SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Mitral Valve Repair Device
Device Trade Name:	MitraClip® Clip Delivery System
Device Procode:	NKM
Applicant Name and Address:	Abbott Vascular 4045 Campbell Avenue Menlo Park, CA 94025
Date of Panel Recommendation:	March 20, 2013
Premarket Approval Application (PMA) Number:	P100009
Date of FDA Notice of Approval:	October 24, 2013
Priority Review:	Granted on December 18, 2008 because the MitraClip device is intended to treat mitral regurgitation and addresses an unmet clinical need in that it represents a breakthrough technology that provides a clinically meaningful advantage over existing technology by being the first available percutaneous mitral valve repair device.

II. INDICATIONS FOR USE

The MitraClip Clip Delivery 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 mitral regurgitation.

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III. CONTRAINDICATIONS

The MitraClip Clip Delivery System is contraindicated in DMR patients with the following conditions:

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MitraClip Clip Delivery System labeling (Instructions for Use).

V. DEVICE DESCRIPTION

The MitraClip Clip Delivery System (CDS) consists of three major components: 1) the Delivery Catheter 2) the Steerable Sleeve, and 3) the MitraClip Device (Figure 1). The 16 Fr Clip Delivery System is introduced into the body through a 24 Fr Steerable Guide Catheter which includes a dilator. The Steerable Guide Catheter and dilator are 510(k) cleared under K083793 on April 27, 2009, K091596 on July 2, 2009, K093866 on January 13, 2010, K100789 on April 21, 2010 and K112239 on August 31, 2011.

The MitraClip Clip Delivery System is used to advance and manipulate the implantable MitraClip Device for proper positioning and placement on the mitral valve leaflets. The MitraClip Device is a single-sized, percutaneously implanted mechanical clip for the reduction of mitral regurgitation. The MitraClip Device grasps and coapts the mitral valve leaflets resulting in fixed approximation of the mitral leaflets throughout the cardiac cycle. The MitraClip Device is placed without the need for arresting the heart or cardiopulmonary bypass. The MitraClip Device is fabricated with metal alloys and polyester fabric (Clip cover) that are commonly used in cardiovascular implants. The MitraClip Device arms can be adjusted to any position from fully opened fully inverted and fully closed. The Grippers can be raised or lowered repeatedly. The key dimensions of the MitraClip Clip Delivery System are listed in Table 1.

Figure 1: The MitraClip Clip Delivery System

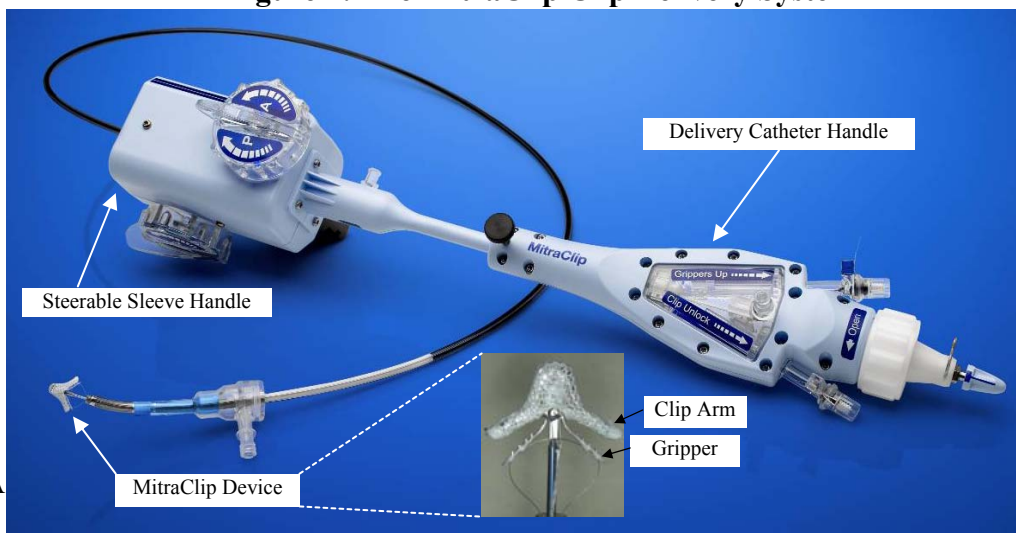


Table 1: Key Dimensions for the MitraClip Clip Delivery System

Dimensional Component	Dimension
Delivery Catheter	
Extended Length (from Sleeve curved at 90 degrees)	45mm - 70 mm
Catheter Shaft Outer Diameter (OD)	3.4 mm (10 Fr)
Steerable Sleeve	
Working Length	1095 mm
Catheter Distal Shaft Outer Diameter (OD)	5.3 mm (16Fr)
MitraClip Device	
Closed Clip Length	15 mm maximum
Grasping Width at 120 degrees	17 mm maximum
Clip Width at 180 degrees	20 mm maximum
Arm Width	5 mm maximum
Arm Length (Coaptation Length)	9 mm maximum

The Steerable Guide Catheter is used to introduce the MitraClip Clip Delivery System into the left side of the heart through the interatrial septum. The Steerable Guide Catheter is also used to position and orient the MitraClip Clip Delivery System to the appropriate location above the mitral valve. The Dilator is used for the introduction of the Steerable Guide Catheter into the femoral vein and left atrium.

Several accessories are used in conjunction with the MitraClip Clip Delivery System including: 1) a Stabilizer, 2) a Lift, 3) a Support Plate, 4) a Silicone Pad and 5) Fasteners. These Class I accessories are assembled to provide a stable working platform for the MitraClip Clip Delivery System.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

- Mitral valve repair surgery is the treatment of choice for operable patients with severe DMR regardless of symptoms.
- Mitral valve replacement surgery is another alternative for operable DMR candidates, typically performed when repair cannot be successfully performed or when possibility of reoperation to correct a repair is not feasible.
- Medical therapy is an option for DMR patients with less than severe MR with normal LV dimensions who are asymptomatic or for DMR patients at prohibitive risk for surgery.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The MitraClip Clip Delivery System received CE mark in March 2008. The device is currently approved for commercial distribution in the following countries. Marketing approval for the device has not been withdrawn for any reason related to its safety or effectiveness.

- Australia
- Austria
- Belgium
- Canada (special Access)
- Colombia
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hong Kong
- Hungary
- Iceland
- Indonesia
- Ireland
- Israel
- Italy
- Kuwait
- Latvia
- Liechtenstein
- Lithuania
- Luxembourg
- Malaysia
- Malta New
- Netherlands
- New Zealand
- Norway
- Poland
- Portugal
- Romania
- Saudi Arabia
- Singapore
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- Turkey
- UK

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse events have been identified as possible complications of the MitraClip procedure.

- Allergic reaction (anesthetic, contrast, Heparin, nickel alloy, latex)
- Aneurysm or pseudo-aneurysm
- Arrhythmias
- Atrial fibrillation
- Atrial septal defect requiring intervention
- Arterio-venous fistula
- Bleeding
- Cardiac arrest
- Cardiac perforation
- Cardiac tamponade/Pericardial Effusion
- MitraClip erosion, migration or malposition
- MitraClip Device thrombosis
- MitraClip System component(s) embolization
- Coagulopathy
- Conversion to standard valve surgery
- Death
- Deep venous thrombus (DVT)
- Dislodgement of previously implanted devices
- Drug reaction to anti-platelet/anticoagulation agents/contrast media
- Dyspnea
- Edema
- Emboli (air, thrombus, MitraClip Device)
- Emergency cardiac surgery
- Endocarditis
- Esophageal irritation
- Esophageal perforation or stricture
- Failure to deliver MitraClip to the intended site
- Failure to retrieve MitraClip System components
- Fever or hyperthermia
- Gastrointestinal bleeding or infarct
- Hematoma
- Hemolysis
- Hemorrhage requiring transfusion
- Hypotension/hypertension
- Infection and pain at insertion site
- Infection and pain at incision site
- Injury to mitral valve complicating or preventing later surgical repair
- Lymphatic complications
- Mesenteric ischemia
- Mitral stenosis
- Mitral valve injury
- Multi-system organ failure
- Myocardial infarction
- Nausea/vomiting
- Peripheral ischemia
- Prolonged angina
- Prolonged ventilation
- Pulmonary congestion
- Pulmonary thrombo-embolism
- Renal insufficiency or failure
- Respiratory failure/atelectasis/pneumonia
- Septicemia
- Single leaflet device attachment (SLDA)
- Skin injury or tissue changes due to exposure to ionizing radiation
- Stroke or transient ischemic attack (TIA)
- Urinary tract infection
- Vascular trauma, dissection or occlusion
- Vessel spasm
- Vessel perforation or laceration
- Worsening heart failure
- Worsening mitral regurgitation
- Wound dehiscence

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

IX. SUMMARY OF PRECLINICAL STUDIES

A series of non-clinical laboratory studies were performed to determine the safety and effectiveness of the MitraClip Clip Delivery System. Studies were conducted on the MitraClip Clip Delivery System, its individual components/materials and on the MitraClip Device.

A. Biocompatibility Testing

The materials that make up the Delivery Catheter, Steerable Sleeve and the MitraClip Device have an extensive history of use in the medical device industry. The Sponsor successfully completed a series of Good Laboratory Practices (GLP) biocompatibility tests of all contact materials in the MitraClip Clip Delivery System in accordance *to ISO10993-1:2003 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing* and *FDA's Blue Book Memoranda #G95-1 – Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices* or obtained the data from the material supplier.

Results demonstrate the components of the MitraClip Clip Delivery System are non-toxic and met the requirements of ISO 10993-1 for a vascular implant and ISO 10993-4 for a blood contacting device. Table 2 and Table 3 list the test performed, test conditions and results obtained from the biocompatibility studies conducted on the Delivery Catheter, Steerable Sleeve and MitraClip Device. There is extensive prior clinical history of the use of the materials utilized in the MitraClip Clip Delivery System in both human vascular tissue and bone implants. The Sponsor provided a scientific rationale for the omission of Chronic Toxicity and Carcinogenicity testing that was accepted by FDA.

Table 2: Biocompatibility Test Summary for Delivery Catheter and Steerable Sleeve

Test Performed	Standards	Results/Comments (units when appropriate)
Cytotoxicity	ISO 10993-5:1999	PASS (Non cytotoxic), Grade 0
Sensitization	ISO 10993-10:2002	PASS (Non sensitizing) Grade 1 (0-8%), Not significant
Irritation / Intracutaneous Toxicity	ISO 10993-10:2002, ISO 10993-12:2002 ISO 10993-10:1995, ISO 10993-12:1996	PASS (non-irritating) Test not significantly > the control, Negligible irritant
Intracutaneous Injection*	ISO 10993-10:2002	PASS
Systemic Toxicity		
Acute Systemic Toxicity	ISO 10993-11:2006, ISO 10993-11:1993	PASS (non toxic) Test not significantly > the control, Negative
Acute Systemic Injection*	ISO 10993-11:1993	PASS

Test Performed	Standards	Results/Comments (units when appropriate)
Material Mediated Pyrogenicity	ISO 10993-11:2006	PASS (non -pyrogenic) No increase in temperature > 0.5 °C, Non-pyrogenic
Hemocompatibility		
Hemolysis	ISO 10993-4: 2002/Amd.1:2006(E) ISO 10993-12:2002	PASS (Non-hemolytic)
Modified Hemolysis	ASTM F 756-08	PASS (Non-hemolytic)
Hemolysis-Direct	ASTM F 756-08	PASS (Non-hemolytic)
Hemolysis-Extraction	ASTM F 756-00	PASS (Non-hemolytic)
Modified Hemolysis	ASTM F 756-08	PASS
Complement activation	ISO 10993-4: 2002/Amd.1:2006(E)	PASS, Test device concentrations of C3a and SC5b-9 were statistically similar to that of the predicate device
Thrombogenicity Partial Thromboplastin Time	ISO 10993-4: 2002/Amd.1:2006(E)	PASS, The test sample demonstrated a similar clotting time when compared to the predicate device

Table 3: Biocompatibility Test Summary for MitraClip Device

Test Performed	Standards	Results/Comments (units when appropriate)
Cytotoxicity		
Cytotoxicity	ISO 10993-5:1999	PASS (Non-cytotoxic), Grade 0
		PASS (Non-cytotoxic), Grade 0
Sensitization	ISO 10993-10:2002	PASS (non-sensitizing) Grade 1 (0-8%), Not significant
Irritation/Intracutaneous Toxicity	ISO 10993-10:2002	PASS (non irritating), Test not significantly > the control, Negligible irritant
Systemic toxicity		
Acute Systemic Toxicity	ISO 10993-11:2006	PASS, Test not significantly different from the control, Negative
Material Mediated Pyrogenicity	ISO 10993-11: 2006	PASS (Non-pyrogenic) No increase in temperature > 0.5°C
Sub-chronic toxicity,72 hour	ISO 10993-11: 2006	PASS (Non-toxic)
Sub-chronic toxicity, 14 day IV	ISO 10993-11: 2006	PASS (Non-toxic) Negative for signs of systemic toxicity due to leachable components
Genotoxicity		
Gene mutation (AMES)	ISO 10993-3:2003	PASS (Non-mutagenic)
Chromosome aberration	ISO 10993-3:2003	PASS (Non-genotoxic)
DNA damage	ISO 10993-3:2003	PASS (Non-mutagenic)
Implantation	ISO 10993-6:2007	PASS, Test 2: Non-reactive
		PASS, Test 1: Mildly reactive
Hemocompatibility		
Hemolysis	ISO 10993-4: 2002/Amd.1:2006(E)	PASS (Non-hemolytic)
Complement activation	ISO 10993-4:2002/Amd.1:2006(E)	PASS complement Activation Assay
Thrombogenicity	ISO 10993-4:2002/Amd.1:2006(E)	PASS, UPTT not significantly different than controls

Test Performed	Standards	Results/Comments (units when appropriate)
Chronic Toxicity	ISO 10993-11:2006	N/A
Carcinogenicity	ISO 10993-3:2003	N/A

B. Animal Studies

Abbott Vascular conducted multiple animal studies in the porcine model to assess the safety of the MitraClip Clip Delivery System.

Two acute GLP studies (n=3, n=4) were conducted in a porcine model to demonstrate that repeated deployment of the MitraClip Device does not cause clinically significant intraoperative trauma to the mitral valve and adjacent structures; and that the use of the MitraClip Device did not cause intracardiac trauma or trauma to the great vessels. The MitraClip Clip Delivery System performed as intended, in this animal model, without causing intracardiac trauma or trauma to the great vessels. There were no procedural deaths or MitraClip Device embolizations. In addition, several acute Non-GLP studies were conducted in a porcine model to help characterize device performance based on the defined product specifications, and gain experience and proficiency to develop appropriate device Instructions for Use and physician training materials. In each case, the MitraClip Clip Delivery System performed as intended and the MitraClip Device was successfully deployed, creating a double orifice.

A chronic GLP animal study (n=21) was conducted to demonstrate the safety, reliability, and performance characteristics of the MitraClip Device according to its intended use. Results were analyzed at 4 weeks, 12 weeks and 24 weeks. The MitraClip Device performed as intended and the long term healing response of the mitral valve leaflets indicate that the MitraClip Device maintains tissue approximation and in a relatively short time, is fully encapsulated within a fibrous endocardial capsule. The MitraClip Device was shown to be safe and effectively delivered when used as intended in a porcine model.

C. Sterilization

The MitraClip Clip Delivery System is sterilized using ethylene oxide (EO) sterilization and has been validated per AAMI/ISO 11135:2007 "*Medical Devices Validation and Routine Control of Ethylene Oxide Sterilization*." Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}. In addition, the amount of EO residual and bacterial endotoxins was verified to be within the specifications limits.

D. Packaging/Shelf Life

Packaging validation and shelf life studies were conducted on the packaging of the MitraClip Clip Delivery System to establish a shelf life/expiration date. Testing included simulated transit, visual inspection, bubble emission testing and peel strength test for the packaging of the MitraClip Clip Delivery System.

In addition, testing to establish device shelf life for the MitraClip Clip Delivery System included double EO sterilization, accelerated aging, transit conditioning, and visual inspection. Further, testing was conducted to verify the functional performance of the MitraClip Clip Delivery System following 12 month accelerated aging and to verify adhesive bond strength following functional testing of the device. The data generated to date support a shelf life of 1 year for the packaging and device of the MitraClip Clip Delivery System.

E. *In Vitro* Engineering Testing

Abbott Vascular successfully completed extensive *in vitro* engineering testing of the MitraClip Clip Delivery System in accordance with its product specification, Instructions for Use (IFU) and applicable standards, which demonstrated acceptable device performance. Testing was performed per internal Abbott Vascular test protocols and reports, which incorporated pre-determined and justified sample sizes, acceptance criteria, applicable standards and testing conditions. Testing was conducted using the MitraClip Clip Delivery System as a whole in conjunction with the Steerable Guide Catheter in a simulated use environment or on subassemblies, as applicable.

Design Specific Performance Studies – Delivery Catheter

Multiple design specific characterization, mechanical and functional tests were performed on the Delivery Catheter and demonstrated acceptable results including: dimensional testing, radiopacity, echogenicity, lubricity, tensile strength, torque strength, compressive strength, axial and rotational stability, arm rotation, rotational ratio and accuracy, catheter cycling, gripper line cycling and removal, fluid management, elongation, actuation forces, clip deployment, lock/unlock testing, physical and mechanical integrity, device compatibility, insertion and retraction testing.

Design Specific Performance Studies – Steerable Sleeve

Multiple design specific characterization, mechanical and functional tests were performed on the Steerable Sleeve and demonstrated acceptable results including: dimensional and visual inspection, radiopacity, leak testing, torsional strength, tensile strength, knob stability, force to curve, clip retraction into introducer, sleeve stability, starting angle and curving range.

Design Specific Performance Studies – MitraClip Device

Multiple design specific mechanical and functional tests were performed on the MitraClip Device and demonstrated acceptable results including: device actuation (open, close, invert), lock engagement, establish final arm angle, clip settling, tensile testing, lock/unlock force, cover attachment, integrity testing, deliverability, and gripper raise/lower testing.

Non-clinical testing has demonstrated the MitraClip Device is magnetic resonance conditional. It can be scanned safely under the following conditions:

- Static magnetic field up to 3 Tesla;
- Maximum spatial gradient in static field of 2500 gauss/cm or less;
- Maximum whole-body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the MitraClip produced a temperature rise of less than 1°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg, as assessed by calorimetry for 15 minutes of MR scanning in a 3T system using a GE Signa HDx 3.0 T MR scanner.

Magnetic resonance image quality may be compromised if the area of interest is in the exact same area, or relatively close to the MitraClip Device. A maximum image artifact of 60 x 70 mm was measured in testing conducted in a 3T magnetic resonance system. It may be necessary to optimize the magnetic resonance imaging parameters due to the presence of the implant.

Material characterization, dimensional and structural performance durability studies were performed on the MitraClip Device and demonstrated acceptable results including: mechanical properties, open circuit potential, metrology, surface analysis, and *in vivo* load determination. Details of additional material characterization and structural performance durability testing performed on the MitraClip Device including the attribute tested, applicable standards, test description and results are provided in Table 4 and Table 5, respectively. A result of "Pass" denotes that the test results met the product specifications. A result of "NA" denotes test results were obtained for characterization purposes. All testing demonstrated the MitraClip Device performed acceptably and FDA had no further concerns regarding the pre-clinical testing.

Table 4: MitraClip Device Material Characterization Testing Summary

Attribute Tested	Standards	Test Description and Results Summary	Results
Material Analysis	ASTM F2633-07 ASTM F2063-05 ASTM F1058-08	Suppliers are required to provide chemical analysis certification that Elgiloy and Nitinol raw material used to manufacture its components meets the chemistry requirements specified in ASTM F1058 and ASTM F2063 respectively. The chemical formulation of Grade 1 Elgiloy consists of Carbon (C 0.15% max), Manganese (Mn 1.5 – 2.5%), Silicon (Si 1.2%), Phosphorus (P 0.015% max), Sulfur (S 0.015% max), Cobalt (CO 39.0 – 41.0%), Chromium (CR 19.0 – 21.0%), Nickel (Ni 14.0 – 16.0%), Molybdenum (Mo 6.0 – 8.0%), Beryllium (Be 0.10% max) and Iron (Fe Balance). The chemical composition of Nitinol consists of Nickel (Ni 54.5 – 57.0%), Carbon (C 0.050% max), Cobalt (Co 0.050% max), Copper (Cu 0.010% max), Chromium (Cr 0.010% max), Hydrogen (H 0.005% max), Iron (Fe 0.050% max), Niobium (Nb 0.025% max), Nitrogen plus oxygen (0.05% max) and Titanium (Ti Balance).	NA
Mean Breakdown Potential (Eb) (Potentiodynamic)	ASTM F2129-08	Corrosion testing was performed on the MitraClip Device according to ASTM F2129-08 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that prior to fatigue testing the finished devices exhibit acceptable corrosion resistance. Results met the product specification.	Pass
Clip Durability: Clip Must be Corrosion Resistant (Potentiodynamic)	ASTM F2129-08	Corrosion testing was performed on the nitinol leaf spring component of the MitraClip Device according to ASTM F2129-08 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that prior to fatigue testing the nitinol leaf spring of the MitraClip exhibits acceptable corrosion resistance. Results met the product specification.	Pass
Clip Durability: Corrosion Performance Post Fatigue Test (Potentiodynamic)	ASTM F2129-06	Corrosion testing was performed on the MitraClip Device according to ASTM F2129-06 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" post accelerated fatigue testing to demonstrate that the MitraClip Device exhibits acceptable corrosion resistance post 600 million cycles accelerated fatigue testing. Results met the product specification.	Pass
Corrosion: Galvanic Corrosion Test	ASTM G71-81 (2009)	Corrosion testing was performed according to ASTM G71-81 (2009), “Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes” to demonstrate that the MitraClip Device exhibits acceptable corrosion resistance. SEM analysis was conducted to detect evidence of surface conditions compared to controls. Results met the product specification.	Pass
Compatibility with Standard Imaging Modalities (Radiopacity)	ASTM F640-07	Testing was performed per Method B of ASTM F640-07, “Standard Test Methods for Determining Radiopacity for Medical Use” to demonstrate that the MitraClip Device is adequately visible under fluoroscopic imaging equipment. Three devices were tested against a reference 0.035 inch guidewire. Results confirmed that the MitraClip Device is adequately visible under fluoroscopic imaging equipment and met the product specification.	Pass
Compatibility with Standard Imaging Modalities (Echogenicity)	NA	Testing was performed to demonstrate that the MitraClip Device is adequately visible using standard echocardiographic imaging equipment. Results confirmed that the MitraClip Device is adequately visible under standard echocardiographic modalities and met the product specification.	Pass

Table 5: MitraClip Device Dimensions and Durability Testing Summary

Attribute Tested	Standard	Test Description and Results Summary	Results
Finite Element Analysis (FEA) - MitraClip Device	None	An in-depth analysis of the MitraClip Device was conducted to ensure that the conditions to which the MitraClip Device will be subjected will not result in failure due to fatigue. The FEA evaluated the structural integrity of the MitraClip Device when subjected to the expected *in vivo* loading conditions. The analysis took into account manufacturing, delivery, implantation and clinical loading over the device life, and predicted that fatigue failures will not likely occur.	NA
Finite Element Analysis (FEA) – MitraClip Gripper	None	An in-depth analysis of the Gripper component of the MitraClip Device was conducted to ensure that the *in vivo* conditions to which the Grippers will be subjected will not result in failure due to fatigue. The FEA evaluated the structural integrity of the Grippers when subjected to the expected loading conditions generated *in vivo*. The analysis took into account manufacturing, delivery, implantation, and clinical loading over the device life, and predicted that fatigue failures will not likely occur.	NA
Finite Element Analysis (FEA) – MitraClip Leaf Spring	None	An in-depth analysis of the leaf spring component of the MitraClip Device was conducted to calculate the *in vivo* leaf spring output force that is applied to the binding plate when the MitraClip Device is in the locked position and deployed. The analysis took into account manufacturing, delivery, implantation, and clinical loading over the device life, and predicted that fatigue failures are not likely to occur.	NA
Clip Durability (Accelerated Fatigue Testing)	ASTM E466-07	Testing was performed to demonstrate that the MitraClip Device with Grippers can adequately withstand expected *in vivo* cyclic loading conditions when deployed, and will not show fatigue failure during simulated 15 year fatigue testing. MitraClip Devices were dynamically cycled under simulated *in vivo* conditions for 1.2 billion cycles. Following cycling, the MitraClips were visually inspected under magnification and SEM. All MitraClip Devices remained locked and were free of fractures (under 20x magnification and X-ray), clip arm partial dislocation or component embolization at 40, 200, 400, and 600 million cycles. No cracks or fractures were observed. Wear was acceptable.	Pass
Clip Durability: SEM Visualization Post Fatigue Test	NA	Surface SEM analysis was performed to visualize the surfaces of the MitraClip Device for wear following fatigue testing to over 1.2 billion cycles. No cracks or breaks were observed. Evidence of wear was deemed to be acceptable.	Pass
Clip Durability (Post Durability Dynamic Load to Failure Testing)	ASTM E466-07	Testing was performed to characterize the failure mode of the MitraClip Device due to excessive *in vivo* cyclic loading conditions post fatigue testing. MitraClip Devices fatigue cycled to over 1.2 billion cycles without failure. Eventual failure did occur after >880,000 additional cycles at increased load (well above the peak expected *in vivo* loading conditions).	Pass
Clip Durability (Gripper Component Fatigue Life)	ISO 5840: 2005	Testing was performed to successfully establish durability of the Gripper component of the MitraClip Device during simulated 15 year (1.2 billion cycle) fatigue testing under 1.5 times the peak *in vivo* loading conditions.	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed multiple clinical studies to establish a reasonable assurance of safety and effectiveness of the MitraClip for the percutaneous reduction of significant symptomatic mitral regurgitation (MR). These clinical studies included evaluation of MitraClip use in surgical candidates and high surgical risk patients as well as in patients with primary abnormality of the mitral apparatus (also referred to as degenerative MR or DMR) and patients with secondary MR (also referred to as functional MR or FMR). Patient follow-up periods for all studies included patient discharge, 30 days, 6, 12, 18 and 24 months, and annually thereafter through 5 years. A summary overview of these clinical studies is provided below.

The targeted patient population has evolved over time based upon emerging data and benefit-risk considerations. Data on patients with significant symptomatic mitral regurgitation due to primary abnormality of the mitral apparatus (DMR) determined to be at prohibitive risk for mitral valve surgery that were collected from these studies are provided in detail below and were the basis for the PMA approval decision.

A. Overview of MitraClip Clinical Program

Beginning in 2003, the Sponsor conducted a series of clinical studies to evaluate the safety and effectiveness of the MitraClip for the treatment of mitral regurgitation. Table 6 provides an overview of the MitraClip clinical program in the United States including study design, enrollment criteria, endpoints and volumes.

The EVEREST II Randomized Controlled Trial (RCT) was a prospective, blinded, randomized, controlled, multi-center study initiated in 2005 as a pivotal study to compare the MitraClip to the standard of care mitral valve repair or replacement surgery in patients who were indicated for and could undergo mitral valve surgery. During the course of the RCT, there were a substantial number of patients with severe MR who could not be randomized because surgeons deemed them to be too high risk for surgery. Therefore, the MitraClip clinical program was expanded in 2007 to add the EVEREST II High Risk Registry (HRR) as a single-arm, self-controlled adjunctive study to evaluate the performance of the MitraClip in patients who were too high risk for mitral valve surgery. Patients were screened for the EVEREST II HRR concurrent with the RCT and enrolled in the arm in which they were eligible (RCT or HRR).

After the RCT and HRR were fully enrolled, a continued access study of the MitraClip (REALISM) was approved and began enrollment in 2009. The REALISM study allowed for collection of additional safety and effectiveness data and permitted patients and physicians continued access to the MitraClip during review of pre-market approval application (PMA). The REALISM Study consisted of two arms, one arm for “RCT eligible” (non-high surgical risk) patients and one arm for “HRR eligible” (high surgical risk) patients. The REALISM Study was closed to enrollment for non-high surgical risk patients in September 2011 and continued enrolling in the High Risk arm through PMA approval. The EVEREST II HRR and REALISM HR studies were adjunctive studies to the RCT and not prospectively planned as stand-alone studies to support approval.

The MitraClip device received CE Mark in March 2008, and the ACCESS-EU post-approval studies were initiated to study of the use of the MitraClip System in patients treated in Europe. The primary objective of the ACCESS-EU studies was to gain health economics and clinical care data, as well as further evidence of device safety and effectiveness in the commercial setting.

Table 6: Overview of MitraClip US Clinical Trials

Type	Study	Key Inclusion Criteria	Key Exclusion Criteria	Endpoint	sites	patients
Feasibility	EVEREST I enrollment 2003-2006	• MR≥3+ • Symptomatic or asymptomatic with[a]: LVEF 30-50% and/or LVESD 50-55mm or LVEF 50-60% and LVESD < 45 mm or LVEF>60 and LVESD 45-55 mm • Candidate for mitral valve surgery including cardiopulmonary bypass	• LVEF<30%, and/or LVESD >55mm • Mitral valve orifice area <4.0 cm2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary: Major Adverse Event rate through 30 days	11	55
Randomized Control Trial	EVEREST II RCT enrollment 2005-2008	• MR≥3+ • Symptomatic with LVEF > 25% and LVESD ≤ 55 mm or asymptomatic with[a]: LVEF 25% to 60% LVESD ≥ 40 mm New onset of atrial fibrillation PASP>50mmHg at rest of >60 mmHg with exercise	• LVEF≤25%, and/or LVESD >55mm • Mitral valve orifice area <4.0 cm^2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary Safety: Major Adverse Event rate through 30 days or discharge, whichever is greater Primary Effectiveness: Freedom from death, MV surgery (for Device group) or re-operation (for Control group), and MR > 2+ at 12 months • Secondary Effectiveness: • Measures of LV Function • SF-36 quality of life • NYHA Functional Class	37	60 roll-in 178 [b] Device 80 [b] Surgery Control
Single-Arm Registry	EVEREST II High Risk Registry Study enrollment 2007-2008	• MR≥3+ • Predicted procedural mortality risk calculated using the STS surgical risk calculator of ≥ 12% or in the judgment of a cardiac surgeon the patient is considered a high risk surgical candidate due to the presence of one of the following indications: 1. Porcelain aorta, mobile ascending aortic atheroma 2. Post-radiation mediastinum 3. Previous mediastinitis 4. Functional MR with EF<40 5. Over 75 years old with EF<40 6. Re-operation with patent grafts 7. Two or more prior chest surgeries 8. Hepatic cirrhosis 9. Three or more of the following STS high risk factors 9.1 Creatinine > 2.5 mg/dL 9.2 Prior chest surgery 9.3 Age over 75 9.4 EF<35	• LVEF<20% and/or LVESD>60mm • Mitral valve orifice area <4.0 cm^2 • Leaflet anatomy which may preclude MitraClip device implantation, proper MitraClip device positioning on the leaflets or sufficient reduction in MR	• Primary Safety: Procedural mortality at 30 days • Major Secondary: • Measures of LV Function • SF-36 quality of life • NYHA Functional Class • CHF Hospitalizations • Secondary Safety: • Major Adverse Event rate at 30 days and 12 months	25	78
Continued Access Registry	REALISM High Risk enrollment 2009-2013	• Same as High Risk Registry with the exception of the requirement for predicted procedural mortality risk ≥ 12%	• Same as High Risk Registry	• Same as High Risk Registry	39	581[c]
	REALISM Non-High Risk enrollment 2009-2011	• Same as RCT	• Same as RCT	• Same as RCT • 6 Minute Walk Test (6MWT) Distance[d]	39	272

[a] Inclusion criteria based on the current indication for mitral valve surgery for mitral regurgitation in the ACC/AHA guidelines for management of valvular dysfunction..
[b] Of the 184 patients randomized to Device, 178 received Device. Of the 95 patients randomized to Control, 80 underwent mitral valve surgery.
[c] As of July 12, 2013
[d] In protocol version dated November 17, 2008, only patients with NYHA Functional Class III or IV in the Non-High Risk arm were considered for a 6-minute walk test. In the amended protocol version dated September 14, 2010, all patients enrolled in REALISM are required to perform the 6-minute walk test.

An original PMA was filed in March 2010 for an indication inclusive of surgical candidates and patients too high risk for surgery with either degenerative or functional MR etiologies. A summary of study design, patient population and results from the studies is provided below.

EVEREST II RANDOMIZED CONTROL TRIAL (EVEREST II RCT)

The EVEREST II RCT was a prospective, randomized, controlled, multi-center study of 279 patients (184 MitraClip, 95 Surgery control) comparing the safety and effectiveness of the MitraClip to the standard of care mitral valve surgery. The intended population was patients with significant symptomatic mitral regurgitation (MR ≥ 3+) of either FMR or DMR etiology that were non-high risk candidates indicated for and who could undergo mitral valve surgery. Study design elements including key inclusion/exclusion criteria and endpoints are provided in Table 6. Patients were evaluated at baseline, discharge, 30 days, 6, 12, 18 and 24 months, and annually thereafter through 5 years. A summary of baseline characteristics and safety and effectiveness results from the EVEREST II RCT are provided in Table 7.

Table 7: Summary of EVEREST II RCT Safety and Effectiveness Results

Baseline Characteristic	**RCT MitraClip % (n/N) (N = 184)**	**RCT Surgery Control % (n/N) (N = 95)**	**p-value**
Age (years), Mean ± SD (N)	67.3±12.8 (184)	65.7±12.9 (95)	0.321
Patients over 75 years of age	29.9% (55/184)	27.4% (26/95)	0.679
Female Gender	37.5% (69/184)	33.7% (32/95)	0.600
Coronary Artery Disease	47.0% (86/183)	46.3% (44/95)	>0.99
Prior Myocardial Infarction	21.9% (40/183)	21.3% (20/94)	>0.99
Atrial Fibrillation History	33.7% (59/175)	39.3% (35/89)	0.415
Prior Stroke	1.6% (3/184)	3.2% (3/95)	0.413
Diabetes	7.6% (14/184)	10.5% (10/95)	0.500
Moderate to Severe Renal Disease	3.3% (6/184)	2.1% (2/95)	0.720
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O_2)	14.8% (27/183)	14.7% (14/95)	>0.99
Previous Cardiovascular Surgery	22.3% (41/184)	18.9% (18/95)	0.541
Previous Percutaneous Coronary Intervention	24.0% (44/183)	15.8% (15/95)	0.124
NYHA Class III/IV Heart Failure	51.1% (94/184)	47.4% (45/95)	0.614
Functional MR Etiology	26.6% (49/184)	27.4% (26/95)	0.888
LV Ejection Fraction (%), Mean ± SD (N)	60.0±10.1 (182)	60.6±11.0 (95)	0.649
LV Internal Diameter systole (cm), Mean ± SD (N)	3.7±0.9 (181)	3.5±0.8 (94)	0.161
30-Day Safety (Major Adverse Event[a]) Endpoint Results			
Intention to Treat Analysis (Superiority δ = 2%)			
Safety Endpoint (%)	15.0% (27/180)	47.9% (45/94)	**p-value (Superiority)**
Difference (MitraClip – Surgery), 95% CI	-32.9% (-45.0%, -20.7%)		< 0.0001
12-Month Effectiveness Endpoint Results			
Per Protocol Analysis (Margin of decreased effectiveness: δ = -31%)			**p-value (Non-inferiority [b])**
Freedom from death, MV surgery or re-op and MR > 2+, n (%)[c]	72.4% (97/134)	87.8% (65/74)	
MitraClip – Surgery, (95% LCB)	-15.4% (-25.4%)		0.0012
Freedom from death, MV surgery or re-op and MR > 1+, n (%)[d]	45.1% (37/82)	68.9% (51/74)	
MitraClip – Surgery, (95% LCB)	-23.8% (-37.7%)		0.1692

[a] MAE defined as combined clinical endpoint of death, myocardial infarction (MI), re-operation for failed surgical repair or replacement, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, ventilation for greater than 48 hours, gastrointestinal (GI) complication requiring surgery, new onset of permanent atrial fibrillation, septicemia, and transfusion of 2 or more units of blood.

[b] Non-inferiority statistical methods were used to calculate this p-value, however, non-inferiority is not implied due to the large margin. Therefore, this test shows whether the results show decreased effectiveness by the margin specified of -31%.

[c] Abbott Vascular pre-specified endpoint

[d] FDA pre-specified endpoint

Although the EVEREST II RCT provided evidence that the MitraClip device could be safely implanted and reduced MR severity in the majority of patients, the device did not reduce MR as often or as completely as the surgical control. Other limitations of the study included the definition of the primary success criterion, effectiveness margin and heterogeneity of MR etiology. Thus, FDA determined that the data did not demonstrate an appropriate benefit-risk profile when compared to standard mitral valve surgery and were inadequate to support approval for the device in a surgical candidate population. Although the trial fell short of supporting use of MitraClip in surgical candidates, it benchmarked the safety, effectiveness and durability of the MitraClip against the surgical gold standard. Additionally, as the RCT enrolled primarily DMR patients, the trial provides a comparison for symptomatic candidates with severe DMR who are at prohibitive risk for mitral valve surgery and treated with the MitraClip.

EVEREST II HIGH RISK REGISTRY (EVEREST II HRR) and EVEREST II CONTINUED ACCESS REGISTRY (REALISM HR)

Following significant discussion with the FDA and physician advisors, the Sponsor narrowed the scope of the PMA indication in April 2011 to include only functional and degenerative MR patients with an unmet need for treatment, who were too high risk for mitral valve surgery.

EVEREST II HRR and REALISM HR were single-arm, self-controlled adjunctive studies to evaluate the safety and effectiveness of the MitraClip in high surgical risk patients The intended population for these studies was patients with significant symptomatic mitral regurgitation (MR ≥ 3+) of either FMR or DMR etiology that were determined to be too high risk to undergo mitral valve surgery based upon the STS predicted procedural mortality replacement score or judgment of a cardiothoracic surgeon.

Study design elements including key inclusion/exclusion criteria and endpoints were identical for the two studies, and are provided in Table 6. Patients were evaluated at baseline, discharge, 30 days, 6, 12, 18 and 24 months, and annually thereafter through 5 years. A summary of baseline characteristics and safety and effectiveness results from the 351 high surgical risk patients from the EVEREST II HRR and REALISM HR studies treated with the MitraClip are provided in Table 8. These data were presented in support of the high risk indication at the FDA Circulatory System Devices Advisory Panel on March 20, 2013.

Table 8: Summary of Integrated High Surgical Risk Cohort Safety and Effectiveness

Baseline Characteristic	Integrated HSR Cohort % (n/N) (N = 351)
Age (years), Mean ± SD (N)	75.7±10.5 (351)
Patients over 75 years of age	58.1% (204/351)
Female Gender	39.0% (137/351)
Coronary Artery Disease	82.2% (287/349)
Prior Myocardial Infarction	50.7% (177/349)
Atrial Fibrillation History	68.5% (217/317)
Prior Stroke	12.8% (45/351)
Diabetes	39.4% (138/350)
Moderate to Severe Renal Disease	30.5% (107/351)
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	28.9% (101/350)
Previous Cardiovascular Surgery	59.8% (210/351)
Previous Percutaneous Coronary Intervention	49.9% (175/331)
NYHA Class III/IV Heart Failure	84.9% (298/351)
Functional MR Etiology	70.1% (246/351)
LV Ejection Fraction (%), Mean ± SD (N)	47.5 ± 14.2 (318)
LV Internal Diameter systole (cm), Mean ± SD (N)	4.4 ± 1.1 (323)
Primary Safety Endpoint	
Procedural Mortality	4.8% (17/351)
97.5% Upper Confidence Bound	7.6%
Average STS Predicted Replacement Mortality Risk (determined at enrollment)	11.3%
Average STS Predicted Repair Mortality Risk (calculated retrospectively using STS version 2.61)	7.6%
Major Effectiveness Endpoint	
Left Ventricular End Diastolic Volume (Change from baseline)	-17.9ml
Left Ventricular Internal Dimension, diastole (Change from baseline)	-0.2cm
Left Ventricular End Diastolic Volume (Change from baseline)	-8.1ml
Left Ventricular Internal Dimension, systole (Change from baseline)	-0.1cm

Limitations of these studies included heterogeneity of MR etiology, data pooling, post hoc control group, post hoc analysis, data accountability, and difficulty defining the surgical risk status of the patient population. At the March 20, 2013 Advisory Panel of experts, Panelists determined that the data on these 351 high surgical risk patients demonstrated reasonable assurance that the MitraClip Clip Delivery System is safe for use in patients too high risk for surgery and the benefits of treatment outweigh the risks in these high surgical risk patients. However, due to the limitations described above, in particular because of difficulty understanding patient risk status and the heterogeneity of MR, the majority of the Advisory Panel were unable to conclude that there was reasonable assurance of effectiveness of the MitraClip in this patient population.

DMR PATIENTS AT PROHIBITIVE RISK FOR SURGERY

Following the FDA Advisory Panel meeting, the Sponsor and FDA worked interactively and determined that patients with primary MR etiology (DMR) at prohibitive risk for surgery (PR DMR) were the appropriate patient population to evaluate the risks and benefits of the MitraClip device. While all patients with significant symptomatic MR who are not surgical candidates have an unmet clinical need, the value of intervention to reduce MR is clearest for patients with DMR etiology. It is broadly accepted that DMR is a mechanical problem in which there is a primary abnormality of the mitral apparatus and the "leaflets are broken". There is no medical therapy for reduction of DMR, which must be treated with mechanical correction of the mitral valve. For secondary or functional MR (FMR), the relative benefits of MR reduction versus optimal medical therapy are less clear because MR is secondary to left ventricular dysfunction, which can and does improve with medical therapy, revascularization, and/or cardiac resynchronization therapy in some patients. Thus, the clinical benefit of MitraClip in FMR could not be discerned with the existing single arm study results. For DMR patients considered surgical candidates, surgery remains the standard of care treatment option and the ACC/AHA Guidelines define surgery for these patients as Class I and IIa indications. The patients indicated for the MitraClip device are DMR patients at prohibitive risk for surgery and therefore have no other effective treatment options.

Patients from the MitraClip studies (EVEREST II, HRR, REALISM) were evaluated by a panel of physicians and 127 patients were determined to be at prohibitive risk for surgical mortality. Results from these 127 PR DMR patients were analyzed, incorporated into the PMA application, and are summarized below. The analysis cohort of 127 subjects was developed post-hoc; this severely limits the statistical interpretability of reported data.

These data were determined to adequately establish the safety, effectiveness, and positive benefit-risk profile of the MitraClip for the indicated population and are the basis for approval of this PMA application. The totality of evidence demonstrates reasonable assurance of safety and effectiveness of MitraClip to reduce MR and provide patient benefit in this discreet and specific patient population (PR DMR), as described below.

Prohibitive Risk DMR MitraClip Patients – Demographics and Patient Accountability

Table 9: Prohibitive Risk DMR MitraClip Cohort – Key Baseline Characteristics

Baseline Characteristic[a]	Prohibitive Risk DMR MitraClip Patients % (n/N) (N = 127)
Age (years), Mean±SD (N)	82.4±8.7 (127)
Patients over 75 years of age	83.5% (106/127)
Female Gender	44.9% (57/127)
Body Mass Index (kg/m^2), Mean±SD (N)	25.0±5.7 (127)
Coronary Artery Disease	72.8% (91/125)
Prior Myocardial Infarction	24.4% (31/127)
Atrial Fibrillation History	70.5% (86/122)
Prior Stroke	10.2% (13/127)
Diabetes	29.9% (38/127)
Moderate to Severe Renal Disease	28.3% (36/127)
Cardiomyopathy	23.6% (30/127)
Chronic Obstructive Pulmonary Disease (w/ or w/o Home O2)	31.5% (40/127)
Hypertension	88.2% (112/127)
Previous Cardiovascular Surgery	48.0% (61/127)
Previous Percutaneous Coronary Intervention	33.3% (42/126)
NYHA Functional Class III/IV Heart Failure	86.6% (110/127)
LV Ejection Fraction (%), Mean±SD (N)	60.6±9.5 (112)
LV Internal Diameter, systole (cm), Mean±SD (N)	3.4±0.8 (113)
STS Mortality Risk (determined at enrollment for replacement)[b], Mean±SD (N)	13.6±7.9 (127)

[a] Sample sizes or denominators smaller than the N reported for the group reflect missing data
[b] STS replacement score calculated using the version of the calculator at the time of enrollment

The PR DMR Cohort was elderly with a high rate of serious comorbidities.

The reasons for prohibitive risk are summarized in Table 10. Patients with STS replacement score ≥ 8% had high rates of additional risk factors not accounted for in the STS calculator, placing these patients at prohibitive risk of morbidity and mortality from mitral valve surgery beyond what is accounted for in the STS calculator. Hostile chest (15.8%), internal mammary artery (IMA) at high risk of injury (20.8%) and frailty (9.9%) were among the most common risk factors in these patients. Among patients with STS replacement score < 8%, one or more additional risk factors not accounted for in the STS calculator placed these patients at prohibitive risk of morbidity and mortality from mitral valve surgery. Porcelain aorta (30.8%), hostile chest (19.2%), severe liver disease or cirrhosis (15.4%), IMA at high risk of injury (15.4%), high risk of aspiration (15.4%) and severe pulmonary hypertension (11.5%) were among the most common reasons for prohibitive risk.

Table 10: Prohibitive Risk DMR MitraClip Cohort - Reasons for Prohibitive Risk

Prohibitive Risk Factor[a]	Patients with STS Replacement Score ≥ 8% (N = 101)	Patients with STS Replacement Score < 8% (N = 26)
Porcelain Aorta	5.0% (5/101)	30.8%(8/26)
Frailty	9.9% (10/101)	7.7%(2/26)
Hostile chest	15.8% (16/101)	19.2%(5/26)
Severe liver disease or cirrhosis	1.0% (1/101)	15.4%(4/26)
Severe pulmonary hypertension	5.0% (5/101)	11.5%(3/26)
Unusual extensive circumstance:		
RV dysfunction with severe tricuspid regurgitation	5.0% (5/101)	0.0% (0/26)
Chemotherapy for malignancy	5.0% (5/101)	3.8%(1/26)
Major bleeding diathesis	5.9% (6/101)	7.7%(2/26)
Immobility	4.0% (4/101)	3.8%(1/26)
AIDS	0.0% (0/101)	3.8%(1/26)
Severe dementia	2.0% (2/101)	7.7%(2/26)
High risk of aspiration	3.0% (3/101)	15.4%(4/26)
IMA at high risk of injury	20.8% (21/101)	15.4%(4/26)[b]

[a] Patients may present at baseline with more than one prohibitive risk factor
[b] These 4 patients also had other risk factors on this list. No patient was considered prohibitive risk solely on the basis of IMA at high risk of injury because mitral valve repair surgery can be done via right thoracotomy.

Table 11 shows the follow-up compliance at 30 days, 12 months and 2 years in the PR DMR Cohort. Compliance to follow-up visits in continuing patients was 98.4%, 98.4% and 94.9% and clinical follow-up occurred in 97.6%, 95.3% and 88.7%, respectively.

Table 11: Prohibitive Risk DMR MitraClip Cohort - Compliance to Follow-up Visits

Follow-up Visit	# Visits	# Missed Visit[†]	# Deaths before visit	# Withdrawn before visit	Not due for visit	Visit Compliance[§]	Clinical Follow-up Occurred In[§§]
Baseline	127	-	-	-	-	100%	100%
30-Day	115	2	9	1	0	98.4%	97.6%
12-Month	91	2	30	4	0	98.4%	95.3%
2-Year	53	5	41	7	21	94.9%	88.7%

[†] A visit is counted as missed if the last date of the visit window is at least 30 days before the cut-off date for this report
[§] Visit Compliance is calculated as (#Visits + #Deaths)/(127 – #Withdrawn before visit – # Not due for visit)
[§§] Clinical follow-up is calculated as (#Visits + #Deaths)/(127 – # Not due for visit)

Prohibitive Risk DMR MitraClip Patients – Procedural Results

The MitraClip procedure is performed under general anesthesia via echocardiographic and fluoroscopic guidance. Data on Procedure Time, Device Time and fluoroscopy duration are summarized in Table 12. The mean Procedure Time, defined as the start time of the transseptal procedure to the time the Steerable Guide Catheter is removed, was approximately 2.5 hours. Device time, defined as the time of insertion of the Steerable Guide Catheter to the time the MitraClip Delivery Catheter is retracted into the Steerable Guide Catheter, averaged 125 minutes. The mean fluoroscopy duration was 46 minutes. As this is primarily an echocardiographic guided procedure, fluoroscopy time is limited to a relatively short percentage of the overall Procedure Time (29%). There were no intra-procedural deaths.

Table 12: Prohibitive Risk DMR MitraClip Cohort - Procedural Results

Procedural Result[a]	Mean±SD (N) Median (Min, Max)
Procedure Time[b] (min)	157±81 (124) 134 (39, 524)
Device Time[c] (min)	125±75 (124) 110 (9, 511)
Fluoroscopy Duration (min)	46±26 (126) 39 (3, 167)

[a] Sample sizes or denominators smaller than 127 reflect missing data.
[b] Procedure time is measured from the time the transseptal procedure starts until the time the Steerable Guide Catheter is removed.
[c] Device time is measured from the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System is retracted into the Steerable Guide Catheter.

The MitraClip device was implanted successfully in a majority (95.3%) of PR DMR patients. The distribution of number of MitraClip devices implanted is shown in Table 13 and the post-procedure ICU/CCU/PACU time is presented in Table 14.

Table 13: Prohibitive Risk DMR MitraClip Cohort – Number of MitraClip Devices Implanted

# Devices Implanted	% (n/N)
0	4.7% (6/127)
1	44.1% (56/127)
2	51.2% (65/127)

Table 14: Prohibitive Risk DMR MitraClip Cohort – Post-Procedure through Discharge

Post-Procedure Stay	Mean±SD (N)
Post-Procedure ICU/CCU/PACU Duration [Days]	1.4±1.8 (127)
Post-Procedure Hospital Stay [Days]	2.9±3.1 (127)

Prohibitive Risk DMR MitraClip Patients – Safety Analysis and Results

A total of 8 PR DMR patients died within 30 days of the MitraClip procedure or discharge post-procedure (whichever is longer), resulting in a procedural mortality rate of 6.3%, which is less than both the mean and median predicted STS mortality risk using either the repair or replacement calculator. In addition, the upper bound of the 95% confidence interval on procedural mortality (12.0%) is lower than both the mean and median STS replacement score.

Table 15: Prohibitive Risk DMR MitraClip Cohort - Procedural Mortality

Observed Procedural Mortality, % (n/N) 95% CI[a,c]	6.3% (8/127) (2.8%, 12.0%)
STS v2.73 Replacement Risk Score Mean (95% CI[b,c]) Median (95% CI[b,c])	 13.2% (11.9%, 14.5%) 12.4% (11.3%, 13.7%)
STS v2.73 Repair Risk Score Mean (95% CI[b,c]) Median (95% CI[b,c])	 9.5% (8.5%, 10.6%) 8.5% (7.6%, 9.3%)

[a] Based on Clopper-Pearson method
[b] CI for mean is calculated based on two-sample t-distribution and CI for median is based on non-parametric methods
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

At 12 months, MAEs occurred at a rate of 35.4% among Prohibitive Risk DMR MitraClip patients, with deaths (23.6%) and transfusions (19.7%) comprising the majority of events. The rate of stroke was 2.4% and rate of non-elective cardiovascular surgery (0.8%) at 12 months.

Table 16: Prohibitive Risk DMR MitraClip Cohort - CEC Adjudicated Major Adverse Events at 30 Days

Description of Event	Prohibitive Risk DMR MitraClip Patients % (n/N) (N = 127)
Death	6.3% (8/127)
Myocardial infarction	0.8% (1/127)
Re-operation for failed surgical repair or replacement	0
Non-elective cardiovascular surgery for adverse events	0.8% (1/127)
Stroke	2.4% (3/127)
Renal Failure	1.6% (2/127)
Deep wound infection	0
Ventilation > 48 hours	3.1% (4/127)
GI complication requiring surgery	0.8% (1/127)
New onset of permanent AF	0
Septicemia	0
Transfusion ≥ 2 units	12.6% (16/127)
Total[a]	**18.9% (24/127)**
Total[a] (Excluding Transfusions ≥ 2 units)	**9.4% (12/127)**

[a] Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events.

Table 17: Prohibitive Risk DMR MitraClip Cohort - CEC Adjudicated Major Adverse Events at 12 Months

Description of Event	Prohibitive Risk DMR MitraClip Patients % (n/N) (N = 127)
Death	23.6% (30/127)
Myocardial infarction	0.8% (1/127)
Re-operation for failed surgical repair or replacement	0
Non-elective cardiovascular surgery for adverse events	0.8% (1/127)
Stroke	2.4% (3/127)
Renal Failure	3.9% (5/127)
Deep wound infection	0.0% (0/127)
Ventilation > 48 hours	4.7% (6/127)
GI complication requiring surgery	2.4% (3/127)
New onset of permanent AF	0.0% (0/127)
Septicemia	4.7% (6/127)
Transfusion ≥ 2 units	19.7% (25/127)
Total[a]	**35.4% (45/127)**
Total[a] (Excluding Transfusions ≥ 2 units)	**26.0% (33/127)**

[a] Total number of patients may not equal the sum of patients in each row since one patient may experience multiple events.

Other secondary safety endpoints occurred at a relatively low rate, consistent with access to the mitral valve achieved via the femoral vein and inferior vena cava. Major vascular complications occurred in 5.5% of patients at 30 days and in 7.1% of patients at 12 months. Major bleeding complications, defined as procedure-related bleeding requiring transfusions of at least 2 units or surgery, occurred at a rate of 12.6% at 30 days. The majority of bleeding events required transfusions rather than surgery. Bleeding events that occurred after 30 days were unrelated to the MitraClip procedure. Clinically significant atrial septal defect requiring treatment occurred at a rate of 2.4% at 12 months. A low rate (2.4%) of mitral stenosis was observed at 12 months, with a total of 3 patients reported to have experienced mitral stenosis defined as Echocardiography Core Laboratory assessed mitral valve area less than 1.5 cm^2 through 12 months. One additional patient is reported to have experienced mitral stenosis at 18 months. The site did not report mitral stenosis for these patients and none of these patients underwent mitral valve surgery for stenosis.

Table 18: Prohibitive Risk DMR MitraClip Cohort - Other Secondary Safety Events at 30 Days and 12 Months

Description of Event	30 Days % (n/N)	12 Months % (n/N)
Major Vascular Complications	5.5% (7/127)	7.1% (9/127)
Major Bleeding Complications	12.6% (16/127)	15.7% (20/127)
Non-Cerebral Thromboembolism	1.6% (2/127)	1.6% (2/127)
New Onset of Persistent Atrial Fibrillation	3.9% (5/127)	3.9% (5/127)
Heart Block/Other Arrhythmia requiring Permanent Pacemaker	0.0% (0/127)	1.6% (2/127)
Endocarditis	0.0% (0/127)	0.0% (0/127)
Thrombosis	0.0% (0/127)	0.0% (0/127)
Hemolysis	0.0% (0/127)	0.0% (0/127)
Atrial Septal Defect	1.6% (2/127)	2.4% (3/127)
Mitral Valve Stenosis	0.0% (0/127)	2.4% (3/127)

There have been no reports of a MitraClip device embolization in the Prohibitive Risk DMR Cohort. A Single Leaflet Device Attachment (SLDA) is defined as the attachment of one mitral leaflet to the MitraClip device. Of the 121 patients with at least one MitraClip device implanted, no SLDAs have been reported.

A descriptive comparator for mortality comes from the Duke University Medical Center database, which consists of patient-level data with echocardiographic, medical history and follow-up data on a large number of patients with MR ≥ 3+. This database allowed for characterization of survival in patients deemed high risk for surgery and managed non-surgically at the Duke University Medical Center despite clear Class I indications for surgery according to the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. Nine hundred and fifty-three (953) patients in the Duke database with 3+ or 4+ MR were identified as too high risk for surgery based on the same high risk criteria as those in the EVEREST II HRR and REALISM studies (i.e. STS mortality risk ≥ 12% or protocol-

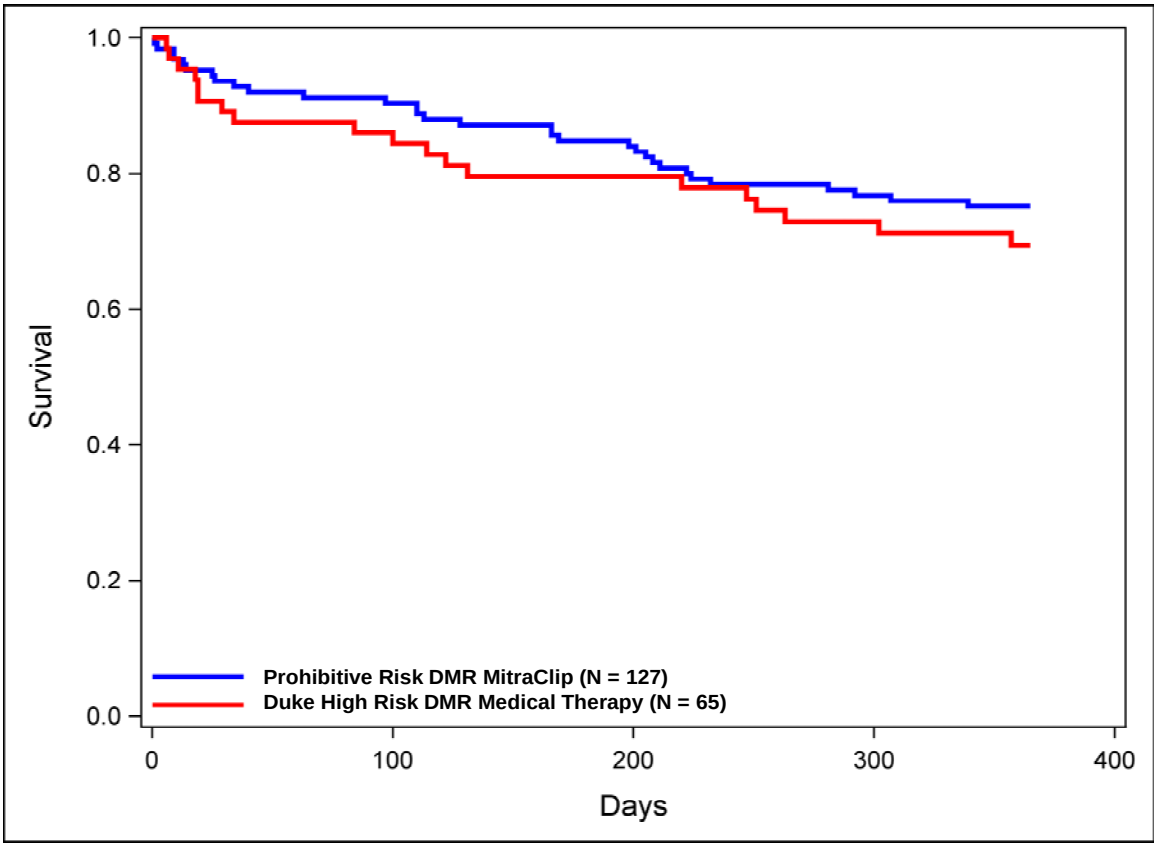
specified surgical risk factors) and managed non-surgically. This made up the Duke High Risk Cohort, of which 65 patients were identified as DMR.
Table 19 shows a comparison of baseline and demographic characteristics between the 127 Prohibitive Risk DMR patients and 65 Duke High Risk DMR patients. Both groups were comprised of elderly patients, with a majority of patients over the age of 75 years. The Duke High Risk DMR Cohort reported a lower LVEF at baseline and a higher proportion of female patients than the Prohibitive Risk DMR Cohort. The Prohibitive Risk DMR Cohort reported a higher proportion of patients with COPD and NYHA III/IV symptoms at baseline. Both groups had high rates of previous MI, atrial fibrillation and previous cardiovascular surgery.

Descriptive mortality comparisons were performed between the 127 Prohibitive Risk DMR patients and the 65 Duke High Risk DMR patients. Figure 2 displays Kaplan-Meier curves comparing survival in the Prohibitive Risk DMR patients to the Duke High Risk DMR patients. Based on these Kaplan-Meier curves, mortality in the Prohibitive Risk DMR Cohort was 6.4% at 30 days and 24.8% at 12 months compared to 10.9% at 30 days and 30.6% at 12 months in the Duke High Risk DMR patients. While these results are descriptive and limited by differences described above, they suggest that there is no elevated risk of mortality in Prohibitive Risk DMR patients who undergo the MitraClip procedure over non-surgical management. This is consistent with the observed safety of MitraClip in the EVEREST II RCT, the consensus of the FDA Advisory Panel that MitraClip is safe in high risk patients, and the commercial experience with the device.

Table 19: Baseline and Demographic Characteristics - Prohibitive Risk DMR MitraClip and Duke High Risk DMR Medical Therapy Cohorts

Baseline Characteristic	Prohibitive Risk DMR MitraClip Cohort % (n/N) (N = 127)	Duke High Risk DMR Medical Therapy Cohort % (n/N) (N = 65)
Age (years), Mean±SD (N)	82.4±8.7 (127)	76.8±11.3 (65)
Patients over 75 years of age	83.5% (106/127)	67.7% (44/65)
Male Gender	55.1% (70/127)	36.9% (24/65)
Body Mass Index (kg/m2), Mean±SD (N)	25.0±5.7 (127)	25.4±5.0(65)
Prior Myocardial Infarction	24.4% (31/127)	33.8% (22/65)
Atrial Fibrillation History	70.5% (86/122)	58.5% (38/65)
Prior Stroke	10.2% (13/127)	18.5% (12/65)
COPD with Home Oxygen	13.4% (17/127)	6.2% (4/65)
Hypertension	88.2% (112/127)	75.4% (49/65)
Diabetes	29.9% (38/127)	36.9% (24/65)
Moderate to Severe Renal Disease	28.3% (36/127)	20.0% (13/65)
Previous Cardiovascular Surgery	48.0% (61/127)	56.9% (37/65)
Previous Percutaneous Coronary Intervention	33.3% (42/126)	58.5% (38/65)
NYHA Functional Class III/IV	86.6% (110/127)	43.8% (28/65)
STS Predicted Mortality Risk	13.2±7.3 (127)	13.3±9.0
LV Ejection Fraction (%), Mean±SD (N)	60.6±9.5 (112)	44.9±11.7 (65)
LV Internal Diameter, systole (cm), Mean±SD (N)	3.4±0.8 (113)	3.4±0.9 (65)

Figure 2: Kaplan-Meier Freedom from Mortality - Prohibitive Risk DMR MitraClip and Duke High Risk DMR Medical Therapy Patients



Number at Risk, Kaplan-Meier Estimates and 95% CIs

Time Post Index Procedure	Baseline	30 Days	6 Months	12 Months
Prohibitive Risk DMR MitraClip Patients (N = 127)				
# At Risk	127	117	106	85
# Events	0	8	19	31
% Event Free	100%	93.6%	84.8%	75.2%
95% CI[a]	-	[87.6%, 96.8%]	[77.2%, 90.0%]	[66.1%, 82.1%]
Duke High Risk DMR Medical Therapy Patients (N = 65)				
# At Risk	65	57	49	39
# Events	0	7	13	19
% Event Free	100%	89.1%	79.6%	69.4%
95% CI[a]	-	[78.5%, 94.7%]	[67.4%, 87.6%]	[56.3%, 79.3%]

[a] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Prohibitive Risk DMR MitraClip Patients – Effectiveness Analysis and Results

MR severity at baseline, discharge and 12 months are presented in Table 20 for patients with data available at each follow-up (Completers Analysis). Immediate improvement in MR severity was noted at discharge with 82.1% and 53.7% of surviving patients reporting MR severity ≤ 2+ and ≤ 1+, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity ≤ 2+ and 36.9% reporting MR severity ≤ 1+. At 12 months, freedom from death and MR>2+ was 61.4% and freedom from death and MR > 1+ was 27.2% patients.

Table 20: Prohibitive Risk DMR MitraClip Cohort - MR Severity at Baseline and Follow-up
Completers Analysis

MR Severity	Baseline % (n/N)	Discharge[a] % (n/N)	12 Months % (n/N)
0 : None	0	1.6% (2/123)	0
1+: Mild	0	52.0% (64/123)	36.9% (31/84)
2+: Moderate	9.7% (12/124)	28.5% (35/123)	46.4% (39/84)
3+: Moderate-to-severe	58.9% (73/124)	13.0% (16/123)	13.1% (11/84)
4+: Severe	31.5% (39/124)	4.9% (6/123)	3.6% (3/84)
Missing	3	3	13
Death	0	1	30
MR ≤ 2+ in surviving patients	9.7% (12/124)	82.1% (101/123)	83.3% (70/84)
MR ≤ 1+ in surviving patients	0.0% (0/124)	53.7% (66/123)	36.9% (31/84)
Freedom from Death and MR > 2+	9.7% (12/124)	81.5% (101/124)	61.4% (70/114)
Freedom from Death and MR > 1+	0.0% (0/124)	53.2% (66/124)	27.2% (31/114)

[a] 30-day MR severity was used if discharge MR was unavailable

Reduced preload as a result of the reduction in MR severity achieved with the MitraClip device resulted in reverse left ventricular remodeling (Table 21), characterized largely by a clinically important decrease in diastolic volume (-16.6 ml) and dimension (-0.2cm).

Table 21: Prohibitive Risk DMR MitraClip Cohort - LV Measurements at Baseline and 12 Months
Patients with Paired Data[a]

LV Measurement	N	Baseline	12-month	Difference (12-month - Baseline)	%Change (12-month - Baseline)
LVEDV, ml					
Mean±SD	69	125.1±40.1	108.5±37.9	-16.6±22.9	-11.5±17.9
Median		119.7	104.7	-12.3	-10.2
95% CI[b,c]				(-22.1, -11.1)	(-15.9, -7.2)
LVIDd, cm					
Mean±SD	80	5.0±0.6	4.8±0.6	-0.2±0.4	-3.7±8.2
Median		5.1	4.9	-0.2	-4.0
95% CI[b,c]				(-0.3, -0.1)	(-5.6, -1.9)
LVESV, ml					
Mean±SD	69	49.1±24.5	46.1±21.4	-3.0±13.7	-1.3±27.0
Median		45.7	41.0	-1.5	-2.7
95% CI[b,c]				(-6.3, 0.3)	(-7.7, 5.2)
LVIDs, cm					
Mean±SD	75	3.4±0.7	3.3±0.7	-0.1±0.5	-0.2±16.4
Median		3.2	3.3	-0.1	-2.3
95% CI[b,c]				(-0.2, 0.1)	(-4.0, 3.6)

[a] Only patients who had a measurement at both Baseline and 12 months are included
[b] 95% CI is based on a t-distribution
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Improvement in LV function resulted in improvements in heart failure symptoms. NYHA Functional Class at baseline and follow-up are presented in Table 22 for patients with data available at each follow-up (Completers Analysis). Immediate improvement in NYHA Class was noted at 30 days with 82.3% of surviving patients reporting NYHA Class I or II symptoms. This improvement was sustained at 12 months, with the majority (86.9%) of surviving patients reporting NYHA Class I or II symptoms. At 12 months, freedom from death and NYHA Class III or IV symptoms was 64.0%. This improvement in NYHA Class symptoms is clinically important given that the majority of these patients (86.6%) were enrolled with NYHA Class III or IV symptoms.

Table 22: Prohibitive Risk DMR MitraClip Cohort - NYHA Functional Class at Baseline and Follow-up

Completers Analysis

NYHA Functional Class	Baseline % (n/N)	30 Days % (n/N)	12 Months % (n/N)
I	2.4% (3/127)	33.6% (38/113)	40.5% (34/84)
II	11.0% (14/127)	48.7% (55/113)	46.4% (39/84)
III	63.8% (81/127)	15.9% (18/113)	10.7% (9/84)
IV	22.8% (29/127)	1.8% (2/113)	2.4% (2/84)
Missing	0	5	13
Death	0	9	30
NYHA I/II in surviving patients	13.4% (17/127)	82.3% (93/113)	86.9% (73/84)
Freedom from Death and NYHA Class III/IV	13.4% (17/127)	76.2% (93/122)	64.0% (73/114)

Table 23 shows the change in NYHA Class at 12 months from baseline. The table shows that 73 of 83 (88%) surviving patients improved by at least 1 class. More importantly, 30 of 83 (36.1%) surviving patients improved by at least 2 classes. Inclusion of deaths in the denominator results in 64.6% of patients alive and improved by at least 1 class and 26.5% alive and improved by at least 2 classes. The MIRACLE trial[17], a randomized, double-blind trial randomizing patients between cardiac resynchronization therapy (CRT) to no CRT showed that only 6% of patients improved by 2 classes in the "no CRT" group and 16% improved by 2 classes in the CRT group.

Table 23: Prohibitive Risk DMR MitraClip Cohort - Change in NYHA Class at 12 Months from Baseline

NYHA Class Change	Number of Patients
3 Class Improvement	4
2 Class Improvement	26
1 Class Improvement	43
No Change	9
1 Class Worsening	2
Death	30
Missing	13

SF-36 quality of life (QOL) questionnaires were administered at baseline, 30 days and 12 months. Table 24 shows a paired analysis of the Physical Component Summary (PCS) and Mental Component Summary (MCS) mean scores at baseline and 12 months. The mean change of +6.0 points in the PCS score from baseline to 12 months after the MitraClip procedure is well above the 2-3 point minimally important difference (MID) threshold reported in the literature[18]. Analysis of a large sample of US Medicare patients showed that a 3-point PCS difference was associated with a 40% higher risk of being unable to work and a 20% increase in mortality rates at two years across a wide range of disease conditions[19]. The mean change of +5.6 points in the MCS score at 12 months is substantially above the 3 point mean threshold reported in the literature[18]. Anchor-based research has determined that a 3

point MCS difference corresponds to a 30% increased risk of depression and use of mental health services[19].

Table 24: Prohibitive Risk DMR MitraClip Cohort - SF-36 Quality of Life at Baseline and 12 Months

Completers Analysis[a]

Component	N	Baseline	12-month	Difference (12-month - Baseline)
Physical Component Summary Score				
Mean±SD	73	33.4±8.6	39.4±10.5	6.0±8.6
Median		32.4	40.7	5.6
95% CI [b,c]				(4.0, 8.0)
Mental Component Summary Score				
Mean±SD	73	46.6±13.4	52.2±10.2	5.6±14.0
Median		49.8	54.0	3.2
95% CI [b,c]				(2.3, 8.9)

[a] Only patients who had a measurement at both Baseline and 12 months are included
[b] 95% CI is based on a t-distribution
[c] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Clinically important improvements in all components of physical score were noted at 12 months, with the exception of Bodily Pain, which would not be expected to improve by MR reduction (Figure 3). All components of the mental score showed consistent improvement at 12 months (Figure 4).

Figure 3: Prohibitive Risk DMR MitraClip Cohort - Components of SF-36 Physical Score at Baseline and 12 Months

Patients with Paired Data (N = 73)

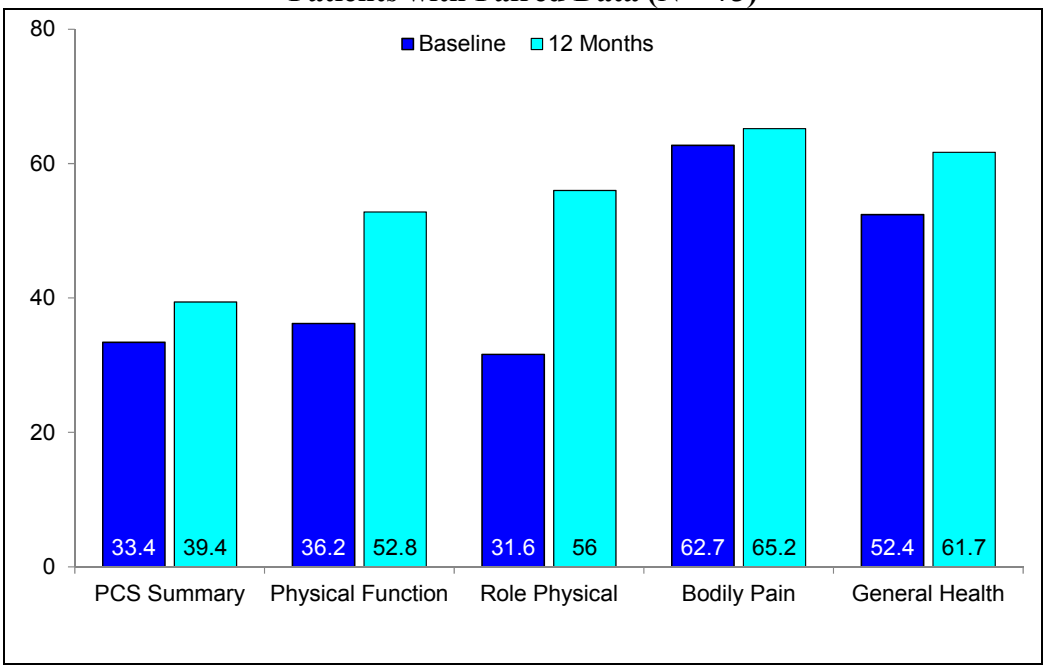
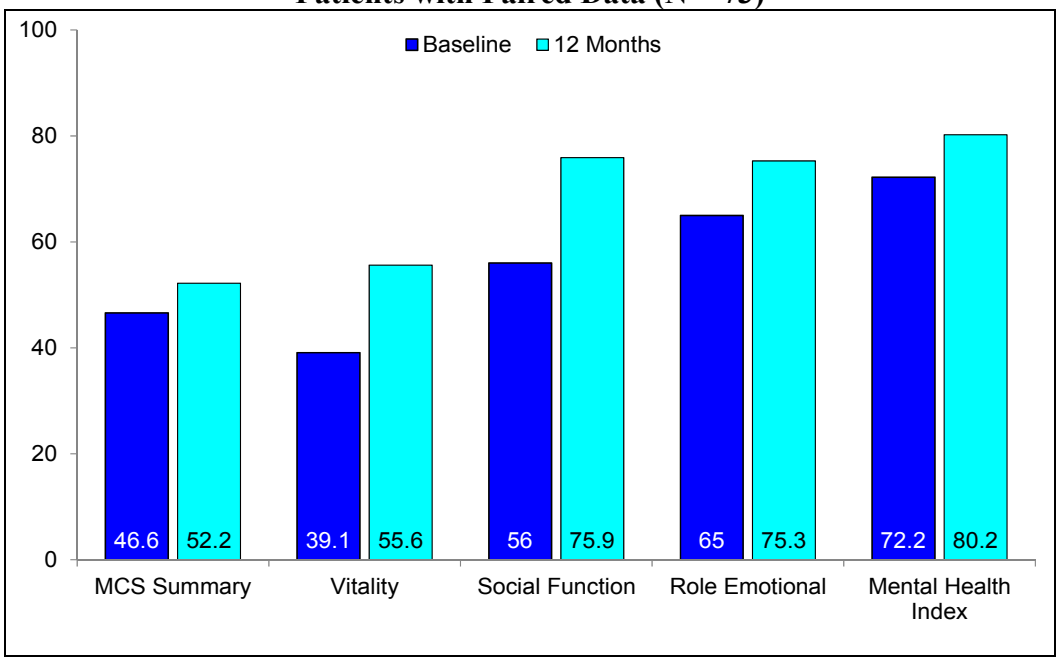


Figure 4: Prohibitive Risk DMR MitraClip Cohort - Components of SF-36 Mental Score at Baseline and 12 Months

Patients with Paired Data (N = 73)



Analysis of individual responders was also performed for both the PCS and MCS scores using distribution-based methods recommended by the SF-36 authors (Significant Change Criteria, SCC) and the Standard Error of Measurement (SEM) method suggested by the FDA in its 2009 PRO Guidance. The SF-36 responder analysis evaluates the proportion of patients with paired data at baseline and 12 months who achieve an improvement in QOL score greater than the responder criteria using each method. The proportion of responders was 63-68% for PCS and 49-53% for MCS.

Table 25: Prohibitive Risk DMR MitraClip Cohort – SF-36 QOL Responder Rate

Component	Minimally Important Difference	Completers Analysis
Physical Component Summary Score	SCC[a] (3.1)	63.0% (46/73)
	SEM[b] (2.2)	68.5% (50/73)
Mental Component Summary Score	SCC[a] (3.8)	49.3% (36/73)
	SEM[b] (2.7)	53.4% (39/73)

[a] SCC (Significant Change Criteria): Significant change assuming baseline-follow-up correlation of .4 and using a 80% CI.
[b] SEM (Standard Error of Measurement): One SEM equals 68% CI.

Heart failure hospitalizations 12 months pre-MitraClip procedure and 12 months post-MitraClip procedure were recorded and analyzed. In this analysis, deaths were censored. A clinically important decrease in the rate of hospitalization for heart failure was observed following discharge from the MitraClip procedure (0.67 to 0.18 per patient-year, a 73% reduction, Table 26) between the pre-enrollment and the post-discharge 12-month periods.

Table 26: Prohibitive Risk DMR MitraClip Cohort - Heart Failure Hospitalizations

	12 months Pre-enrollment	Post-discharge through 12 months
# Patients for Analysis	127	120
# Patients with Events	48	13
# Events	85	17
Follow-up (Patient-Years)	127	97
Rate[a]	0.67	0.18
(95% Two-sided CI [a,b])	(0.54, 0.83)	(0.11, 0.28)
# days hospitalized (Mean±SD)	6.0±4.5	5.9±3.8

[a] CI is obtained from a Poisson regression model
[b] Confidence intervals are provided to illustrate the variability of the corresponding summary statistic. They should not be used to draw statistical inference.

Effectiveness results demonstrate that 82.1% (101/123) of completers experienced MR reduction from 3+ or 4+ to 2+ or less at discharge following the MitraClip procedure (Table 20). Reduction of MR at 12 (n=84) was sustained to ≤ 2+ in 83.3% (70/84), and ≤ 1+ in 36.9% (31/84) of patients for whom echocardiographic data was available.. Reduction in MR severity was associated with reverse left ventricular remodeling characterized largely by clinically important decreases in diastolic volume and dimension. Patients also experienced clinically important improvement in NYHA Functional Class at 12 months; more than 80% of patients experienced NYHA Class III or Class IV symptoms at baseline, which reduced to

less than 15% at 12 months. Despite the elderly and highly co-morbid nature of the population, quality of life as measured by the SF-36 quality of life physical and mental component scores showed clinically important improvement. Sensitivity analyses showed that these effectiveness results are robust to missing data. Finally, heart failure hospitalizations showed clinically important reduction in the 12 months post-MitraClip procedure from the 12 months pre-MitraClip procedure, including in a sensitivity analysis where death is included in the analysis as a heart failure hospitalization.

Table 27: Effectiveness in Prohibitive Risk DMR MitraClip Cohort

Effectiveness Measure[§]	Prohibitive Risk DMR MitraClip Cohort (N=127)
Improvement in LVEDV at 1 year	-17±23
Improvement in LVESV at 1 year	-3±14
Improvement in SF-36 PCS at 1 year	6.0±8.6
Improvement in SF-36 MCS at 1 year	5.6±14.0
NYHA Class III or IV: Baseline → 1 year	85% → 13%

[§] LVEDV, LVESV, SF-36 PCS and MCS results are in patients with paired data, and NYHA Class results are in Completers

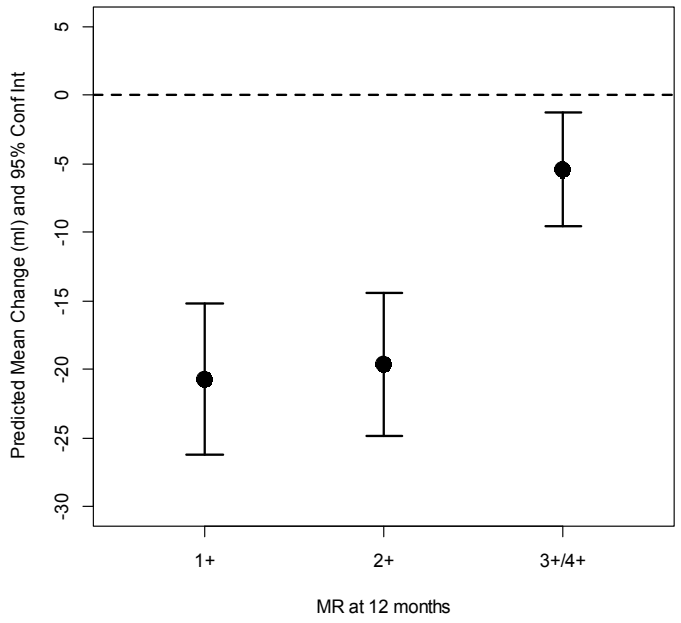
Reduction in MR severity was assessed in patients who have 2-year follow-up available. Table 28 shows that MR reduction in surviving patients to ≤ 2+ and ≤ 1+ is 82.5% (33/40) and 35.0% (14/40), respectively, at 2 years. Therefore, there is no evidence of deterioration of MR severity from 12 months to 2 years in surviving patients.

Table 28: Prohibitive Risk DMR MitraClip Cohort - Durability of MR Reduction

MR Severity	Baseline % (n/N)	12 Months % (n/N)	2 Years % (n/N)
0 : None	0	0	0
1+: Mild	0	36.9% (31/84)	35.0% (14/40)
2+: Moderate	9.7% (12/124)	46.4% (39/84)	47.5% (19/40)
3+: Moderate-to-severe	58.9% (73/124)	13.1% (11/84)	15.0% (6/40)
4+: Severe	31.5% (39/124)	3.6% (3/84)	2.5% (1/40)
MR ≤ 2+ in surviving patients	9.7% (12/124)	83.3% (70/84)	82.5% (33/40)
MR ≤ 1+ in surviving patients	0.0% (0/124)	36.9% (31/84)	35.0% (14/40)

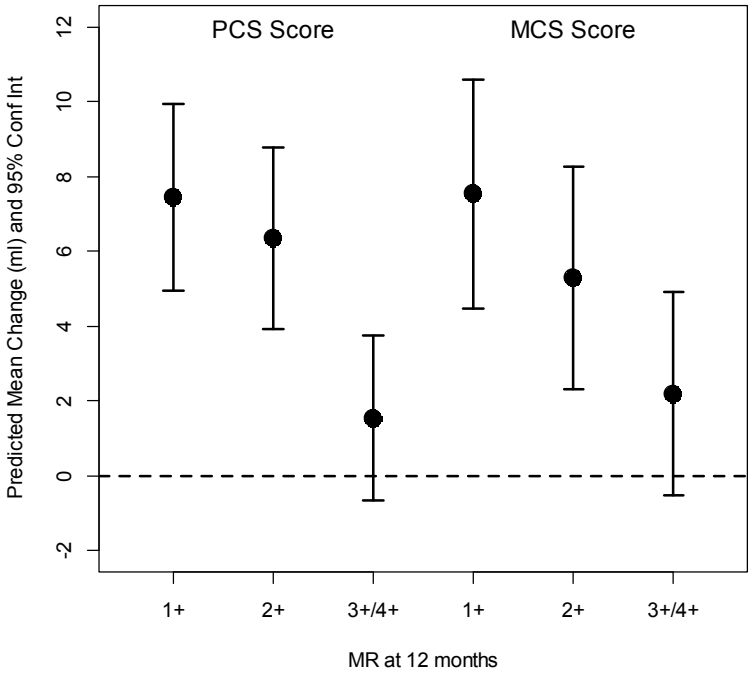
In order to evaluate the relationship between MR severity and measures of effectiveness, statistical models were fit to the effectiveness data. MR severity was importantly associated with LVEDV in the Prohibitive Risk DMR MitraClip patients (Figure 5). Reduction of MR severity to ≤ 2+ at 12 months resulted in clinically important decreases in LVEDV. No clinically important difference in LVEDV reduction is observed between MR 1+ and 2+. Reduction of MR to 2+ or less is associated with a decrease in left ventricular size that is not observed with ongoing MR of 3+ or greater.

Figure 5: Prohibitive Risk DMR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in LVEDV 12 Months over Baseline



MR severity was importantly associated with PCS and MCS (p=0.018) scores in Prohibitive Risk DMR MitraClip patients. Reduction of MR severity to ≤ 2+ at 12 months resulted in clinically important improvement in PCS and MCS scores. When MR severity remained 3+/4+, the changes in PCS and MCS scores were small and not clinically important (Figure 6). Reduction of MR to 2+ or less is thus associated with an improvement in quality of life that is not observed with ongoing MR of 3+ or greater.

Figure 6: Prohibitive Risk DMR MitraClip Cohort - Dose-Response Relationship between MR Severity and Change in SF-36 12 Months over Baseline



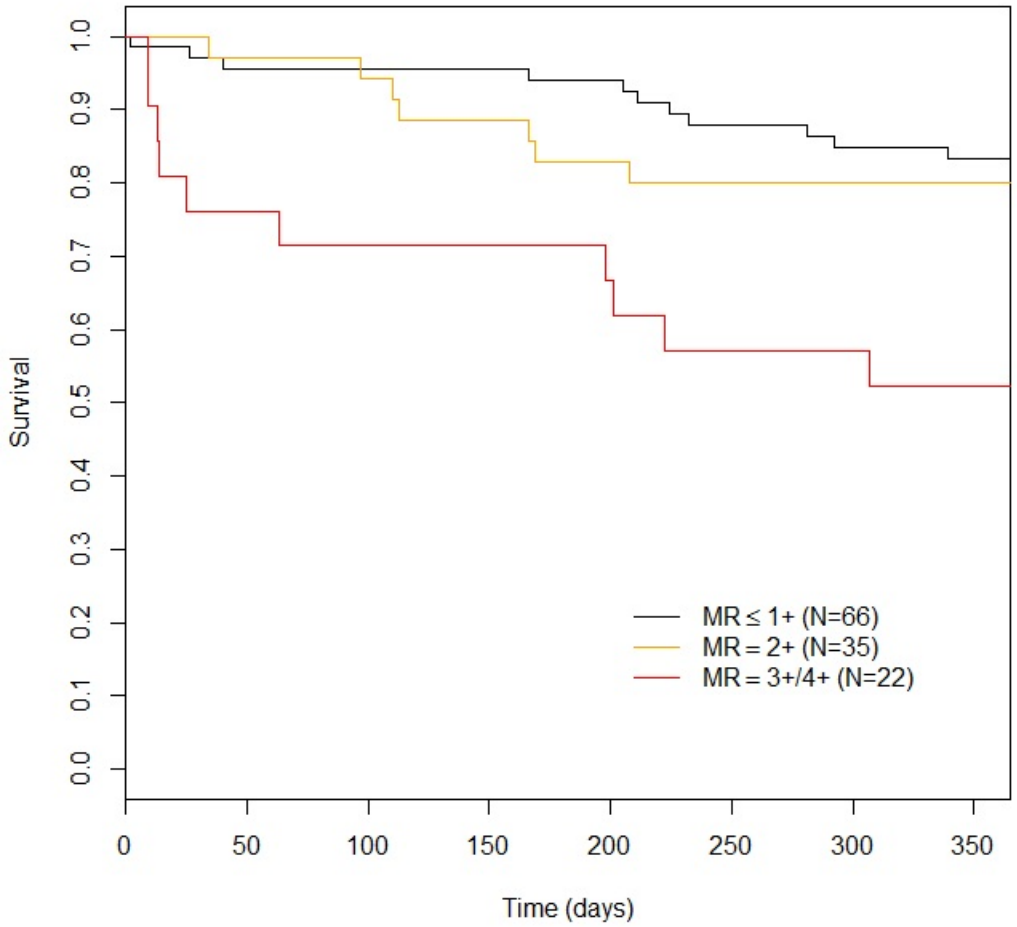
The observed number and corresponding estimated proportions of NYHA Classes at 12 months by two discharge MR groups are summarized in Table 29. The results demonstrate that reduction of MR to 2+ or less at discharge is associated with improved NYHA Functional Class that is not observed with MR of 3+ or greater at discharge.

Table 29: Prohibitive Risk DMR MitraClip Cohort - Summary of Binary NYHA Functional Class Data By Discharge MR Severity

Discharge MR	NYHA Functional Class at 12 Months	
	I/II	III/IV/Death
≤ 2+	66/93 (0.710)	27/93 (0.290)
3+/4+	7/19 (0.368)	12/19 (0.632)

Kaplan-Meier survival curves are plotted for each group based on discharge MR (Figure 7). There was no clinically important difference between the "≤1+" discharge MR group and the "2+" discharge MR group; however, there was a clinically important difference between the "≤1+" discharge MR group and the "3+/4+" discharge MR group and between the "2+" discharge MR group and the "3+/4+" discharge MR group. Reduction of MR to 2+ or less is associated with decreased mortality compared to ongoing MR of 3+ or greater.

Figure 7: Prohibitive Risk DMR MitraClip Cohort - Kaplan-Meier Survival Curves by Discharge MR Severity (≤1+, 2+, 3+/4+)



XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

In commercial use outside the US, the Sponsor estimates that over 8300 patients have been implanted with the MitraClip device since Sept 2008, with over 2500 of these patients enrolled in some form of published trial or registry in the EU [2-16]. Nearly all studies included a site-utilized definition of high or prohibitive surgical risk and the inclusion of a heart team approach for patient selection. Mean EuroSCORE across the studies ranged from 12 to 36. The breakdown of etiology was approximately one-third DMR and two-thirds FMR in the majority of studies. Mean age was ≥ 72 years, and often the baseline incidence of NYHA Class III/IV exceeded 80%. Baseline echocardiographic measurements were indicative of dilated left ventricles and impaired ejection fractions.

The mortality rates reported in prohibitive-risk patients undergoing the MitraClip procedure do not appear to be elevated as a result of the MitraClip procedure and are not unexpected given the age and burden of co-morbidities of the patients treated. Reported in-hospital mortality ranged between 0-4% and reported 30-day mortality rates ranged between 0-9.1% in the highest-risk DMR subset (mean EuroSCORE 33). Mortality at longer-term follow-up

(6-12 months) in these high or prohibitive surgical risk patients was in the range of 8-24% in these studies, reflecting the underlying burden of co-morbidities in these patients.

Over 75% of prohibitive-risk patients in these studies experienced MR reduction to ≤ 2+ post-MitraClip. Echocardiographic follow-up at 6-12 months post-MitraClip showed reduction in left ventricular volumes (ranging between 1.6-46ml for LVEDV and between 8-35ml for LVESV) or dimensions (reported at 1mm for LVEDD and 7mm for LVESD), consistent with a beneficial remodeling. Reported improvements in six-minute walk test (6MWT) distance ranged from +60 m to > +100 m, exceeding the generally accepted placebo threshold of 40 m, indicating clinically meaningful functional improvement post-MitraClip. Most patients improved to NYHA Class I or II, ranging from 48%-97% of patients NYHA Class I/II at follow-up. Several studies showed improved quality of life, with reported improvements of 10-14 points for the Minnesota Living With Heart Failure and 4 to 6 points for the Short Form survey, a clear reversal of the trend in patients who would otherwise be expected to continue to decline and have worsening quality of life if their MR were left untreated. In general, effectiveness measures showed improvement from baseline and these improvements were in the same direction and generally of the same magnitude across studies.

In summary, the results published from commercial use outside the US are consistent with, and supportive of the finding or reasonable assurance of safety and effectiveness in the US IDE studies.

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

A. Panel Meeting Recommendation

An advisory meeting of the Circulatory System Devices Panel was held on March 20, 2013, evaluating the MitraClip for a broader indication in high surgical risk patients of both FMR and DMR etiology. Three questions were held for vote with the following results:

Question 1
The Panel voted 8 to 0 that the data shows reasonable assurance that the MitraClip Clip Delivery System is safe for use in patients who meet the criteria specified in the proposed indication.

Question 2
The panel voted 4 to 5 that there is not reasonable assurance that the MitraClip Clip Delivery System is effective for use in patients who meet the criteria specified in the proposed indication. (Chair voted as tie breaker). Two Panel members indicated that clear labeling defining the patient population would cause them to change to a positive effectiveness vote.

Question 3
The panel voted 5 to 3 that the benefits of the MitraClip Clip Delivery System do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

The Advisory Panel indicated that there was an unmet clinical need, and evidence of safety and effectiveness was present within the patient population studied, and that labeling defining the appropriate high risk patients could provide additional confidence to support effectiveness of the device.

B. FDA's Post-Panel Action

As discussed in detail in the Clinical Section, the Sponsor and FDA worked interactively following the panel meeting and determined that patients with primary MR etiology (DMR) at prohibitive risk for surgery (PR DMR) were the appropriate patient population to evaluate the risks and benefits of the MitraClip device. FDA worked interactively with the Sponsor on the submission of a PMA Amendment including supporting data for the Prohibitive Risk DMR population, refinement of the labeling, and Post Approval Study protocols to meet all of the recommendations of the Panel and the FDA.

XIII. CONCLUSION DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The results from the pre-clinical and clinical studies performed on MitraClip Clip Delivery System demonstrate that this device is safe and suitable for long-term implantation. In prohibitive risk DMR patients studied, there was no increased risk of procedural mortality compared to both the mean and median predicted STS mortality risk using either the repair or replacement calculator and no increased risk of mortality at 12 months when compared to a matched cohort of medically managed patients. Device related complications were rare. The Advisory Panel and FDA believe that there is a reasonable assurance of safety in this limited patient population.

B. Effectiveness Conclusions

The pre-clinical data demonstrate that the MitraClip Clip Delivery System performs acceptably. In prohibitive risk DMR patients studied, there were clinically important improvements in MR grade and left ventricular dimensions, as well as subjective parameters such as NYHA Class and Quality of Life parameters. Dose-response analyses show a reduction of MR to 2+ or less provides patient benefit. The FDA believes that there is a reasonable assurance of effectiveness in this limited patient population that has no other effective treatment options.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of the MitraClip Clip Delivery System include reduction of mitral regurgitation, reduced symptoms and hospitalizations, improved quality of life, and reverse LV remodeling.

The probable risks of the MitraClip Clip Delivery System include procedure related complications such as death (6.3%), stroke (3.4%), prolonged ventilation (3.1%) and

transfusion > 2 units (12.6%), major vascular complications (5.4%), non-cerebral thrombo-embolism (1.6%), new onset of atrial Fibrillation (3.9%), and atrial septal defect (1.6%).

In conclusion, given the available information above, the data support that 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 mitral regurgitation, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The pre-clinical and clinical studies conducted demonstrated that the MitraClip Clip Delivery System provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIV. CDRH DECISION

FDA issued an approval order on October 24, 2013. The final conditions of approval cited in the approval order are described below.

Two post approval studies (PAS) must be conducted as described below:

1. PAS 1 Device Registry (Prohibitive Risk DMR Serial Enrollment Patient Registry): The sponsor has agreed to a study outline to assess the long term safety and effectiveness in a broad patient population and to study how prohibitive risk is being interpreted in the real world use of the device to ensure the device is used in appropriate circumstances. The study will be a prospective observational cohort registry.

   Newly enrolled patients will be serially enrolled, from varying institutions, until a total of 2000 patients are enrolled or until the MitraClip PAS Analysis Cohort (PAS 2) enrollment is complete. Patients will be followed annually through 5 years. The safety endpoints will include NYHA Class, hospitalizations, stroke, and mortality through 1 year post implant. Annual follow-up data (e.g., death, stroke, surgical intervention, hospitalizations) from year 2 through year 5 post-implant will be obtained by linking to the Center for Medicare and Medicaid Services (CMS) database.

   If a patient goes on to mitral valve surgery within the first year, the following effectiveness endpoints should be collected: echo parameters at baseline and changes in left ventricular end-diastolic volume (LVEDV), in left ventricle internal diameter diastole (LVIDd), and in mitral regurgitation (MR) from baseline. Prohibitive risk status will be audited by a qualified central review committee through a random sampling of prohibitive risk patients according to a predefined schedule throughout the enrollment period.

Should the Mitral Module of the National Transcatheter Aortic Valve Replacement (TVT) registry housed jointly by the American College of Cardiology and Society for Thoracic Surgeons be used, the data collection for this study (i.e. pre-procedure, peri-procedure, post-procedure, discharge, 30-day, and one-year follow-up) will be nested within this registry.

2. PAS 2 MitraClip Registry (Analysis Cohort): The sponsor has agreed to a study outline to characterize longer term (5 year) MitraClip device performance by defining a) long term safety and effectiveness, and b) patient and procedure characteristics that potentially lead to maximum benefit from MitraClip. This study will consist of a subset of patients enrolled in the Device Registry (PAS 1) who meet specific pre-defined entry criteria as determined by a heart team at baseline.

   The primary safety objective is to compare the adverse event (AE) rate at 30 days to a performance goal of 80%. The primary safety endpoints will include freedom from a composite of death and device-related complications including single leaflet device attachment (SLDA), device and/or component embolization, mitral valve stenosis resulting in mitral valve surgery, and any catastrophic device failure resulting in an AE. The secondary safety objective is to compare freedom from death at 1 year to a performance goal of 66%, and freedom from device-related complications through 1 year to a performance goal of 90%. Device related complications will include SLDA, device and/or component embolization, mitral valve stenosis resulting in mitral valve surgery, and any catastrophic device failure resulting in an AE.

   The primary effectiveness endpoint is to compare change in 6 minute walk test distance (6MWT) at 1 year to baseline. The secondary effectiveness endpoints will include changes of MR Severity, LVEDV and LVIDd, Kansas City Cardiomyopathy Questionnaire (KCCQ), and NYHA Functional Classes at 1 year to baseline. Echo parameters will be collected at 1 year. Primary and secondary effectiveness endpoints will also be reported based on MR at discharge or the last visit (whichever is later).

   Other endpoints which will be descriptively reported include baseline demographics and clinical characteristics, procedure time, device time, radiation exposure, time in catheterization laboratory (cath lab), short-term device success and procedure success, and long-term mortality heart failure (HF) hospitalization, stroke, and surgical intervention through 5 years.

   A minimum of 420 evaluable patients at 12-month post-implant will be followed through 5 years. There will be a minimum of 15 sites and maximum of 40 sites with no more than 10% of patients enrolled into PAS 2 per site. Active follow-up of patients will be performed through 1 year. Annual follow-up (e.g., death, stroke, surgical intervention, hospitalizations) from year 2 through year 5 post-implant will be obtained by the link to the CMS database established in PAS 1.

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

XV. APPROVAL SPECIFICATIONS

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

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

Post-Approval Requirements and Restrictions: See Approval Order.

XVI. REFERENCES

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