumed to enroll patients who are similar to patients enrolled in the EVEREST II High Risk Registry and REALISM High Risk studies.

4.4 Statistical Methods

The trial has two co-primary endpoints, including one primary safety endpoint and one primary effectiveness endpoint, and one secondary endpoint. All endpoints will be analyzed separately for the DMR and FMR patients.

4.4.1 Primary Safety Endpoint

To demonstrate the long term safety of the MitraClip device the primary safety composite endpoint will be compared to a pre-specified performance goal.

Hypothesis:
The null and alternative hypotheses for the primary safety endpoint are:

$\mathbf{H_0}$: Freedom from composite death and stroke events at 12 months ≤ 70%
$\mathbf{H_1}$: Freedom from composite death and stroke events at 12 months > 70%

Analysis:
Since this is a 12-month endpoint, all data will be truncated at 12 months for the analysis. Kaplan Meier survival estimate, together with the variance estimated by the Greenwood method, may be used to set up the test of the null hypothesis as a Z-test. The null hypothesis will be rejected at the 5% level of significance if the test statistic is less than -1.645.

4.4.2 Primary Effectiveness Endpoint

To demonstrate long term effectiveness of the MitraClip device the endpoint of freedom from mitral valve surgery at 24 months will be compared to a performance goal.

Hypothesis:
The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: Freedom from mitral valve surgery at 24 months ≤ 80%
$\mathbf{H_1}$: Freedom from mitral valve surgery at 24 months > 80%

Analysis:
Since this is a 24-month endpoint, all data will be truncated at 24 months for the analysis. Kaplan Meier survival estimate, together with the variance estimated by the Greenwood method, may be used to set up the test of the null hypothesis as a Z-test. The null hypothesis will be rejected at the 5% level of significance if the test statistic is less than -1.645.

4.4.3 Secondary Safety Endpoint

4.4.3.1 Composite 30-Day Secondary Safety Endpoint

A composite of all-cause death, stroke (major and minor), MI, and non-elective cardiovascular surgery for device related complications at 30 days will be used as a secondary measure of safety. The analysis of this secondary safety endpoint is a one-group test against an objective performance goal for the proportion of subjects free from the composite of secondary safety events at 30 days.

Hypothesis:
The null and alternative hypotheses may be stated as:

$\mathbf{H_0}$: $P_D(30) \leq 0.80$
$\mathbf{H_1}$: $P_D(30) > 0.80$

where, $P_D(30)$ is the proportion of subjects free from composite of secondary safety events at 30 days.

A performance goal of 80% is set under a conservative assumption that the event rate of the composite is obtained additively from the individual components (see **Section 5.4.7: Power and Sample Size** for details).

Analysis:
An exact test for a single proportion will be performed at the 5% level of significance.

4.4.4 Adjustment for Multiple Testing

The secondary endpoints will be evaluated if the primary endpoints are met.

4.4.5 Power and Sample Size

A total sample size of 1200 subjects in each arm, accounting for 10% attrition at 12 months will provide at least 90% power for each of the primary endpoints. The details are provided below.

4.4.5.1 Primary Safety Endpoint

Table 1 lists the event rates assumed for the components of the composite primary safety endpoint in the Control and Device groups.

Table 1: Assumptions for Primary Safety Endpoint Event Rates at 12 Months

Event	DMR Group	FMR Group
Death	24%	23%
Stroke	3%	4%
Total	**27%**	**27%**

These event rates were derived from data on the 351 EVEREST Integrated High Risk patients who have completed 1 year of follow-up. One thousand (1000) simulations were performed to calculate sample size and power for the primary safety endpoint. A total of 1200 patients, accounting for 10% attrition at 12 months, provides approximately 90% power to reject the null hypothesis at the 5% significance level.

4.4.5.2 Primary Effectiveness Endpoints

The EVEREST II REALISM High Risk data for the freedom from mitral valve surgery at 24 months (N=133) provide an estimate of 93.5% with a 95% confidence interval of (85.2%, 97.2%). One thousand (1000) simulations were performed by assuming freedom from mitral valve surgery rate of 85% at 24 months, a withdrawal rate of 10% by 12 months and a mortality rate of 24% by 12 months[i]. One thousand two hundred (1200) patients per arm provides greater than 95% power to reject the null hypothesis at the 5% significance level.

4.4.5.3 Secondary Safety Endpoints

Table 2 lists the event rates assumed for the components of the composite secondary safety endpoint.

Table 2: Assumptions for Secondary Safety Event Rates at 30 Days

Event	DMR Group	FMR Group
Death	7%	5%
Stroke	3%	3%
MI	0%	2%
Non-elective CV Surgery for Device Related Complications	0%	1%
Total	**10%**	**11%**

These event rates were derived from data on the 351 EVEREST Integrated High Risk patients who have completed 1 year of follow-up. From **Table 2** the 30-day safety composite event rates are estimated at 11%, thus 89% are free of 30-day composite events with 95% lower confidence bound of 86.9%. Assuming 86.9% of patients are free

[i] Exponential withdrawal and mortality rates are assumed

from 30-day safety events, 1200 patients provides greater than 95% power at the 5% significance level.

4.4.6 Study Success

The study will be considered successful if the primary safety and primary effectiveness endpoints are met.

4.4.7 Additional Endpoints

Additional descriptive endpoints will also be reported as described below.

4.4.7.1 Device-Related Adverse Events

The number and proportion of subjects experiencing any device related adverse events, such as Single Leaflet Device Attachment or MitraClip device or MitraClip component embolization, will be reported on an annual basis out to 5 years.

4.4.7.2 Device and Procedure-Related Endpoints

The following device and procedure-related acute endpoints will be reported:

- Implant Rate: defined as the rate of successful delivery and deployment of MitraClip device implant(s) with echocardiographic evidence of leaflet approximation and retrieval of the delivery catheter
- Device Procedure Time: defined as the time elapsed from the start of the transseptal procedure to the time the Steerable Guide Catheter is removed
- Total Procedure Time: defined as the time elapsed from the first of any of the following: intravascular catheter placement, anesthesia or sedation, or TEE, to the removal of the last catheter and TEE.
- Device Time: defined as the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System (CDS) is retracted into the Steerable Guide Catheter.

4.4.7.3 Clinical Endpoints

The following additional endpoints will be summarized and reported for all patients who undergo the MitraClip procedure. No hypotheses are specified for these endpoints.

- Proportion of surviving patients with reduction in MR Severity to < 2+ at 12 months and 24 months
- Proportion of surviving patients with reduction in MR Severity to < 1+ at 12 months and 24 months
- Proportion of patients with improved Six minute Walk Distance > 24 meters between baseline and 12 months and between baseline and 24 months.
- Proportion of patients with improved KCCQ Quality of Life Score greater than 5 points between baseline and 12 months and between baseline and 24 months

- Proportion of patients with reduction in NYHA to class I/II between baseline and 12 months and between baseline and 24 months
- Annual rate of freedom from death (all cause, cardiovascular cause)
- Annual rate of freedom from mitral valve surgery and death
- All new onset atrial fibrillation at discharge, 30 days, 12 months and 2, 3, 4 and 5 years
- Annualized heart failure hospitalization rate through 12 months and 24 months
- Surgical mitral valve replacement rates at 12 months and 2, 3, 4 and 5 years (stratified by MR etiology)
- Surgical mitral valve repair rates at 12 months and 2, 3, 4 and 5 years (stratified by MR etiology)
- Left ventricular end diastolic volume (LVEDV) at baseline 12 months and 24 months
- Left ventricular end systolic volume (LVESV) at baseline 12 months and 24 months
- Left ventricular internal dimension at end diastole (LVIDd) at baseline 12 months and 24 months
- Left ventricular internal dimension at end systole (LVIDs) at baseline 12 months and 24 months

5.0 QUALITY CONTROL

5.1 Recruitment Strategy for Sites and Patients

Site selection will focus on recruiting both interventionalists and surgeons as Investigators at established centers, beginning with sites that have been actively participating in the EVEREST II REALISM Continued Access Registry. Investigators will have an established history of both successful manipulations of catheter-based devices into the vasculature and the heart, as well as skills in managing the potential intra-operative risks thereof. Primary consideration for the MitraClip PAS will be given to Investigators who have already been trained in the implantation of the MitraClip device. Formal training sessions (described below) will be provided to new sites and personnel who previously have not been trained in the implantation of the MitraClip device. As site ramp-up continues, it is expected that the majority of eventual sites for the MitraClip PAS will not be the same sites used in the EVEREST II RCT and HRR.

5.2 Determination of Patient Eligibility

Patients will be included or excluded from enrollment in the PAS based on the labeling which will reflect the population approved for treatment with the Device. Two cardiothoracic surgeons, one of whom has at least 25 mitral valve repair experience in the prior year must agree that the patient is too high risk for mitral valve surgery before s/he can be included in the study. The PAS is assumed to enroll patients who are similar to patients enrolled in the EVEREST II High Risk Registry and REALISM High Risk studies.

5.3 Adjudication of Clinical Endpoints

The Clinical Events Committee (CEC) is an independent multi-disciplinary team comprised of physicians who are not investigators in the trial. The CEC is responsible for adjudicating primary and secondary safety endpoints, including relationship to the Device and/or procedure (regardless of temporal relationship to the procedure), based on specific definitions of clinical events in the trial. The composition, guiding policies, and operating procedures governing the CEC are described in a separate **CEC Manual of Operations**.

5.4 Echocardiographic Assessments

An independent Echocardiography Core Laboratory (ECL) will assess baseline echocardiograms for patient eligibility, and follow-up echocardiograms at 12 months and 24 months.

5.5 Training Strategy for Physicians and Correlation to Patient Safety Outcomes

MitraClip PAS will include multi-disciplinary physician teams made up of at minimum an interventional cardiologist, a cardiac surgeon who has completed at least 25 mitral valve surgeries in the prior year, and an echocardiologist. The multi-disciplinary team will have a range of previous experience in structural heart interventions and MitraClip device use prior to their involvement in the PAS.

Abbott Vascular proposes to specify training requirements based on the level of physician experience with the MitraClip procedure and structural heart interventions. Experience level will correspond to the degree of training that will be required to achieve certification as a skilled MitraClip device user. The designated level of an implanting site will be determined by the level of experience at that site. The following categorization is proposed:

1. Level 1 Physician Operator: Defined as an Operator with no prior experience implanting the MitraClip device or with no current experience (within the past 6 months), and who may or may not have transseptal experience. Level 1 Operators will be required to complete a minimum initial number (5 in a 90 day period) of MitraClip device training cases as a primary operator. In addition to the initial minimum case requirement, Level 1 Operators must complete a minimum of 1 case per month going forward. A MitraClip device implant procedure training program (details of which are described below) will be administered by an Abbott Vascular Clinical Specialist who will provide on-site instruction and monitoring during the physician training phase.

2. Level 2 Physician Operator: Defined as an Operator who has prior experience implanting the MitraClip device, i.e., current EVEREST II and REALISM investigators. Level 2 Operators have adequate experience in both structural heart interventions and MitraClip device implantation. Level 2 Operators will require training based on the final approved device labeling prior to commercial use of the MitraClip device, and they will be required to complete a minimum of 2 cases per month as primary operator.

Use of the MitraClip System will be restricted to those operators who have completed training to the final approved Instructions for Use.

A minimum of 2 MitraClip procedures per month is the recommended caseload. If no MitraClip device implant cases are performed for 90 days, then Abbott Vascular will provide mandatory retraining to the operators and staff in order to ensure that they maintain procedural expertise.

Regardless of the experience level of the physician operator, Abbott Vascular intends to provide a trained Clinical Specialist to attend every case throughout the duration of the PAS. This is to maximize the ability to achieve continued safe outcomes.

All surgeons in the multi-disciplinary team will have a minimum clinical experience of 25 mitral valve repair experience in the prior year, and will also undergo formal training to the MitraClip explant procedures.

Abbott Vascular understands that the content of the training program is critical to ensuring both safe clinical outcomes at all sites, and reducing the learning curve for the multi-disciplinary team at each site over time. Because a multi-disciplinary team approach is essential to performing the MitraClip device implant procedure, only centers with established expertise in interventional cardiology, cardiac surgery, and echocardiography will be considered for commercial use and the PAS. Among those sites, only centers who have demonstrated successful clinical cross-collaborations within these disciplines will actually qualify to be MitraClip device implanting sites. The following criteria will be used to ensure team success in generating safe outcomes:

a. Implanter selection and qualifications: Experience treating patients with left-heart disease is essential. While catheter manipulation skills are important, prospective implanters will also be trained to evaluate and adhere to labeling regarding patient criteria for the MitraClip device. If the implanting physician has not been involved with the MitraClip device, then the implanting physician must first complete training.

b. Center selection criteria: Potential MitraClip device implanting centers must demonstrate evidence of a multi-disciplinary team (minimum of interventional cardiologist, cardiac surgeon, and echocardiologist) and present the credentials of this team to Abbott Vascular. All potential sites will participate in startup training conducted by Abbott Vascular.

c. Didactic training sessions (standard inservices): The Physician Training Program is conducted by Abbott Vascular and is approximately 22 hours in length and is generally delivered in 3-5 days. The Training Program is designed to train physicians using a systematic approach to the key topics that are essential to ensuring safe patient outcomes. The Training Program includes lectures, presentations and hands-on uses of a demo system which includes a heart model. Specifically, physicians are trained to the following areas in the Training Program:

- The MitraClip System including components, features and design
- Patient Screening
- Imaging
- Pre Procedure Preparation
- Procedure
- Transseptal
- Steering and Positioning
- Grasping and Leaflet Insertion Assessment
- MitraClip device deployment
- Post Procedure Considerations
- Situational Steering Scenarios
- Procedural Troubleshooting Techniques
- MitraClip Instructions for Use

d. Peer-to-Peer training sessions: In the peer-to-peer training sessions, the following topics are covered:

- How to setup a successful MitraClip program: the multi-disciplinary team
- Patient Selection
- Patient consent
- Screening process
- Pre-procedural reminders
- Room set-up
- Intraprocedural considerations
  - Hemodynamics
  - Echo
  - Fluoro
  - Anesthesia
  - Groin care
  - Second MitraClip intervention decision process
- Post care management
- Patient follow-up
- Referral network

e. Case proctoring by trainer: A trained Abbott Vascular Clinical Specialist will be available to review and attend all MitraClip device implant cases throughout the PAS period.

f. Qualifications to become a trainer: The certification process for the Abbott Vascular Clinical Specialist consists of both didactic coursework and field observation and training. The curriculum consists of classroom lecture, simulated cases, computer based training modules, case study analysis, workshops, case observation, skills assessments, transesophogeal echocardiographic (TEE)

visualization and mentor guided activities. The Abbott Vascular Clinical Specialist's competency is evaluated through the use of written exams, practical exams and on the job skills assessments. All Abbott Vascular Clinical Specialists are required to complete continuing education.

g. Abbott Vascular Clinical Specialist ongoing support: In addition to a commitment to being present at every case, Abbott Vascular Clinical Specialists will continue to support the implanting team and site as required. The Abbott Vascular Clinical Specialist will have continued responsibilities for ongoing education and ensuring that scheduled caseloads and any other relevant activities are communicated to Abbott Vascular.

h. Acute success: To be considered a successful case, the MitraClip device must be implanted with a resulting MR $\leq$ 2+.

All outcomes in the PAS will be analyzed by both physician level of experience and site level of experience to ensure adequate and effective training. The following evaluation metrics will be compiled:

1. Procedural Safety Metrics: Device time, implant rate, and reduction of MR

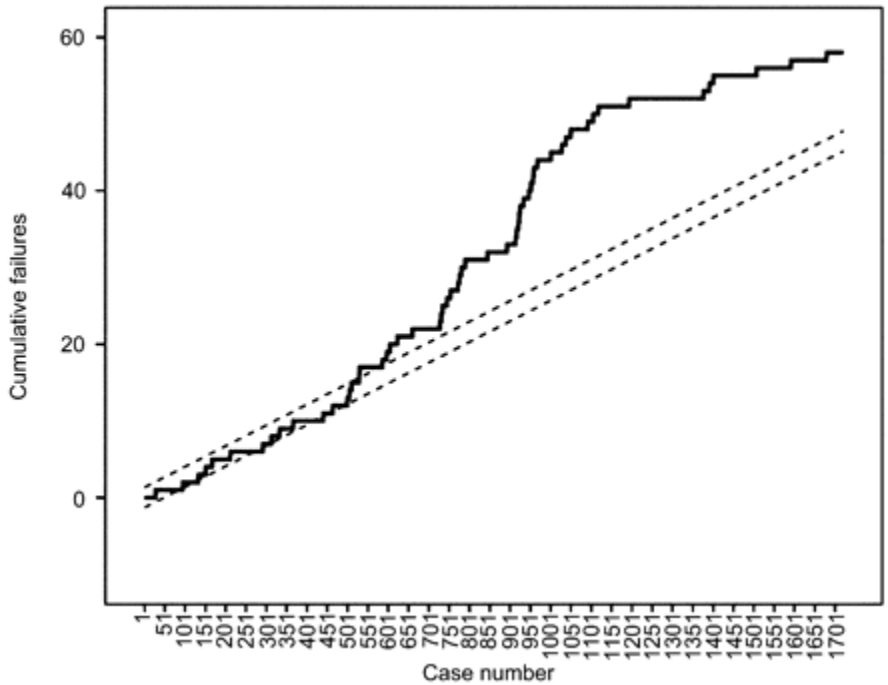
2. Post-Procedural Safety Metrics: Number of Single Leaflet Device Attachments (SLDA) and number of Device embolizations

These evaluation metrics will be tracked every 6 months. If a site or operator performs outside established bounds for other sites/investigators, retraining will be considered and performed if necessary. On a caseload basis, any implanter (or team) who does not perform at least one MitraClip device implant procedure within any 90 day period, after an initial 6 months ramp-up time, will be required to retrain.

Additional criteria for retraining are established based on Abbott Vascular monitoring of adverse events through the use of CUSUM control charts for each site. CUSUM control charts have been used in hospitals to track surgical quality measures such as mortality and morbidity[i]. The y-axis on the CUSUM is the number of failures and the x-axis is the number of cases. For each case, the y-axis increases by 1 unit if there is a failure or stays flat is there is not a failure. An example of a CUSUM chart that was used to track mortality is shown in Figure 1 below.

[i] Biau, D, Resche‐Rigon M, et. al., "Quality control of surgical and interventional procedures: a review of the CUSUM", Qual Saf Health Care. 2007 June; 16(3): 203–207.

Figure 1: Cumulative failure chart for hospital mortality[i], n=1772
(For illustrative purposes)



. ----- alert line for unacceptable cumulative failure rates, constructed as explained. The start of the unacceptable performance is situated around case number 551

A CUSUM chart will be created for each site for Unsuccessful Implant, SLDA, Device Embolization and Device Failure. The alert limits will established at the beginning of enrollment in the PAS. The alert limits for the CUSUM chart will be calculated using the sequential probability ratio test[ii]. The parameters required are the acceptable rate of the outcome, the unacceptable rate of the outcome, type I and II error. The acceptable and unacceptable rates of each of the outcomes will be based on the rates from EVEREST I, EVEREST II, and REALISM trials. Alpha will be set at 0.05 and beta will be set at 0.2. As a site control chart crosses an alert limit, Abbott Vascular will assess the situation and may contact the site for retraining.

[i] Figure from Noyez, L, *Control charts, Cusum techniques and funnel plots. A review of methods for monitoring performance in healthcare*, Interact CardioVasc Thorac Surg 2009;9:494-499.
[ii] Wald A. "Sequential tests in industrial statistics". Ann Math Stat. 1945;6:117–186