SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Left Atrial Appendage Closure System
Device Trade Name:	WATCHMAN® LAA Closure Technology
Device Procode:	NGV
Applicant's Name and Address:	Boston Scientific Corporation One Scimed Place Maple Grove, MN 55311
Date(s) of Panel Recommendation:	December 11, 2013 October 8, 2014
Premarket Approval Application (PMA) Number:	P130013
Date of FDA Notice of Approval:	March 13, 2015
Priority Review:	Granted on August 7, 2013 because the device affects a condition that is life-threatening or irreversibly debilitating and there is no approved alternative.

II. INDICATIONS FOR USE

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc[1] scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

III. CONTRAINDICATIONS

The WATCHMAN LAA Closure Technology is contraindicated if:

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An atrial septal defect repair or closure device or a patent foramen ovale repair or closure device is present.
- The LAA anatomy will not accommodate a device (refer to the implant selection guide in the WATCHMAN LAA Closure Technology DFU).

- Any of the customary contraindications for other percutaneous catheterization procedures (e.g., patient size too small to accommodate TEE probe or required catheters) or conditions (e.g., active infection, bleeding disorder) are present.
- There are contraindications to the use of warfarin, aspirin, or clopidogrel.
- The patient has a known hypersensitivity to any portion of the device material or the individual components (refer to the Device Description in the WATCHMAN LAA Closure Technology DFU) such that the use of the WATCHMAN Device is contraindicated.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the WATCHMAN LAA Closure Technology labeling (Directions for Use).

V. DEVICE DESCRIPTION

The WATCHMAN LAA Closure Technology consists of:
- WATCHMAN LAA Closure Device (also referred to as "WATCHMAN Device", "WATCHMAN LAAC Device", "Device", and "Implant")
- WATCHMAN Delivery System (consisting of Delivery Catheter and loaded Implant)
- WATCHMAN Access System (consisting of Access Sheath and Dilator)

The WATCHMAN LAAC Device, which is constrained within the Delivery Catheter, is a self-expanding nitinol structure with a porous membrane on the proximal face and is available in five sizes as shown in Table 1. The Access System and Delivery Catheter provide femoral venous access and a means to cross into the left atrium via the interatrial septum.

Table 1: WATCHMAN LAAC Device Sizes

Description	Implant Diameter	Delivery Catheter Diameter
WATCHMAN LAA Closure Device & Delivery System	21 mm	12 Fr
WATCHMAN LAA Closure Device & Delivery System	24 mm	12 Fr
WATCHMAN LAA Closure Device & Delivery System	27 mm	12 Fr
WATCHMAN LAA Closure Device & Delivery System	30 mm	12 Fr
WATCHMAN LAA Closure Device & Delivery System	33 mm	12 Fr

The WATCHMAN Access System is available in three different curves as defined in Table 2.

Table 2: WATCHMAN Access System

Accessory	Diameter	Length
WATCHMAN Access System, Single Curve	14 Fr	75 cm
WATCHMAN Access System, Double Curve	14 Fr	75 cm
WATCHMAN Access System, Anterior Curve	14 Fr	75 cm

A. WATCHMAN LAAC Device

The WATCHMAN LAAC Device (Figure 1) is the implantable component of WATCHMAN LAAC Technology and is designed to be permanently implanted in the LAA (Figure 2). The Device is composed of:

- A laser-cut nitinol frame that is formed to an umbrella-like shape and electropolished. Fixation anchors are located on the outer edge of the frame struts to provide stabilization in situ.
- A heat-shaped knit permeable fabric, which is placed over the top of the Device and secured to the struts of the implant frame with sutures and to the top of the frame with a threaded insert.
- A threaded insert is attached to the frame by a welded dowel pin. The threaded insert provides the mechanism for attaching the Device to the threaded core wire on the Delivery Catheter.

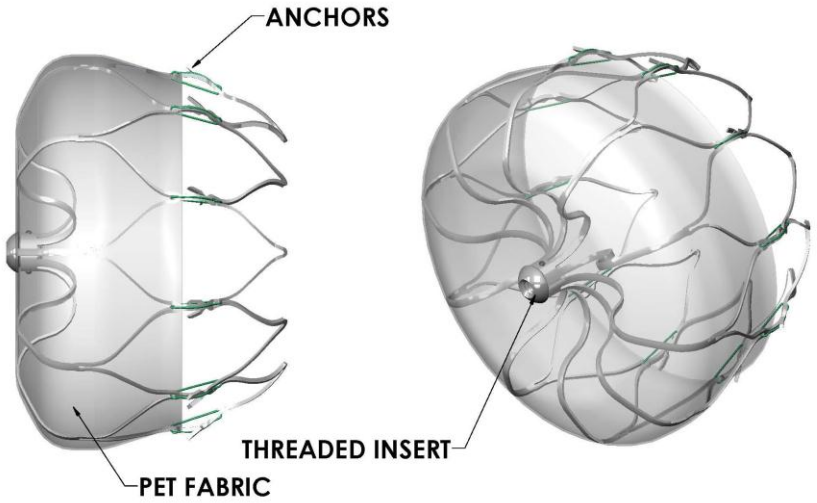

Figure 1: WATCHMAN LAAC Device

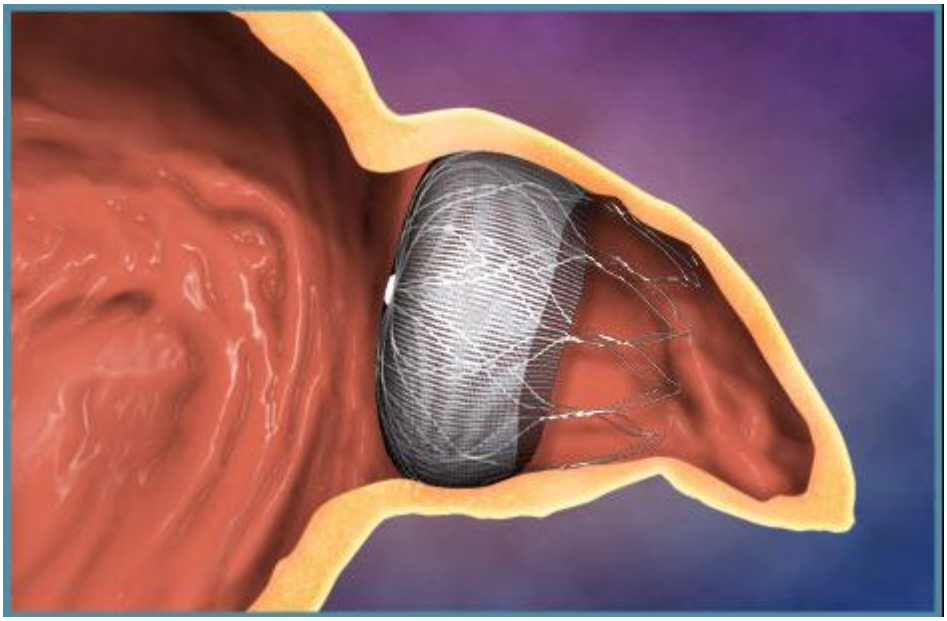

Figure 2: WATCHMAN LAAC Device in situ at the ostium of the LAA

B. WATCHMAN Delivery System

The WATCHMAN Delivery System is comprised of a Delivery Catheter (Figure 3) with a preloaded WATCHMAN Device. The Delivery Catheter is a 12 Fr reinforced catheter with a distal radiopaque marker band for in situ visualization.

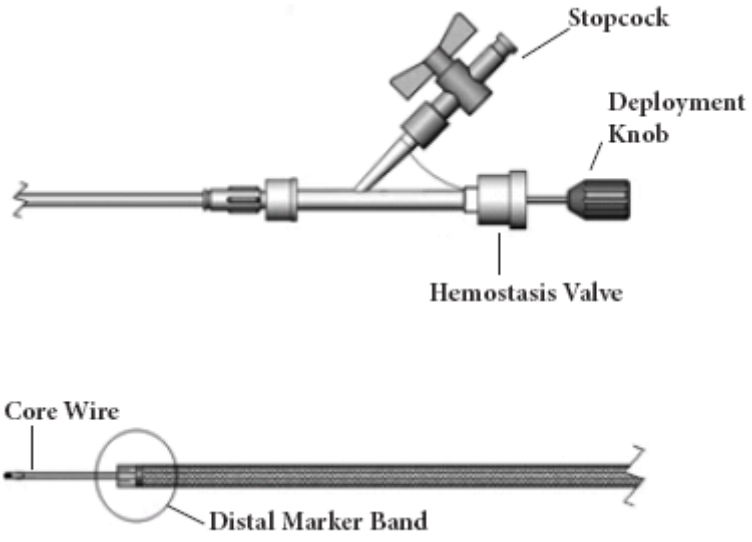

Figure 3: Delivery Catheter

A threaded core wire within the Delivery System provides the mechanism for deployment and release or recapture of the Device. The distal section of the core wire is tapered and the entire core wire is encased within a reinforced catheter shaft; this configuration provides the rigidity necessary to deploy the Device and the flexibility to allow the Device to remain in its natural state in the LAA, without bias from the Delivery Catheter. After the self-expanding Device is deployed and positioning is confirmed, the Device is released by turning the deployment knob counterclockwise, which unscrews the core wire from the threaded insert on the Device.

In addition to the deployment knob, the Delivery Catheter proximal handle assembly includes a Y-adapter hemostasis valve and a 2-way stopcock.

C. WATCHMAN Access System

The WATCHMAN Access System includes an Access Sheath (Figure 4) and a Dilator. The Access Sheath is a reinforced 14 Fr catheter with an overall working length of 75 cm. The proximal end of the Access Sheath has a Tuohy-Borst style hemostasis valve with an attached side port; the hemostasis valve allows for snap-fit connection with the WATCHMAN Delivery System. The soft radius distal tip contains radiopaque marker bands for in situ visualization and vent holes for contrast distribution.

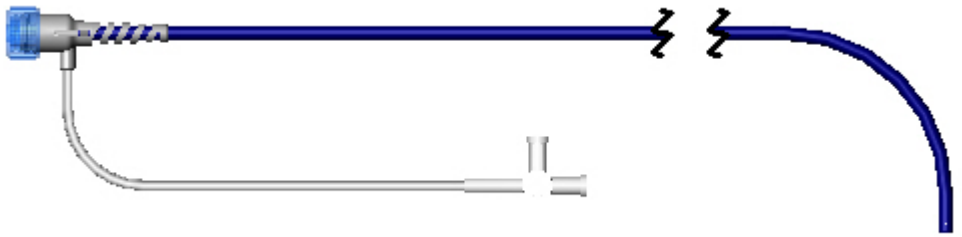

Figure 4: Access Sheath

The Dilator is composed of a polymer shaft with a proximal flush port hub and a standard luer taper and threads. The distal tip of the Dilator is tapered for septal crossing and curved to an approximate 90 degree angle. The hub is designed for snap fit connection to the Access Sheath hemostasis valve.

The Access System is available with single curve (90 degree angle), double curve and anterior curve distal tip configurations.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for reducing the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation.

Warfarin and other approved oral anticoagulants effectively reduce the risk of cardioembolic stroke and are the most commonly used treatments in at-risk patients with non-valvular atrial fibrillation.

The AtriCure AtriClip® and Terumo/Maquet/LAAx Tigerpaw® are indicated for the occlusion of the LAA under direct visualization, in conjunction with other open cardiac surgical procedures.

An alternative to using a device for LAA closure is direct closure during open-heart surgery (nearly always as an adjunct procedure to treat another primary cardiac condition). LAA closure is commonly performed following or in tandem with an open MAZE procedure for atrial fibrillation or other open heart procedures such as mitral valve repair or replacement.

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. MARKET HISTORY

The WATCHMAN LAA Closure Technology is commercially available in the following countries:

- Argentina
- Australia
- Austria
- Iceland
- Indonesia
- Iran
- Peru
- Philippines
- Poland

- Belgium
- Brazil
- Brunei
- Bolivia
- Bulgaria
- China
- Colombia
- Costa Rica
- Cyprus
- Czech Republic
- Denmark
- Dutch Antilles
- Ecuador
- Egypt
- Estonia
- Finland
- France
- Germany
- Greece
- Guatemala
- Hong Kong
- Hungary
- Ireland
- Israel
- Italy
- Jordan
- South Korea
- Kazakhstan
- Kuwait
- Latvia
- Liechtenstein
- Lithuania
- Luxembourg
- Macau
- Malaysia
- Malta
- Mexico
- Morocco
- Netherlands
- New Zealand
- Norway
- Pakistan
- Panama
- Paraguay
- Portugal
- Romania
- Russia
- Saudi Arabia
- Serbia
- Singapore
- Slovakia
- Slovenia
- South Africa
- Spain
- Sweden
- Switzerland
- Taiwan
- Tunisia
- Turkey
- UAE
- Ukraine
- United Kingdom
- Venezuela
- White Russia

The device has not been withdrawn from marketing for any reason related to its safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Air embolism
- Airway trauma
- Allergic reaction to contrast media/medications or device materials
- Altered mental status
- Anemia requiring transfusion
- Anesthesia risks
- Angina
- Anoxic encephalopathy
- Arrhythmias
- Atrial septal defect
- AV fistula
- Bruising, hematoma or seroma
- Cardiac perforation
- Chest pain/discomfort
- Confusion post procedure
- Congestive heart failure

- Contrast related nephropathy
- Cranial bleed
- Decreased hemoglobin
- Deep vein thrombosis
- Death
- Device embolism
- Device fracture
- Device thrombosis
- Edema
- Excessive bleeding
- Fever
- Groin pain
- Groin puncture bleed
- Hematuria
- Hemoptysis
- Hypotension
- Hypoxia
- Improper wound healing
- Inability to reposition, recapture, or retrieve the device
- Infection/pneumonia
- Interatrial septum thrombus
- Intratracheal bleeding
- Major bleeding requiring transfusion
- Misplacement of the device / improper seal of the appendage / movement of device from appendage wall
- Myocardial erosion
- Nausea
- Oral bleeding
- Pericardial effusion / tamponade
- Pleural effusion
- Prolonged bleeding from a laceration
- Pseudoaneurysm
- Pulmonary edema
- Renal failure
- Respiratory insufficiency / failure
- Surgical removal of the device
- Stroke – Ischemic
- Stroke – Hemorrhagic
- Systemic embolism
- TEE complications (throat pain, bleeding, esophageal trauma)
- Thrombocytopenia
- Thrombosis
- Transient ischemic attack (TIA)
- Valvular damage
- Vasovagal reactions

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

A series of non-clinical studies were performed to evaluate:

- the LAA Closure Device (preloaded)
- the Delivery System
- the Access System

1. Biocompatibility Studies

Biocompatibility and toxicology testing of the WATCHMAN LAA Closure Technology was conducted on the WATCHMAN LAAC Device, Delivery System, and Access System in accordance with Good Laboratory Practices Regulations (21 CFR § 58) and ISO 10993-1: *Biological Evaluation of Medical Devices: Evaluation and Testing (2009)*. According to ISO 10993, the WATCHMAN Delivery System and Access System are classified as blood contacting, externally communicating with limited, less than 24 hour exposure devices. The WATCHMAN LAA Closure Device is classified as a blood contacting, permanent duration implant. The results of the biocompatibility studies are summarized in Table 3.

Table 3: Biocompatibility Test Summary

Biocompatibility Study	Results
WATCHMAN LAA Closure Device (Implant)	
Cytotoxicity (MEM Elution) / ISO 10993-5	Pass
Irritation (Intracutaneous Injection) / ISO 10993-10	Pass
Sensitization (Kligman Maximazation/Senstitization) / ISO 10993-10	Pass
Acute Systemic Toxicity (Systemic Injection) / ISO 10993-11	Pass
Pyrogenicity (Material Medicated/Rabbit Pyrogen) / ISO 10993-11	Pass
Genotoxicity (Salmonella typhimurium and Escherichia coli reverse Mutation Assay, Chromosomal Aberration Assay, and Roden Bone Marrow Micronucleus Assay) / ISO 10993-3	Pass
Implant / Chronic Toxicity (Subcutaneous Implant) / ISO 10993-6 ISO 10993-11	Pass
Hemocompatibility (In-vitro Hemocompatibility, Lee & White, Hemolysis – Direct and Indirect Methods, and Direct Contact Complement Activation – C3a and Sc5b-9) / ISO 10993-4	Pass
USP Physico-Chemical Test (USP<25> and <661>) / ISO 10993-18	Pass
Delivery System	
Cytotoxicity (MEM Elution) / ISO 10993-5	Pass
Irritation (Intracutaneous Reactivity) / ISO 10993-10	Pass
Sensitization (Murine Local Lymph Node Assay [LLNA]) / ISO 10993-10	Pass
Acute Systemic Toxicity (Acute Systemic Injection) / ISO 10993-11	Pass
Pyrogenicity (Material Medicated / Rabbit Pyrogen) / ISO 10993-11	Pass
Hemocompatibility (In-vitro Hemolysis – Direct and Indirect	Pass

Methods) / ISO 10993-4	
Access System	
Cytotoxicity (MEM Elution) / ISO 10993-5	Pass
Irritation (Intracutaneous Reactivity / ISO 10993-10	Pass
Sensitization (Kligman – GPMT) / ISO 10993-10	Pass
Acute Systemic Toxicity (Acute Systemic Injection) / ISO 10993-11	Pass
Pyrogenicity (Rabbit Pyrogen) / ISO 10993-11	Pass
Hemocompatibility (Hemolysis – Direct and Indirect Methods) / ISO 10993-4	Pass

2. *In Vitro* Engineering Testing

The in vitro engineering studies conducted are summarized in Table 4. "Pass" denotes that the test results met product specifications.

Table 4: Engineering Testing

Device/Component Characteristic	Test Description	Results
Implant		
Implant Threaded Insert to NiTi Tube Joint Tensile Separation	This test quantitatively assessed the tensile force required to separate the threaded insert from the nitinol frame of the WATCHMAN implant.	Pass
Core Wire Assembly Wire through Implant Threaded Insert Tensile Strength	This test quantitatively assessed the tensile strength of the distal core wire assembly, including the thread mate to the implant threaded insert.	Pass
Implant Filtration	This test quantitatively assessed the flow rate and particle exclusion properties of the LAA implant filter.	Pass
Implant Deployment and Recapture Force	This test quantitatively assessed the forces required to deploy and recapture the LAA implant via the delivery system and access system.	Pass
Implant Mechanical Integrity (including Individual Barb Mechanical Integrity)	This test evaluated the mechanical integrity of the implant after a half recapture and full recapture, as well as evaluating the implant barb integrity using a cleat test that deflects the barb a predetermined amount that simulates the barb strain/deflection incurred during the implant recapture.	Pass
Implant Radial Force	This test quantitatively assessed the radial force of a properly constrained WATCHMAN implant.	Pass
Implant Diameter Recovery	This test quantitatively assessed the diameter recovery of the WATCHMAN implant following deployment, partial recapture, and re-deployment.	Pass

Implant Dislodgement Force	This test quantitatively assessed the force required to dislodge a properly sized and positioned WATCHMAN implant.	Pass
MRI Field Interactions	This test assessed the conditions under which the device may be scanned safely.[2] Additional MRI information is provided below this table.	Pass
Implant Corrosion Resistance	This test quantitatively assessed the corrosion resistance of the WATCHMAN LAA implant.	Pass
Implant Durability/Fatigue (Test articles were cycled up to the equivalent of 10 years of use or 400,000,000 cycles)	This test demonstrated the resistance of the Watchman implant device to *in-vivo* fatigue-related damage.	Pass
Finite Element Analysis (for characterization)	This test assessed the stress/strain levels in key areas of the device throughout the various stages of the implant forming and implantation.	Pass
Delivery System		
Delivery System Tensile Strength	This test quantitatively assessed the tensile force required to separate the hub, shaft, and any bond/joint areas of the WATCHMAN Delivery System.	Pass
Snap Fit Luer Connection Compressive and Tensile Properties	This test assessed the force of connection and detachment of the Delivery System to the Access System hemostasis valve.	Pass
Core Wire Torque Properties	This test quantitatively assessed delivery system core wire assembly torque properties, specifically the torque required to release the implant, and the torque required to fail the core wire.	Pass
Core Wire Assembly Torquer Bond Strength	This test quantitatively assessed the tensile, compressive, and rotational strength of the core wire assembly torquer bond.	Pass
Kink Resistance – Delivery System	This test quantitatively assessed the kink resistance of the Watchman Delivery System shaft.	Pass
Contrast Flow Rate – Delivery System	This test evaluated the Delivery System for constant pressure flow rate using saline through the loaded Delivery System.	Pass
Leak Free Conduits - Delivery System	This test evaluated the Delivery System under two conditions: leak integrity under positive pressure and under negative pressure.	Pass
Corrosion Resistance – Delivery System	This test qualitatively assessed the susceptibility of the Delivery System and/or its components to corrosion.	Pass
Access System		

WATCHMAN Access System – Tensile Testing	This test evaluated the tensile strength of the Watchman Access Sheath critical bond/fusion joints.	Pass
Kink Resistance – Access System	This test quantitatively assessed the kink resistance of the Watchman Access System shaft.	Pass
Contrast Flow Rate	This test evaluated the Access System for constant pressure flow rate using saline through the open lumen.	Pass
Leak Free Conduits – Access System	This test evaluated the Access System under two conditions; leak integrity under positive pressure and under negative pressure.	Pass
Access System Distal Tip Deflection	This test quantitatively assessed the force required to deflect the distal tip of the WATCHMAN Access System sheath.	Pass
Dilator Tensile Strength	This test quantitatively assessed the minimum tensile force required to separate the shaft and any bond/joint areas of the WATCHMAN Access System dilator component.	Pass

Non-clinical testing demonstrated that the WATCHMAN Device is MR Conditional. A patient with the WATCHMAN Device can be scanned safely, immediately after placement of this implant, under the following conditions:

- Static magnetic field of 1.5 or 3.0 Tesla or less
- Spatial gradient field of 2500 Gauss/cm or less
- Maximum whole-body averaged specific absorption rate (SAR) shall be limited to 2.0 W/kg (normal operating mode only) for 15 minutes of scanning
- Normal operating mode of the MRI scanner

Non-clinical testing of RF-induced heating in the WATCHMAN LAA Closure Device was performed at 64 MHz in a 1.5 Tesla whole body coil MR scanner (Intera, Software Release 10.6.2.4, 2006-03-10, Philips Medical Systems, Andover, MA) and produced a temperature rise of <1.5°C at an MR extrapolated SAR of 2.0 W/kg for 15 minutes of continuous MR scanning. The WATCHMAN LAA Closure Device produced a temperature rise of <1.1°C at a maximum MR system-reported SAR of 2.0 W/kg as measured by calorimetry for 15 minutes of continuous MR scanning in a 3.0 Tesla MR system (Excite, Software G3.0-052B, GE Healthcare, Milwaukee, WI). These calculations do not take into consideration the cooling effects of blood flow.

3. <u>Sterilization</u>

The WATCHMAN LAA Closure Technology is sterilized using ethylene oxide sterilization and the sterilization process has been validated per AAMI/ISO 11135:1994 *"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}.

The amount of bacterial endotoxin was verified to be within the ANSI/AAMI ST72 specification limit.

4. Shelf Life

Shelf life studies were conducted to establish a shelf life/expiration date for the WATCHMAN LAA Closure Technology. In addition, testing to establish package integrity and functional testing of the WATCHMAN LAA Closure Technology were conducted on aged product to ensure that the WATCHMAN LAA Closure Technology continues to meet specifications throughout its shelf life. The data generated support a 3-year shelf life for the WATCHMAN LAAC Device, Delivery System, and Access System, and the device is labeled accordingly.

B. Animal Studies

Because detailed arterial histopathology and histomorphometry data cannot be obtained through human clinical studies, a series of animal studies were conducted to evaluate safety, vascular compatibility, and acute product performance.

Four studies were conducted to assess the safety and vascular compatibility of the WATCHMAN LAA Closure Technology, and are summarized in Table 5. The safety, vascular compatibility, and acute performance of WATCHMAN LAA Closure Technology were evaluated in the non-injured canine left atrial appendage model. Studies were conducted in accordance with §21 CFR 58 (Good Laboratory Practices (GLP)).

Table 5: Summary of Animal Studies

Study	No. of Animals and Study Duration; Species/Strain	Objectives	Results
SR1007, GLP Left Atrial Appendage Thrombus (LAAT) Filter System Study This study was conducted with an earlier generation of the WATCHMAN LAA Closure Technology.	14 animals: (2) 72 hours (6) 45 days (6)181-182 days Canine/ Purpose Bred Hounds Adult, Male	To demonstrate the overall safety & functionality of the 1st Generation WATCHMAN system. Safety; ease of implantation; demonstrate that device does not promote organized thrombus 72 hrs post implant on atrial filter surface; assess level of endothelialization at 45 days; assess implant integrity and tissue response at 180 days post implant	The Atritech LAA Filter System met the requirements for establishing pre-clinical safety and functionality with regard to not promoting thrombus formation, endothelialization, implant integrity and tissue response.

SR1014, GLP Animal Study of the LAA Thrombus Filter System (WALAA) Study This study was conducted with an earlier generation of the WATCHMAN LAA Closure Technology.	10 animals: (4) 3 days (3) 15 days (3) 33 days Canine/Purpose Bred Mongrel, Adult, Male	To evaluate the safety and effectiveness of the modified implant anchoring features with respect to positioning, stability/fixation, and effects on adjacent tissues at 3 and 15 days post implant. To evaluate and document the safety and performance of the modified Delivery System and implant with regard to implant deployment and retrieval.	The Atritech WATCHMAN LAA Filter System II met the requirements for establishing pre-clinical safety with regard to anchoring and positioning, stability/fixation, and effects on adjacent tissues.
SR1029, GLP Animal Study LAA Thrombus Filter System with Aspirin/Plavix (ALAA) Study This study was conducted with an earlier generation of the WATCHMAN LAA Closure Technology.	9 animals: (3) 3 days (3) 49 days (3) 91 days Canine, Mongrel Adult, Male	Pathological and histological studies to evaluate: 1) The tissue integration of the implant atrial facing surface, reporting the extent and type of tissue response (thrombus formation, endothelial coating) 2) The heart and kidneys (microscopically) to determine levels of systemic embolization. 3) The acute stability/fixation of the long filter implant.	The Atritech WATCHMAN LAA Filter System II met the requirements for establishing pre-clinical safety.
SR1040, WATCHMAN LAA Short Implant GLP Animal Study (LAAS) This study was conducted with the current generation of the WATCHMAN LAA Closure Technology that is the subject of this PMA.	6 animals: (3) 3 days (3) 47 days Canine/Purpose Bred Hound Adult; 4 males; 2 females	To demonstrate : 1) An acceptable local pathological response associated with the Short Implant, specifically with regard to distal tine perforation. 2) An adequate implant position. Gross inspection and pathology studies will assess implant position and filter span at the LA/LAA ostium up to 72 hours and at 45 days.	The WATCHMAN LAA Short Implant showed an acceptable pathological response regarding the left atrial appendage and underlying circumflex coronary artery with no distal tine perforation or erosion visible acutely or at 45 days. All implants exhibited good proximal face position, at or slightly distal to the ostium, with complete filter coverage. The study results demonstrated an acceptable implant position and filter span at the ostium of the left atrial appendage.

Overall, the results of the study studies indicate an acceptable tissue healing response to the implanted WATCHMAN. Animal studies performed on earlier generations of the device are relevant to the performance of the current generation WATCHMAN. The device promotes endocardial overgrowth and completely seals the LAA from the left atrium within 45 days. There were no visible strut fractures, and that the device caused no significant effects on adjacent tissues. Device implantation procedural methods were reproducible and safe.

IX. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed several clinical studies to demonstrate a reasonable assurance of safety and effectiveness of transcatheter left atrial appendage closure with the

WATCHMAN Left Atrial Appendage Closure Technology for reducing the risk of thromboembolism from the LAA in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy. Studies were performed in the U.S., Germany, and Czech Republic under IDE # G020312. Data from these clinical studies were the basis for the PMA approval decision. The clinical data that demonstrate a reasonable assurance of safety and effectiveness of the WATCHMAN Left Atrial Appendage Closure Technology came from the following studies:

- PROTECT AF (**Section X.1**)
- PREVAIL (**Section X.2**)
- CAP (**Section XI.1**)
- CAP2 (**Section XI.2**)

A summary of each study design is presented in Table 6.

Table 6: Summary of WATCHMAN Clinical Studies

Patient Population	Subjects with non-valvular atrial fibrillation who were deemed by their physicians to be suitable for warfarin therapy to reduce the risk of ischemic stroke and systemic embolism			
Study	**PROTECT AF**	**CAP**	**PREVAIL**	**CAP2**
Purpose	Demonstrate safety and effectiveness compared to long-term warfarin	Continued access registry	Demonstrate safety and effectiveness compared to long-term warfarin	Continued access registry
Study Design	2:1 Randomized, non-inferiority	Non-randomized	2:1 Randomized, non-inferiority	Non-randomized
Primary Endpoints	Effectiveness: Stroke, cardiovascular death, and systemic embolism Safety: Life-threatening events which would include events such as device embolization requiring retrieval and bleeding events		1. Effectiveness: Stroke, systemic embolism, and cardiovascular/unexplained death 2. Effectiveness: Ischemic stroke or systemic embolism occurring after seven days post-randomization or WATCHMAN implantation procedure 3. Safety: Death, ischemic stroke, systemic embolism and procedure/device-related complications within seven days of the implantation procedure	
Number of Patients Enrolled	800 enrolled • 93 roll-in WATCHMAN • 707 randomized ○ 463 WATCHMAN ○ 244 Control	566 WATCHMAN subjects	461 enrolled • 54 roll-in WATCHMAN • 407 randomized ○ 269 WATCHMAN ○ 138 Control	579 WATCHMAN subjects
Status of Subject Follow-Up	Study Complete 2717 patient-years	Study Ongoing 2022 patient-years	Study Ongoing 860 patient-years	Study Ongoing 332 patient-years
Scheduled Follow-Up Duration	5 years			

X.1 PROTECT AF

A. Study Design

Patients were treated between February 14, 2005 and June 30, 2008. The database for this PMA reflected the final data collected through closure of the study and included 800 patients and 2717 patient-years of follow-up. There were 59 investigational sites.

The study was a multicenter, prospective, randomized, controlled pivotal clinical study intended to evaluate the safety and effectiveness of the WATCHMAN LAA Closure Technology in patients with non-valvular atrial fibrillation who were eligible for warfarin therapy. Patients were randomized in a 2:1 ratio to either the WATCHMAN LAA Closure Technology (WATCHMAN group) or long-term warfarin therapy (Control group).

The primary analysis population was the intent-to-treat (ITT) population, and a Bayesian model was used in the statistical analysis. The statistical analysis plan called for an initial interim evaluation after 600 patient-years of follow-up, with subsequent interim evaluations after each additional 150 patient-years, up to 1,500 patient years of follow-up.

The study utilized an independent Data Safety Monitoring Board (DSMB) to oversee study progress and review clinical data and safety, an independent Clinical Events Committee (CEC) that was responsible for adjudicating all serious adverse events and all adverse events that are potentially related to the procedure or device, and an independent Echocardiography Core Lab for the interpretation of all echocardiographic data.

1. Clinical Inclusion and Exclusion Criteria

   Key study eligibility criteria are provided in Table 7.

Table 7: PROTECT AF Key Eligibility Criteria

Key Inclusion Criteria
The subject is 18 years of age or older
The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
The subject is eligible for long-term warfarin therapy
The subject has a calculated $CHADS_2$ score of 1 or greater
Key Exclusion Criteria
The subject requires long-term warfarin therapy
The subject is contraindicated for warfarin therapy
The subject is contraindicated for aspirin
The subject has a history of atrial septal repair or has an atrial septal defect (ASD)/patent foramen ovale (PFO) closure device
Key Echo Exclusion Criteria
The subject has Left Ventricular Ejection Fraction (LVEF) < 30%
The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
The subject has a high risk PFO defined as a PFO with an atrial septal aneurysm (total excursion >15 mm or length≥15 mm) or a large shunt (early, within 3 beats with a substantial passage of bubbles)
The subject has significant mitral valve stenosis
The subject had complex atheroma with mobile plaque in the descending aorta and/or aortic arch
The subject has a cardiac tumor

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 45 days, 6 months, 9 months, 12 months, and semi-annually through 5 years. The key time points and evaluations conducted in the study are shown in Table 8.

Table 8: Follow-Up Schedule of Evaluations for the PROTECT AF Study

Study Requirements	**45-Day Follow-up**	**6-Month Follow-up**	**9-Month Follow-up** (via telephone)	**12-Month and Annual Follow-up**	**Semi-Annual Follow-up** (via telephone)
Device Group:					
TEE	√	√		√	
INR[a]	√	Monthly if required	Monthly if required	Monthly if required	Monthly if required
Control Group:					
INR[a]	√	√	√	√	√
All Enrolled Subjects:					
Resting Heart Rate, Blood Pressure	√			√	
Neurological Assessment[b]				√ c	
NIH Stroke Scale[d]	√	√		√	
Barthel Index (BI)[e]	√	√	√	√	√
Modified Rankin Scale (MRS)[e]	√	√	√	√	√
SF-12v2 Health Survey				√ f	
Brain Imaging (CT/MRI) and Stroke Scales[g]	As needed	As needed	As needed	As needed	As needed

[a] For WATCHMAN subjects, INR checks required every other week through 45-Day Follow-up Visit. If WATCHMAN subjects continued warfarin beyond 45-Day visit, INR checks should be done every other week through 6 months and monthly thereafter (if subjects were still taking warfarin). For Control subjects, INR should be obtained every other week from randomization through 6 months and monthly thereafter.

[b] Neurological assessment by neurologist.

[c] At 12 and 24 months only.

[d] Neurological consult required if the NIHSS score increases ≥ 2 points from previous visit.

[e] Neurological consult required if the BI decreases ≥ 15 points or the MRS increases ≥1 point from the previous assessment, and the increase/decrease is NOT attributed to a non-neurological cause

[f] At 12 months only

[g] Following a stroke or TIA event including neurological assessment by a Neurologist.

3. Clinical Endpoints

The primary effectiveness endpoint was the composite of stroke (ischemic and hemorrhagic), systemic embolism, and cardiovascular or unexplained death. The criterion for establishing non-inferiority at an interim analysis required that the

posterior probability that the primary effectiveness event rate for the WATCHMAN group being less than 2 times the event rate for the Control group be at least 0.975 (or equivalently, the upper bound of the equitailed 2-sided 95% credible interval for the rate ratio be less than 2). The criterion for establishing superiority was a posterior probability that the event rate for the WATCHMAN group was less than the event rate for the Control group of at least 0.95. The superiority test was only performed if non-inferiority had been established.

The primary safety endpoint was the occurrence of life-threatening events as determined by the Clinical Events Committee, which included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion, and any bleeding related to the device or procedure that necessitates an operation. There was no pre-specified hypothesis for the primary safety endpoint.

B. Subject Accountability

Of the 800 enrolled patients , 62.9% (503) patients were available for analysis at the completion of the study, the 5 year post-operative visit. Table 9 shows the accountability of patients during the study. Subjects who died or were withdrawn were not counted as having expected visits.

Table 9: Accountability summary table

	Device Group	Control Group
Visit	**Attended/ Expected (%)**	**Attended/ Expected (%)**
45 Day	433/438 (98.9%)	236/240 (98.3%)
6 Month	400/402 (99.5%)	226/231 (97.8%)
9 Month	386/392 (98.5%)	216/223 (96.9%)
12 Month	379/386 (98.2%)	203/219 (92.7%)
18 Month	374/381 (98.2%)	198/214 (92.5%)
24 Month	351/369 (95.1%)	174/201 (86.6%)
30 Month	341/358 (95.3%)	169/192 (88.0%)
36 Month	320/349 (91.7%)	149/176 (84.7%)
42 Month	321/338 (95.0%)	142/165 (86.1%)
48 Month	320/332 (96.4%)	140/156 (89.7%)
54 Month	316/324 (97.5%)	136/150 (90.7%)
60 Month	304/308 (98.7%)	135/145 (93.1%)
Total:	4245/4377 (97.0%)	2124/2312 (91.9%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a nonvalvular atrial fibrillation study performed in the US. Patient demographics and risk factors are summarized in Table 10 and Table 11, respectively.

Table 10: PROTECT AF Baseline Demographics

Characteristic	Device N=463	Control N=244	P-value
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	72.7 ± 9.2 (244) (41.0, 95.0)	0.179
Sex			0.928
Female	137/463 (29.6%)	73/244 (29.9%)	
Male	326/463 (70.4%)	171/244 (70.1%)	
Race/Ethnicity			0.779
Asian	4/463 (0.9%)	1/244 (0.4%)	
Black/African American	6/463 (1.3%)	5/244 (2.0%)	
Caucasian	425/463 (91.8%)	222/244 (91.0%)	
Hispanic/Latino	25/463 (5.4%)	15/244 (6.1%)	
Hawaiian/Pacific Islander	1/463 (0.2%)	1/244 (0.4%)	
Other	2/463 (0.4%)	0/244 (0.0%)	

Table 11: PROTECT AF Baseline Risk Factors

Characteristic	Device N=463	Control N=244	P-value
$CHADS_2$ Score			0.411
1	156/463 (33.7%)	66/244 (27.0%)	
2	158/463 (34.1%)	88/244 (36.1%)	
3	89/463 (19.2%)	51/244 (20.9%)	
4	37/463 (8.0%)	24/244 (9.8%)	
5	19/463 (4.1%)	10/244 (4.1%)	
6	4/463 (0.9%)	5/244 (2.0%)	
$CHADS_2$ Score (Continuous)	2.2 ± 1.2 (463) (1.0, 6.0)	2.3 ± 1.2 (244) (1.0, 6.0)	0.072
$CHADS_2$ Risk Factors			
Congestive Heart Failure (CHF)	124/463 (26.8%)	66/244 (27.0%)	0.9392
Hypertension	415/463 (89.6%)	220/244 (90.2%)	0.8243
Age ≥ 75	190/463 (41.0%)	115/244 (47.1%)	0.1198
Diabetes	113/463 (24.4%)	72/244 (29.5%)	0.1423
Previous TIA/Ischemic Stroke	82/463 (17.7%)	49/244 (20.1%)	0.4404
CHA_2DS_2-VASc Score			0.469
1	44/460 (9.6%)	16/239 (6.7%)	
2	105/460 (22.8%)	54/239 (22.6%)	
3	139/460 (30.2%)	64/239 (26.8%)	
4	91/460 (19.8%)	47/239 (19.7%)	
5	45/460 (9.8%)	32/239 (13.4%)	
6	27/460 (5.9%)	19/239 (7.9%)	
7	5/460 (1.1%)	5/239 (2.1%)	
8	2/460 (0.4%)	2/239 (0.8%)	
9	0/460 (0.0%)	0/239 (0.0%)	
CHA_2DS_2-VASc Score (Continuous)	3.2 ± 1.4 (460)	3.5 ± 1.5 (239)	0.022

D. Safety and Effectiveness Results

1. Safety Results

The safety endpoint analysis was based on the intent to treat cohort of 503 patients available for the 5 year evaluation, with a total of 2717 patient-years of follow-up. The key safety outcomes for this study are presented below in Table 12. The primary safety endpoint rate was 3.5 events per 100 patient years for the WATCHMAN group and 3.2 events per 100 patient years for the Control group resulting in a relative risk ratio of 1.08. A description of the adverse effects is presented in Table 13.

Table 12: PROTECT AF Primary Safety Results
(Intent-to-Treat, 2717 patient-years)
Randomization Allocation (2 Device: 1 Control)

WATCHMAN Rate (N events / total pt-yrs)	Control Rate (N events / total pt-yrs)	Relative Risk (95% CrI)
3.5 (60/1729.6)	3.2 (29/904.9)	1.08 (0.72, 1.77)

Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)
Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.
Crl = credible interval

Adverse effects that occurred in the PROTECT AF study:

A summary of all serious adverse events for the WATCHMAN and Control groups is presented in Table 13.

Table 13: PROTECT AF Serious Adverse Events

Event	WATCHMAN			Control		
	Number of Events	Number of Subjects	Percent of Subjects	Number of Events	Number of Subjects	Percent of Subjects
Death	59	59	12.7%	44	44	18.0%
Gastrointestinal Bleeding	32	26	5.6%	27	22	9.0%
Stroke – Ischemic	26	24	5.2%	11	10	4.1%
Stroke - Hemorrhagic	3	3	0.6%	10	10	4.1%
Systemic Embolization	3	3	0.6%	0	0	0
Other Study Related	18	17	3.7%	2	2	0.8%
Cranial Bleed	4	4	0.9%	1	1	0.4%
Major Bleed Requiring Transfusion	2	2	0.4%	1	1	0.4%
Rectal Bleeding	1	1	0.2%	1	1	0.4%
AV Fistula	1	1	0.2%	0	0	0
Adjudicated as Non-Event	1	1	0.2%	0	0	0
Anemia Requiring Transfusion	2	2	0.4%	1	1	0.4%
Arrhythmias	2	2	0.4%	0	0	0
Bleeding from Varicose Veins	1	1	0.2%	0	0	0
Bruising - Hematoma	5	5	1.1%	0	0	0
Cardiac Perforation	7	7	1.5%	0	0	0
Device Embolization	4	3	0.6%	0	0	0
Device Thrombus	2	2	0.4%	0	0	0
Epistaxis	4	4	0.9%	0	0	0
Hematuria	4	4	0.9%	0	0	0
Infection	2	2	0.4%	0	0	0
Oral Bleeding	0	0	0	1	1	0.4%
Pericardial Effusion with Cardiac Tamponade	13	13	2.8%	0	0	0
Pericardial Effusion-Serious	4	4	0.9%	0	0	0
Pleural Effusion	1	1	0.2%	0	0	0
Pseudoaneurysm	3	3	0.6%	0	0	0
Pulmonary Edema	1	1	0.2%	0	0	0
Thrombosis	1	1	0.2%	0	0	0
Transient Ischemic Attack	5	5	1.1%	0	0	0

2. Effectiveness Results

The effectiveness endpoint analysis was based on the intent to treat cohort of 503 patients available for the 5 year evaluation, with a total of 2717 patient-years of follow-up. Key effectiveness outcomes are presented in Table 14. The primary effectiveness event rate was 2.2 events per 100 patient years for the WATCHMAN group and 3.7 events per 100 patient years for the Control group, resulting in a relative risk or rate ratio of 0.61. The criteria for non-inferiority and superiority of the WATCHMAN group vs. the Control group were met and were driven by the rates of hemorrhagic stroke and cardiovascular/unexplained death in favor of the WATCHMAN group. The ischemic stroke rate numerically favored the control group. The primary effectiveness endpoint for PROTECT AF is shown as time to event in a Kaplan-Meier curve in Figure 5.

Table 14: PROTECT AF Primary Effectiveness Results and % of subjects who experienced 1 or more events (Intent-to-Treat, 2717 patient years)

Randomization Allocation (2 Device: 1 Control)

	WATCHMAN		Control		
	Event Rate (per 100 Pt-yrs)	**Event Rate / Subject**	**Event Rate (per 100 Pt-yrs)**	**Event Rate / Subject**	**Rate Ratio (95% Crl)***
Primary effectiveness	2.2 (40/1788)	8.6% (40/463)	3.7 (34/929)	13.9% (34/244)	0.61 (0.42, 1.07)
Ischemic stroke	1.3 (24/1782)	5.2% (24/463)	1.1 (10/933)	4.1% (10/244)	
Hemorrhagic stroke	0.2 (3/1838)	0.6% (3/463)	1.1 (10/946)	4.1% (10/244)	
Systemic embolism	0.2 (3/1837)	0.6% (3/463)	0.0 (0/949)	0.0% (0/244)	
Death (CV/unexplained)	1.0 (19/1843)	4.1% (19/463)	2.3 (22/949)	9.0% (22/244)	
Ischemic stroke and systemic embolism	1.5 (26/1781)	5.6% (26/463)	1.1 (10/933)	4.1% (10/244)	
Stroke (all)	1.5 (26/1782)	5.6% (26/463)	2.2 (20/929)	8.2% (20/244)	

*Posterior probability >0.999 for non-inferiority and 0.954 for superiority

The Rate Ratio is based on the event rates per 100 pt-yrs

CrI = credible interval

Rate = event rate per 100 patient years (calculated as 100*N events/Total patient-years)

Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate.

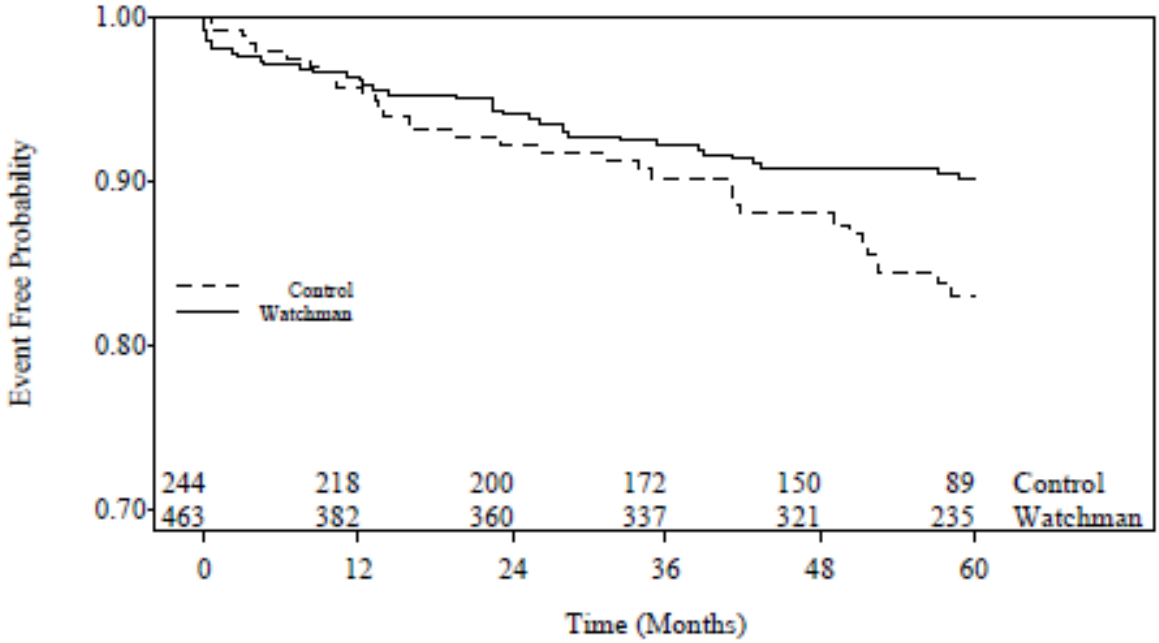

Figure 5: PROTECT AF Primary Effectiveness (2717 patient-years)

PROTECT AF Major Bleeding Analysis

The rates of major bleeding complications, defined as bleeding events adjudicated as serious adverse events, are shown in Table 15. There were more bleeding events in the WATCHMAN group immediately post-procedure through day 45 with a lower rate of bleeding thereafter. The overall major bleeding rates were similar between the WATCHMAN group and the Control group.

Table 15: PROTECT AF Major Bleeding

	WATCHMAN		**Control**	
Major Bleeding	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)
Procedure-related	28/463 (6.0%)	NA	NA	NA
Non-procedure related	24/463 (5.2%)	1.3 (24/1803.7)	29/244 (11.9%)	3.2 (29/904.9)
0-45 days	5/463 (1.1%)	9.2 (5/54.6)	2/244 (0.8%)	6.7 (2/29.7)
46 days – 6 months	4/431 (0.9%)	2.6 (4/153.6)	4/239 (1.7%)	4.6 (4/87.8)
>6 months	15/397 (3.8%)	0.9 (15/1595.5)	23/228 (10.1%)	2.9(23/787.5)
Total major Bleeding	50/463 (10.8%)	2.9 (50/1743.4)	29/244 (11.9%)	3.2 (29/904.9)

PROTECT AF Device Thrombus Rates

The device thrombus-related stroke rate was 0.1 events per 100 patient-years as shown in Table 16.

Table 16: PROTECT AF Device-related Thrombus

	N=408
Thrombus Subjects	16 (3.9%)
Thrombus Events	17
Experienced Ischemic Stroke	2
Experienced Serious Adverse Event	3
Device Thrombus-Related Stroke Rate (per 100 pt-yrs)	0.1

Implant success and discontinuation of warfarin among WATCHMAN subjects

WATCHMAN Device implant success (defined as successful release of the device) was achieved in 408/449 (90.9%) subjects who underwent the implant procedure. Among subjects successfully implanted with the WATCHMAN Device, 87% discontinued warfarin therapy by 45 days, and 93% discontinued warfarin therapy by 12 months.

3. Subgroup Analyses

The primary effectiveness endpoint in the PROTECT AF study results was analyzed for selected subgroups as shown in Table 17. This study was not powered for subgroup analyses, and these results should be considered to be

exploratory. No statistically significant interactions were detected by sex, age, or baseline $CHADS_2$ score. Results by race were not performed due to the small sample sizes.

Table 17: Subgroup Analysis for the PROTECT AF Primary Effectiveness Endpoint

Subgroup	WATCHMAN % (n/N)	Control % (n/N)
Sex		
Female	13.1 (18/137)	13.7 (10/73)
Male	6.7 (22/326)	14.0 (24/171)
Age		
≤72 years	6.4 (15/235)	8.5 (9/106)
>72 years	11.0 (25/228)	18.1 (25/138)
$CHADS_2$		
1-3	7.2 (29/403)	11.2 (23/205)
4-6	18.3 (11/60)	28.2 (11/39)

Table 18 summarizes the relationship between a prior history of ischemic stroke and the incidence of new ischemic stroke observed post-randomization. The data demonstrate patients in both the WATCHMAN and Control groups with a prior ischemic stroke are at a higher risk of recurrent ischemic strokes.

Table 18: PROTECT AF Incidence of Ischemic Stroke or Systemic Embolism by History of Ischemic Stroke

	WATCHMAN % (n/N)	Control % (n/N)
PROTECT AF no prior ischemic stroke	4.5 (19/418)	2.8 (6/212)
PROTECT AF prior ischemic stroke	15.6 (7/45)	12.5 (4/32)

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The PROTECT AF clinical study included 159 investigators, of which none were full-time or part-time employees of the sponsor and 5 of investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 1
- Significant equity interest held by investigator in sponsor of covered study: 1

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

X.2 PREVAIL

A. Study Design

Patients were treated between November 1, 2010 and June 28, 2012. The database for this PMA reflected data collected through June 28, 2014 and included 461 patients with a median follow-up of 26.9 months for a total of 860 patient-years of follow-up. There were 41 investigational sites.

The study was a multicenter, prospective, randomized, controlled pivotal clinical study intended to evaluate the safety and effectiveness of the WATCHMAN LAA Closure Technology in patients with non-valvular atrial fibrillation who are eligible for warfarin therapy. Patients were randomized in a 2:1 ratio to either the WATCHMAN LAA Closure Technology (WATCHMAN group) or long-term warfarin therapy (Control group).

The primary analysis was according to intent-to-treat (ITT) principles, and a Bayesian adaptive design with discounted historical priors based on the PREVAIL-eligible population from PROTECT AF and CAP trials was used for the statistical analysis. The statistical analysis plan called for final analyses after all patients had been followed for at least 6 months. Some analyses were conducted using only data from new subjects enrolled in the PREVAIL study without the prior PROTECT AF study information (that was used in the Bayesian analysis). Analyses based on data from these PREVAIL subjects are referred to as "PREVAIL Only" analyses.

The study utilized an independent Data Safety Monitoring Board (DSMB) to oversee study progress and review clinical data and safety, an independent Clinical Events Committee (CEC) that was responsible for adjudicating all serious adverse events and all adverse events that are potentially related to the procedure or device, and an independent Echocardiography Core Lab for interpreting all echocardiographic data.

1. Clinical Inclusion and Exclusion Criteria

Key eligibility criteria are provided in Table 19.

Table 19: PREVAIL Key Eligibility Criteria

Key Inclusion Criteria
The subject is 18 years of age or older
The subject has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
The subject is eligible for long-term warfarin therapy
The subject has a calculated $CHADS_2$ score of 2 or greater; Subjects with a $CHADS_2$ score of 1 may be included if any of the following apply (consistent with the recommendations presented in the ACC/AHA/ESC 2006

Guidelines for the Management of Patients with Atrial Fibrillation): • The subject is a female age 75 or older • The subject has a baseline LVEF ≥ 30% and < 35% • The subject is age 65-74 and has diabetes or coronary artery disease • The subject is age 65 or greater and has documented congestive heart failure
Key Exclusion Criteria
The subject requires long-term warfarin
The subject is contraindicated for warfarin therapy
The subject is contraindicated or allergic to aspirin
The subject has a history of atrial septal repair or has an ASD/PFO closure device
Key Echo Exclusion Criteria
The subject has LVEF <30%
The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
The subject has a high risk PFO defined as an atrial septal aneurysm (excursion > 15 mm or length > 15 mm) or large shunt (early, within 3 beats and/or substantial passage of bubbles)
The subject has significant mitral valve stenosis
The subject had complex atheroma with mobile plaque of the descending aorta and/or aortic arch
The subject has a cardiac tumor

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 45 days, 6 months, 9 months, 12 months, semi-annually through 3 years and annually through 5 years. The key time points and evaluations conducted at all time points are shown in Table 20.

Table 20: Follow-up schedule of evaluations

Evaluation Requirements	45 Day Visit	6 Month Visit	9 Month Telephone	12 Month Visit	18 month 30 month Telephone	Annual Visits
TEE	Device Group	Device Group		Device Group		
Brain Imaging (CT/MRI)[a]	As required[a]	As required[a]	As required[a]	As required[a]	As required[a]	As required[a]
INR Monitoring[b]	X	X	X	X	X	X
Review Medication Regimen	X	X	X	X	X	X
Vital Signs	X	X		X		X
Neurologist Assessment[c]				X		
NIH Stroke Scale	X	X		X		X
Barthel Index / Modified Rankin	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X

a Brain MRI or CT was required if subject suffered a stroke or TIA

b INR monitoring was required at least every 28 days for as long as a subject is taking warfarin
c Neurology consultation was required at 12 months and if a subject experienced a stroke or TIA throughout the duration of the study

3. Primary Endpoints

The first primary effectiveness endpoint was the 18 month rates of the composite of hemorrhagic stroke, ischemic stroke, systemic embolism or cardiovascular or unexplained death.

The second primary effectiveness endpoint was the 18 month rates of ischemic stroke or systemic embolism excluding the first 7 days post randomization.

A Bayesian approach based on a piecewise exponential model was used to evaluate the first and second primary endpoints based on time to first event. In addition, this approach included prior PROTECT AF historical data from subjects with the same CHADS2 enrollment criteria as the PREVAIL subjects with a discounting weight of 50%.

For the first primary effectiveness endpoint, the non-inferiority success criterion for the WATCHMAN group vs. the control group was a rate ratio of less than 1.75 with posterior probability of at least 97.5% (or equivalently that the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio would be less than 1.75).

For the second primary effectiveness endpoint, the non-inferiority success criterion for the WATCHMAN group vs. the control group was either: (1) a rate ratio of less than 2.0, or (2) a rate difference of less than 0.0275, each with a posterior probability of at least 97.5% (or equivalently that (1) the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio would be less than 2.0 or (2) the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate difference would be less than 0.0275).

The third primary (safety) endpoint was the percentage of WATCHMAN subjects that experienced one of the following events between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Events such as percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and non-surgical treatments of access site complications were not included from this endpoint.

For the third primary endpoint, a Bayesian approach based on a beta-binomial model was used to incorporate historical data from the PROTECT AF study and CAP registry through a prior distribution (without discounting) from subjects with the same CHADS2 score enrollment criteria as the PREVAIL subjects. The third primary endpoint event rate was compared to a performance goal of 2.67%.

B. Accountability of PMA Cohort

Table 21 shows an accounting of follow-up visit attendance of the PREVAIL Only subjects. Visit windows which closed prior to the June 28, 2014 dataset were denoted as 'expected.' Subjects who exited the study due to death or withdrawal were not counted as having expected visits after the date of study exit.

Table 21: Follow-up Visit Attendance

	Device	Control
Visit	**Attended/ Expected (%)**	**Attended/ Expected (%)**
45-Day	259/261 (99%)	132/137 (96%)
6-Month	239/241 (99%)	129/132 (98%)
9-Month	233/237 (98%)	124/128 (97%)
12-Month	234/236 (99%)	119/124 (96%)
18-Month	225/230 (98%)	118/118 (100%)
2 Years	208/211 (99%)	96/99 (97%)
2-1/2 Years	127/129 (98%)	67/69 (97%)
3 Years	61/62 (98%)	26/26 (100%)
Total	1586/1607 (99%)	811/833 (97%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a nonvalvular atrial fibrillation study performed in the US. Patient demographics and risk factors are summarized in Table 22 and Table 23, respectively.

Table 22: PREVAIL Baseline Demographics

Characteristic	**Device N=269**	**Control N=138**	**P-value**
Age (years)	74.0 ± 7.4 (269) (50.0 ,94.0)	74.9 ± 7.2 (138) (53.0 ,90.0)	0.260
Sex			0.146
Female	87/269 (32.3%)	35/138 (25.4%)	
Male	182/269 (67.7%)	103/138 (74.6%)	
Race/Ethnicity			0.603
Asian	1/269 (0.4%)	1/138 (0.7%)	
Black/African American	6/269 (2.2%)	1/138 (0.7%)	
Caucasian	253/269 (94.1%)	131/138 (94.9%)	
Hispanic/Latino	6/269 (2.2%)	5/138 (3.6%)	
Native American Indian/Alaskan Native	1/269 (0.4%)	0/138 (0.0%)	
Other	2/269 (0.7%)	0/138 (0.0%)	

Table 23: PREVAIL Baseline Risk Factors

Characteristic	**Device N=269**	**Control N=138**	**P-value**
$CHADS_2$ Score (Categorical)			0.484
1	21/269 (7.8%)	12/138 (8.7%)	
2	137/269 (50.9%)	62/138 (44.9%)	

Characteristic	Device N=269	Control N=138	P-value
3	65/269 (24.2%)	36/138 (26.1%)	
4	33/269 (12.3%)	21/138 (15.2%)	
5	12/269 (4.5%)	7/138 (5.1%)	
6	1/269 (0.4%)	0/138 (0.0%)	
$CHADS_2$ Score (Continuous)	2.6 ± 1.0 (269) (1.0 ,6.0)	2.6 ± 1.0 (138) (1.0 ,5.0)	0.838
$CHADS_2$ Risk Factors			
CHF	63/269 (23.4%)	32/138 (23.2%)	0.958
History of Hypertension	238/269 (88.5%)	134/138 (97.1%)	0.003
Age ≥ 75	140/269 (52.0%)	78/138 (56.5%)	0.391
Diabetes	91/269 (33.8%)	41/138 (29.7%)	0.401
Previous TIA/Ischemic Stroke	74/269 (27.5%)	39/138 (28.3%)	0.873
CHA_2DS_2 VASc Score (Categorical)			0.300
2	19/269 (7.1%)	7/138 (5.1%)	
3	78/269 (29.0%)	44/138 (31.9%)	
4	95/269 (35.3%)	35/138 (25.4%)	
5	50/269 (18.6%)	37/138 (26.8%)	
6	20/269 (7.4%)	12/138 (8.7%)	
7	6/269 (2.2%)	3/138 (2.2%)	
8	1/269 (0.4%)	0/138 (0.0%)	
CHA_2DS_2 VASc Score (Continuous)	4.0 ± 1.1 (269) (2.0 ,8.0)	4.1 ± 1.2 (138) (2.0 ,7.0)	0.399

D. Safety and Effectiveness Results

1. Third Primary (Safety) Endpoint Results

The third primary endpoint (safety) analysis was based on the intent-to-treat population and was evaluated in WATCHMAN subjects only. The key safety outcomes for this study are presented below in Tables 24 to 27. Of 269 PREVAIL Only subjects randomized to the WATCHMAN group, 6 experienced a third primary endpoint event between the time of randomization and within 7 days of the procedure or by hospital discharge, corresponding to an event rate of 2.2% as shown in Table 24. A description of the 6 subjects with third endpoint events (safety endpoint events) is provided in Table 25. Based on the Bayesian analysis incorporating prior information from PROTECT AF and CAP via a beta-binomial model, the one-sided 95% credible interval upper bound was 2.652%, which met the performance goal of 2.67%. The specific adverse effects are reported in Table 26.

Table 24: PREVAIL Third Primary Endpoint Results (Intent-to-Treat)

WATCHMAN Group		
N Subjects	**% (n/N)**	**95% CrI**
269	2.2% (6/269)	2.652%

CrI is one-sided, N = number, CrI = credible interval

Table 25: Third Primary Endpoint Events by Type Initial Event (Intent-to-Treat)

Device Group		
Type	**N Events**	**% of Subjects**
Device Embolization	2	0.7%
AV Fistula	1	0.4%
Cardiac Perforation	1	0.4%
Pericardial Effusion with Cardiac Tamponade	1	0.4%
Major Bleed Requiring Transfusion	1	0.4%

Adverse effects that occurred in PREVAIL Only subjects:

A summary of all serious adverse events for the WATCHMAN and Control groups is presented in Table 26.

Table 26: PREVAIL Serious Adverse Events

	Device				Control			
Event Type	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**	**Events**	**% of Events**	**Subjects with Events**	**% of Subjects**
AV Fistula	1	1.0	1	0.4	0	0.0	0	0.0
Anemia Requiring Transfusion	3	3.1	3	1.1	0	0.0	0	0.0
Bleeding, Other	0	0.0	0	0.0	2	6.1	2	1.4
Cardiac Perforation	1	1.0	1	0.4	0	0.0	0	0.0
Cranial Bleed	1	1.0	1	0.4	0	0.0	0	0.0
Death	22	22.7	22	8.2	13	39.4	13	9.4
Device Embolization	2	2.1	2	0.7	0	0.0	0	0.0
Device Thrombus	1	1.0	1	0.4	0	0.0	0	0.0
Epistaxis	2	2.1	1	0.4	2	6.1	2	1.4
Gastrointestinal Bleeding	14	14.4	14	5.2	7	21.2	7	5.1
Hematoma	2	2.1	2	0.7	0	0.0	0	0.0
Hematuria	1	1.0	1	0.4	2	6.1	2	1.4
Infection	3	3.1	3	1.1	0	0.0	0	0.0
Major Bleed Requiring Transfusion	4	4.1	4	1.5	1	3.0	1	0.7
Other Study Related	7	7.2	6	2.2	1	3.0	1	0.7
Pericardial Effusion with Cardiac Tamponade	4	4.1	4	1.5	0	0.0	0	0.0
Pseudoaneurysm	1	1.0	1	0.4	0	0.0	0	0.0
Rectal Bleeding	1	1.0	1	0.4	0	0.0	0	0.0

	Device				Control			
Event Type	Events	% of Events	Subjects with Events	% of Subjects	Events	% of Events	Subjects with Events	% of Subjects
Respiratory Failure	2	2.1	2	0.7	0	0.0	0	0.0
Respiratory Insufficiency	1	1.0	1	0.4	0	0.0	0	0.0
Stroke - Hemorrhagic	2	2.1	2	0.7	2	6.1	2	1.4
Stroke - Ischemic	14	14.4	13	4.8	1	3.0	1	0.7
Subdural Hematoma	2	2.1	2	0.7	0	0.0	0	0.0
Systemic Embolism	1	1.0	1	0.4	0	0.0	0	0.0
Transient Ischemic Attack (TIA)	5	5.2	4	1.5	2	6.1	2	1.4

2. Effectiveness Results

The analyses of effectiveness (first and second primary endpoints) was based on the intent-to-treat to treat population and utilized a Bayesian approach that combined data collected from PREVAIL Only subjects with 50% discounted historical data from the PREVAIL-eligible subjects randomized in the PROTECT AF study. There were two analyses of the PREVAIL trial results: (1) a pre-specified dataset lock in January 2013 and (2) an updated dataset lock in June 2014. The January 2013 pre-specified analyses were based on the data available after all PREVAIL Only subjects had reached 6 months of follow-up; the mean follow-up post-randomization in January 2013 was 11.8±5.8 months, and 113 of 407 (28%) randomized subjects reached or passed the window for their 18-month follow-up visit, In the updated June 2014 dataset, the mean follow-up duration for PREVAIL Only subjects was 25.9±9.7 months, and all randomized subjects reached or passed the window for their 18-month follow-up visit [and 310 randomized subjects (76%) reached or passed the window for their 24-month follow-up visit]. The subject follow-up from PROTECT AF and PREVAIL that contributed to each dataset is summarized in Table 27.

Table 27: Total Patient-Years for PREVAIL Only Subjects and Prior Data Borrowed from PROTECT AF With 50% Discount

Dataset	PREVAIL Only data in pt-yrs			PROTECT AF Prior Information in pt-yrs		
	WATCHMAN	Control	Total	WATCHMAN	Control	Total
January 2013	256.2	140.0	396.2	395.3	223.5	618.8
June 2014	562.6	297.7	860.3	395.3	223.5	618.8

First Primary Endpoint

Results of the Bayesian analysis for the first primary endpoint of all stroke, systemic embolism, and death (cardiovascular or unexplained) are shown in Table 28. The 18-month rate is the model-based probability of an event occurring within 18 months. In the January 2013 Bayesian analysis, the 18-month event rate was 0.064 for the WATCHMAN group and 0.063 for the control group. The Bayesian estimate for the 18-month rate ratio was 1.07 with a 95% credible interval of 0.57 to 1.89. The upper bound of 1.89 was not lower than the non-inferiority margin of 1.75 defined in the statistical analysis plan; therefore, the non-inferiority criterion was *not* met (posterior probability of non-inferiority was 95.69%). In the June 2014 Bayesian analysis, the 18-month rate was 0.065 for the Device group and 0.057 for the Control group. The Bayesian estimate for the 18-month rate ratio was 1.21 with a 95% credible interval of 0.69 to 2.05. Since the upper bound of 2.05 was not lower than the non-inferiority margin of 1.75 defined in the statistical analysis plan, the non-inferiority criterion was not met (posterior probability of non-inferiority was 92.6%).

Table 29 shows the individual event rates of the composite endpoint for subjects enrolled in the PREVAIL Only subjects. The ischemic stroke rate (2.3 vs. 0.3) favored to the Control group, while the hemorrhagic stroke rate (0.4 vs. 0.7) and death (cardiovascular or unexplained) rate (1.4 vs. 2.3) favored the WATCHMAN group. The primary effectiveness endpoint analysis from the June 2014 dataset for the PREVAIL Only subjects is shown as time to event in a Kaplan-Meier curve in Figure 6.

Table 28: PREVAIL First Primary Endpoint Results (Intent-to-Treat)

Bayesian Approach	**WATCHMAN 18-Month Rate**	**Control 18-Month Rate**	**18-Month Rate Ratio (95% CrI)**	**Posterior Probability of NI**	**Rate Ratio NI Criterion 95% CrI Upper Bound <1.75 (Post Probability ≥ 97.5%)**
Prior PROTECT AF information (618.8 pt-yrs) + PREVAIL Only January 2013 Dataset (396.2 pt-yrs)	0.064	0.063	1.07 (0.57, 1.89)	95.69%	No
Prior PROTECT AF information (618.8 pt-yrs) + PREVAIL Only June 2014 Dataset (860.3 pt-yrs)	0.065	0.057	1.21 (0.69, 2.05)	92.60%	No

CrI = credible interval, NI = non-inferiority

Table 29: PREVAIL Effectiveness Results and % of subjects who experienced 1 or more events – June 2014 Dataset (PREVAIL Only Subjects)

Randomization Allocation (2 Device: 1 Control)

	WATCHMAN	**Control**

Component of First Primary Endpoint	Event Rate (per 100 Pt-yrs)	Event Rate / Subject	Event Rate (per 100 Pt-yrs)	Event Rate / Subject
Stroke - Ischemic	2.3 (13/565)	4.8% (13/269)	0.3 (1/298)	0.7% (1/138)
Stroke - Hemorrhagic	0.4 (2/577)	0.7% (2/269)	0.7 (2/300)	1.4% (2/138)
Systemic Embolism	0.2 (1/577)	0.4% (1/269)	0.0 (0/300)	0.0% (0/138)
Death (Cardiovascular or Unexplained)	1.4 (8/578)	3.0% (8/269)	2.3 (7/300)	5.1% (7/138)
Ischemic Stroke and Systemic Embolism	2.5 (14/563)	5.2% (14/269)	0.3 (1/298)	0.7% (1/138)
All stroke	2.7 (15/564)	5.6% (15/269)	1.0 (3/298)	2.2% (3/138)

Figure 6: PREVAIL Only Subjects – First Primary Endpoint Event

Second Primary Endpoint

Results of the Bayesian analysis for the second primary endpoint are shown in Table 30. The 18-month rate is the model-based probability of an event occurring within 18 months. In the January 2013 Bayesian analysis, the 18-month rate was 0.0253 for the WATCHMAN group and 0.0200 for the control group. The non-inferiority criterion was met for the rate difference of 0.0053 with an upper bound of 0.0273, which was less than the allowable 95% upper credible interval upper bound of 0.0275. The non-inferiority criterion was not met for the rate ratio of 1.6 with an upper bound of 4.2, which exceeded the allowable 95% credible interval upper bound of 2.0.

In the June 2014 Bayesian analysis, the 18-month rate was 0.0294 for the WATCHMAN group and 0.0131 for the control group. The non-inferiority criterion was not met for either the rate difference (0.0163 with an upper bound of 0.0342, which exceeded the allowable 95% upper credible interval upper bound of 0.0275) or the rate ratio (2.8 with an upper bound of 7.3, which exceeded the allowable 95% credible interval upper bound of 2.0). The posterior probability of non-inferiority was 37.3% for the rate ratio and 89.5% for the rate difference, not meeting the criterion of 97.5%.

The second primary effectiveness endpoint for the PREVAIL Only subjects (June 2014 dataset) is shown as time to event analysis in a Kaplan Meier curve in Figure 7.

Table 30: PREVAIL Second Primary Endpoint Results (Intent-to-Treat)

	Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	18-Month Rate Difference (95% CrI)	Rate Ratio Non-Inferiority Criterion or Rate Difference Non-Inferiority Criterion 95% CrI Upper Bound <0.0275
Prior information (618.8 pt-yrs) + PREVAIL January 2013	0.0253	0.0200	1.6 (0.5, 4.2)	0.0053 (-0.0190, 0.0273)	Yes

Dataset (396.2 pt-yrs)					
Prior information (618.8 pt-yrs) +PREVAIL June 2014 Dataset (860.3 pt-yrs)	0.0294	0.0131	2.8 (0.9,7.3)	0.0163 (-0.0023, 0.0342)	No

CrI = credible interval

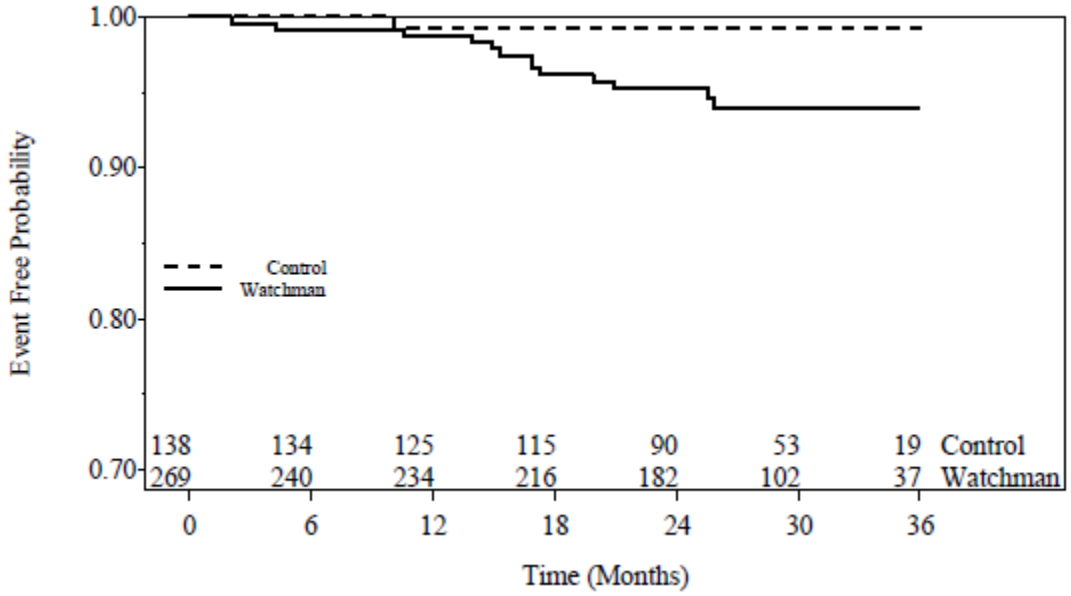

Figure 7: PREVAIL Only Subjects – Second Primary Endpoint Event

PREVAIL Major Bleeding Analysis

The rates of major bleeding complications, defined as events adjudicated as serious adverse events, are shown in Table 31. There were more bleeding events in the WATCHMAN group (compared to the Control group) immediately post-procedure through 6 months with a lower rate of new bleeding events beyond 6 months. The overall major bleeding rates were similar between the WATCHMAN group and the Control group.

Table 31: PREVAIL-Only Major Bleeding

	WATCHMAN		**Control**	
	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)	N Events/ Subjects (%)	Rate (N Events/ Total Pt-Yrs)
Procedure-related	12/269 (4.5%)	NA	NA	NA
Non-procedure related	20/269 (7.4%)	3.6 (20/550.1)	14/138 (10.1%)	5.0 (14/282.1)
0-45 days	8/269 (3.0%)	25.0 (8/31.9)	0/138 (0.0%)	0.0 (0/16.9)
46 days – 6 months	7/269 (2.6%)	7.9 (7/88.6)	3/138 (2.2%)	6.0 (3/50.4)
>6 months	5/269 (1.9%)	1.2 (5/429.6)	11/138 (8.0%)	5.1 (11/214.8)
Total major bleeding	29/269 (10.8%)	5.5 (29/531.1)	14/138 (10.1%)	5.0 (14/282.1)

PREVAIL Device Thrombus Rates

The device thrombus-related stroke rate was 0.2 events per 100 patient-years as shown in Table 32.

Table 32: PREVAIL Only Device-related Thrombus

	N=252
Thrombus Subjects	15 (6.0%)
Thrombus Events	16
Experienced Ischemic Stroke	1
Experienced Serious Adverse Event	1
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.2

Implant success and discontinuation of warfarin among WATCHMAN subjects

WATCHMAN Device implant success (defined as successful release of the device) was achieved in 252/265 (95%) subjects who underwent the implant procedure. Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 92% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

3. Subgroup Analyses

The PREVAIL Only study primary effectiveness endpoint results were analyzed for selected subgroups (Table 33), The study was not powered for subgroup analyses, and these results should be considered to be exploratory. No statistically significant interactions were detected by sex, age, or baseline $CHADS_2$ score. Results by race were not performed due to the small sample sizes.

Table 33: Subgroup Analysis for the PREVAIL First Primary Effectiveness Endpoint

Subgroup	WATCHMAN % (n/N)	Control % (n/N)
Sex		
Female	3.4% (3/87)	5.7% (2/35)
Male	11.5% (21/182)	6.8% (7/103)
Age		
≤72 years	6.4% (7/109)	6.1% (3/49)
>72 years	10.6% (17/160)	6.7% (6/89)
$CHADS_2$		
1-3	7.6% (17/223)	3.6% (4/110)
4-6	15.2% (7/46)	17.9% (5/28)

Table 34 summarizes the relationship between a prior history of ischemic stroke and the incidence of new ischemic stroke observed post-randomization. The data

demonstrate patients in both the WATCHMAN and Control groups with a prior ischemic stroke are at a higher risk of recurrent ischemic strokes.

Table 34: PREVAIL Incidence of Ischemic Stroke or Systemic Embolism by History of Ischemic Stroke

	WATCHMAN % (n/N)	Control % (n/N)
PREVAIL- no prior ischemic stroke	4.1 (9/217)	0.0 (0/112)
PREVAIL- prior ischemic stroke	9.6 (5/52)	3.8 (1/26)

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The PREVAIL clinical study included 92 investigators of which none were full-time or part-time employees of the sponsor and 4 of investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 2
- Proprietary interest in the product tested held by the investigator: 1
- Significant equity interest held by investigator in sponsor of covered study: 1

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

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

XI.1 CAP Registry

Primary Objective: To collect additional safety and effectiveness data on the WATCHMAN Device in subjects with non-valvular atrial fibrillation who are deemed by their physicians to be suitable for warfarin therapy.

Design: The CAP registry is a multi-center prospective, non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Up to 30 investigative centers with prior WATCHMAN Device experience in the PROTECT AF study were allowed to participate. Study participants were required to be at least 18 years of age with non-valvular atrial fibrillation, a $CHADS_2$ score of 1 or greater, and be

eligible for long-term warfarin therapy. Following baseline evaluation and device implantation, subjects were seen at 45 days, 6, 9, and 12 months and semi-annually thereafter through 5 years.

The endpoints of the CAP registry were similar to those in the PROTECT AF study, but there were no pre-defined statistical hypotheses. The primary effectiveness endpoint was the rate of the composite of stroke (ischemic or hemorrhagic), systemic embolism, and cardiovascular or unexplained death. The primary safety endpoint was the rate of life-threatening events as determined by the CEC, which included device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeding requiring transfusion, and any bleeding related to the device or procedure that necessitated a surgical procedure.

Enrollment: A total of 26 centers (24 U.S., 2 European) participated by enrolling at least one subject. A total of 566 subjects were enrolled. The average $CHADS_2$ score was 2.5±1.2, the mean CHA_2DS_2-VASc score was 3.9±1.5, the mean age was 74 years, and 66% of subjects were male as shown in Table 35 and Table 36.

Table 35: CAP Registry Baseline Demographics

Characteristic	**Mean±SD (N) Min,Max or N/Total (%)**
Age (years)	74.0 ± 8.3 (566) 44.0, 94.0
Sex	
Female	195/566 (34.5%)
Male	371/566 (65.5%)
Race/Ethnicity	
Asian	9/566 (1.6%)
Black/African American	11/566 (1.9%)
Caucasian	520/566 (91.9%)
Hispanic/Latino	20/566 (3.5%)
Hawaiian/Pacific Islander	1/566 (0.2%)
Other	5/566 (0.9%)

Table 36: CAP Registry Baseline Risk Factors

Characteristic	**Mean±SD (N) Min,Max or N/Total (%)**
$CHADS_2$ Score (Categorical)	
1	131/566 (23.1%)
2	200/566 (35.3%)
3	122/566 (21.6%)
4	77/566 (13.6%)
5	32/566 (5.7%)
6	4/566 (0.7%)
$CHADS_2$ Score (Continuous)	2.5 ± 1.2 (566) 1.0, 6.0
CHA_2DS_2-VASc Score (Categorical)	
1	23/564 (4.1%)
2	71/564 (12.6%)

Characteristic	Mean±SD (N) Min,Max or N/Total (%)
3	152/564 (27.0%)
4	149/564 (26.4%)
5	83/564 (14.7%)
6	53/564 (9.4%)
7	28/564 (5.0%)
8	4/564 (0.7%)
9	1/564 (0.2%)
CHA_2DS_2-VASc Score (Continuous)	3.9 ± 1.5 (564) 1.0, 9.0
Risk Factors	
CHF	108/566 (19.1%)
Hypertension	503/565 (89.0%)
Diabetes	141/566 (24.9%)
Stroke/TIA	172/566 (30.4%)
Previous MI	79/566 (14.0%)
LVEF 40% or Less	43/565 (7.6%)
Age <65	61/566 (10.8%)
Age 65-75	212/566 (37.5%)
Age >75	293/566 (51.8%)

Results: For the primary effectiveness endpoint, a rate of 2.6 events/100 patient-years was observed, with cardiovascular or unexplained death and ischemic stroke being the two most common events over a mean follow-up duration of 44 months as shown in Table 37 and Table 38.

Table 37: CAP Primary Effectiveness Endpoint

Event Type	Rate Per 100 Pt-yrs (N Events/Pt-yrs)	(95% CI)
Primary Effectiveness	2.6 (53/2021.8)	2.0, 3.4

Table 38: CAP Events Contributing to Primary Effectiveness Endpoint

Type	N Events	% of Subjects
Death (Cardiovascular or Unexplained)	25	4.4%
Stroke - Ischemic	24	4.2%
Stroke - Hemorrhagic	2	0.4%
Systemic Embolism	1	0.2%

*Implant success and discontinuation of warfarin among WATCHMAN subject*s: The WATCHMAN Device was successfully implanted in 534/566 (94%) subjects. Among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 96% discontinued warfarin therapy by 45 days, and 96% discontinued warfarin therapy by 12 months.

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN is presented in Table 39.

Table 39: CAP Registry Serious Adverse Events

Event	Number of Events	Number of Subjects	% of Subjects
Death	80	80	14.1%
Stroke - Ischemic	28	24	4.2%
Stroke - Hemorrhagic	3	2	0.4%
Systemic Embolization	1	1	0.2%
Gastrointestinal Bleeding	66	42	7.4%
Other Study Related	22	20	3.5%
Transient Ischemic Attack (TIA)	13	11	1.9%
Major Bleed Requiring Transfusion	9	8	1.4%
Pericardial Effusion with Cardiac Tamponade	7	7	1.2%
Anemia Requiring Transfusion	5	4	0.7%
Pericardial Effusion	5	5	0.9%
Pseudoaneurysm	5	5	0.9%
Prolonged Bleeding from a Laceration	3	3	0.5%
Cranial Bleed	2	2	0.4%
Epistaxis	2	2	0.4%
Hematuria	2	2	0.4%
Ventricular Tachyarrhythmia	2	2	0.4%
Arrhythmias	1	1	0.2%
Bruising - Hematoma	1	1	0.2%
Cardiac Perforation	1	1	0.2%
Chest Pain/Discomfort	1	1	0.2%
Device Embolization	1	1	0.2%
Device Thrombus	1	1	0.2%
Rectal Bleeding	1	1	0.2%

CAP Device Thrombus Rates

The device thrombus-related stroke rate was 0.05 events per 100 patients as shown in Table 40.

Table 40: CAP Device-related Thrombus

	N=534
Thrombus Subjects	12 (2.2%)
Thrombus Events	19
Experienced Ischemic Stroke	1
Experienced Serious Adverse Event	1
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.05

XI.2 CAP2 Registry

Primary Objective: To collect additional safety and effectiveness data on the WATCHMAN Device in subjects with non-valvular atrial fibrillation who are deemed by their physicians to be suitable for warfarin therapy.

Design: The CAP Registry is a multi-center prospective, non-randomized study allowing continued access to the WATCHMAN Device during regulatory review of the pre-market application for the WATCHMAN Device. Up to 60 investigative centers with prior WATCHMAN experience in the PROTECT AF or PREVAIL studies were allowed to participate. Study participants were required to be at least 18 years of age with non-valvular atrial fibrillation, be eligible for long-term warfarin therapy, and have a $CHADS_2$ score of at least 2. Subjects with a $CHADS_2$ score of 1 were also permitted to enroll if they had any of the following characteristics (consistent with the recommendations presented in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation):

- The subject was female age 75 or older.
- The subject had a baseline LVEF ≥30 and <35%.
- The subject was age 65-74 and had diabetes or coronary artery disease.
- The subject was age 65 or greater and had documented congestive heart failure.

Following baseline evaluation and device implantation, subjects were seen at 45 days, 6 and 12 months, semi-annually through 3 years and annually thereafter through 5 years.

The endpoints of the CAP2 registry were similar to those used in the PREVAIL study, but there were no pre-defined hypotheses. There were three primary endpoints (two effectiveness and one safety) as follows: 1) the rate of the composite of stroke (including hemorrhagic and ischemic), systemic embolism, and cardiovascular or unexplained death; 2) the rate of the composite of ischemic stroke and systemic embolism, excluding events occurring in the first 7 days following implantation; and 3) the occurrence of all-cause mortality, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular intervention between the time of randomization and 7 days of the procedure or by hospital discharge, whichever is later.

Demographics: A total of 47 U.S. investigational sites actively participated by enrolling at least one subject in the study. A total of 579 subjects were enrolled. The average $CHADS_2$ score was 2.7±1.1, the mean CHA_2DS_2-VASc score was 4.5 ± 1.3, the mean age was 75 years, and 61% of subjects were male as shown in Table 41 and Table 42.

Table 41: CAP2 Registry Baseline Demographics

Characteristic	
Age at Enrollment (years)	75.3±8.0 (576) (33.0, 94.0)
Sex	
Female	39.4% (227/576)
Male	60.6% (349/576)
Race	
American Indian or Alaskan	0.3% (2/576)
Asian	0.7% (4/576)

Characteristic	
Black/African American	1.2% (7/576)
Caucasian	94.1% (542/576)
Hispanic/Latino	2.1% (12/576)
Hawaiian/Pacific Islander	0.0% (0/576)
Other	0.7% (4/576)

Table 42: CAP2 Registry Baseline Risk Factors

Characteristic	
$CHADS_2$ Score (Categorical)	
1	6.8% (39/576)
2	46.2% (266/576)
3	24.3% (140/576)
4	15.8% (91/576)
5	5.9% (34/576)
6	1.0% (6/576)
$CHADS_2$ Score (Continuous)	2.7±1.1 (576) (1.0, 6.0)
$CHADS_2$ Risk Factors	
CHF	27.1% (156/576)
History of Hypertension	92.5% (533/576)
Age ≥ 75	59.7% (344/576)
Diabetes	33.7% (194/576)
History of TIA / Ischemic Stroke	29.0% (167/576)
CHA_2DS_2-VASc Score (Categorical)	
1	0.0% (0/576)
2	1.7% (10/576)
3	21.9% (126/576)
4	32.5% (187/576)
5	22.2% (128/576)
6	13.9% (80/576)
7	5.2% (30/576)
8	2.3% (13/576)
9	0.3% (2/576)
CHA_2DS_2-VASc Score (Continuous)	4.5±1.3 (576) (2.0, 9.0)

Values presented are mean ± standard deviation, n (minimum, maximum) or number of subjects/total number of subjects (%) as appropriate

The CAP2 Registry is ongoing. Current follow-up of the 579 subjects is 332 patient-years.

Results

First Primary Endpoint: A rate of 3.3 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 7 months as shown in Table 43 and Table 44.

Table 43: CAP2 First Primary Endpoint

Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI for Rate
3.3 (11/329.5)	(1.9, 5.6)

Table 44: CAP2 Events Contributing to First Primary Endpoint

Endpoint Event Type	N Events	% of Subject
Stroke - Ischemic	9	1.6%
Stroke - Hemorrhagic	0	0.0%
Systemic Embolism	2	0.3%
Cardiovascular/Unexplained Death	0	0.0%

Second Primary Endpoint: A rate of 2.7 events/100 patient-years was observed, with ischemic stroke being the most common event over a mean follow-up duration of 7 months as shown in Table 45 and Table 46.

Table 45: CAP2 Second Primary Endpoint

Rate Per 100 Pt-yrs (N Events/Pt-yrs)	95% CI for Rate
2.7 (9/329.7)	(1.5, 4.8)

Table 46: CAP2 Events Contributing to Second Primary Endpoint

Endpoint Event Type	N Events	% of Subjects N=579
Stroke - Ischemic	7	1.2%
Systemic Embolism	2	0.3%

Third Primary Endpoint: Five subjects experienced a third primary endpoint event between time of enrollment and within 7 days of procedure or by hospital discharge corresponding to an event rate of 0.9% as shown in Table 47 and Table 48.

Table 47: CAP2 Third Primary Endpoint

% (n/N)	95% CI
0.9% (5/579)	[0.3%, 2.0%]

Table 48: CAP2 Events Contributing to Third Primary Endpoint

Type	N Events	% of Subjects
Cardiac Perforation	3	0.5%
Stroke (Ischemic)	1	0.2%
Death	1	0.2%

Implant success and discontinuation of warfarin among WATCHMAN subjects: The WATCHMAN Device was successfully implanted in 545/575 (95%) subjects (no implant attempt in 4 subjects). The CAP2 Registry is ongoing and data collection is ongoing; however, among subjects successfully implanted with the WATCHMAN Device and followed for at least 12 months, 98% discontinued warfarin therapy by 45 days, and 99% discontinued warfarin therapy by 12 months.

Serious Adverse Events: A summary of all serious adverse events for the WATCHMAN is presented in Table 49.

Table 49: CAP2 Registry Serious Adverse Events

Type	N Events	% (N Pats with Event /579)
Death - Non-cardiovascular	2	0.3% (2/579)
Stroke (Ischemic)	6	1.0% (6/579)
Systemic Embolism	2	0.3% (2/579)
Gastrointestinal Bleeding	3	0.5% (3/579)
Other (Study Related)	11	1.7% (10/579)
Transient Ischemic Attack (TIA)	2	0.3% (2/579)
Major Bleed Requiring Transfusion	13	2.2% (13/579)
Pericardial Effusion with Cardiac Tamponade	8	1.2% (7/579)
Anemia Requiring Transfusion	1	0.2% (1/579)
Pericardial Effusion	3	0.5% (3/579)
Pseudoaneurysm	1	0.2% (1/579)
Hematuria	3	0.5% (3/579)
Arrhythmias	1	0.2% (1/579)
Hematoma	2	0.3% (2/579)
Subdural Hematoma	3	0.5% (3/579)
Cardiac Perforation	3	0.5% (3/579)
Device Thrombus (thrombus on the atrial facing side of the device)	5	0.9% (5/579)
Respiratory Failure	2	0.3% (2/579)
Oral Bleeding	2	0.3% (2/579)

Type	N Events	% (N Pats with Event /579)
Bleeding from Varicose Veins	1	0.2% (1/579)
Bleeding, Other	1	0.2% (1/579)
Respiratory Insufficiency	1	0.2% (1/579)
Valvular Damage	1	0.2% (1/579)
Infection	1	0.2% (1/579)

CAP2 Device Thrombus Rates

The device thrombus-related stroke rate was 0.9 events per 100 patients as shown in Table 50.

Table 50: CAP2 Device-related Thrombus

	N=545
Thrombus Subjects	10 (2.2%)
Thrombus Events	10
Experienced Ischemic Stroke	3
Experienced Serious Adverse Event	5
Device Thrombus-related Stroke Rate (per 100 pt-yrs)	0.9

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

A. Panel Meeting Recommendations

An advisory panel meeting was held on December 11, 2013. At this meeting, the Circulatory System Device Panel voted 13-1 that there is reasonable assurance the device is safe, 13-1 that there is reasonable assurance that the device is effective, and 13-1 that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. Information from this advisory meeting can be found on FDA's website at the following:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM378634.pdf.
After the first advisory panel meeting, new clinical data and information regarding associated adverse events including stroke was received by FDA, prompting the scheduling of a second advisory panel meeting.

At the second advisory panel meeting held on October 8, 2013, the Circulatory System Devices Panel voted 12-0 that there is reasonable assurance the device is safe, 7-6 (with the panel chair acting as a tiebreaker) that there is not a reasonable assurance of effectiveness, and 6-5 (1 abstention) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. Several panelists noted that part of their positive vote was based on anticipation of a more limited, revised indication, or that they would have voted positively had the indication been limited to a more specific patient population. Information from this advisory meeting can be found on FDA's website at the following:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM418653.pdf

B. FDA's Post-Panel Action

Despite the split panel vote at the October 8, 2014 panel meeting, the comments from panel members made it clear that the panel believed that approval of this device with a revised indication would be appropriate and in the interest of public health. FDA worked interactively with the sponsor to revise the indications for use from what was presented at the October 8, 2014 panel meeting to the current indications for use.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the PROTECT AF study, the pre-specified Bayesian analyses showed that there was a >99.9% posterior probability that the WATCHMAN LAA Closure Technology was non-inferior to warfarin and a 95.4% posterior probability that the WATCHMAN LAA Closure Technology was superior to warfarin for the primary effectiveness endpoint (composite of all stroke, systemic embolism, and cardiovascular or unexplained death). The criteria for non-inferiority and superiority of the WATCHMAN Device vs. the Control group were met, and were driven by the rates of hemorrhagic stroke and cardiovascular or unexplained death in favor of the WATCHMAN group. The ischemic stroke rate numerically favored the Control group. The overall major bleeding rates were similar between the WATCHMAN group and the Control group. Although the WATCHMAN device met the primary effectiveness endpoint in PROTECT AF, there were concerns regarding the clinical study execution and the robustness of the data analyses such that additional clinical data were needed to demonstrate a reasonable assurance of WATCHMAN safety and effectiveness.

There were two analyses of the PREVAIL trial results: (1) a pre-specified dataset lock in January 2013 and (2) an updated dataset lock in June 2014. Both analyses demonstrated that the non-inferiority criterion was not met for the first primary endpoint. For the second primary endpoint, non-inferiority was met in the January 2013 Bayesian analysis, but not the June 2014 Bayesian analysis. In an analysis of PREVAIL Only subjects, the ischemic stroke rate favored the Control group, while the hemorrhagic stroke rate and death (cardiovascular or unexplained) rates favored the WATCHMAN group. The overall major bleeding rates were similar between the WATCHMAN group and the Control group.

The randomized studies demonstrate that the WATCHMAN device provide less protection from ischemic stroke than warfarin. However, the rates of hemorrhagic stroke and cardiovascular or unexplained death favored the WATCHMAN group, and there were similar rates of major bleeding events in the WATCHMAN and Control groups.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical studies conducted to support PMA approval as described above. The results from the nonclinical laboratory and animal studies performed on the WATCHMAN LAA Closure Technology demonstrate that this device is suitable for long-term implant. The potential risks associated with the device include procedure-related complications such as cardiac tamponade, device embolization requiring retrieval, and procedure-related major bleeding complications. The primary safety endpoint in PREVAIL (third primary endpoint) demonstrated an acceptable rate of major procedure-related complications, and the peri-procedural event rate met the pre-specified performance goal.

C. Benefit-Risk Conclusions

The probable risks of the WATCHMAN device include procedure-related serious adverse events (such as cardiac tamponade, device embolization requiring retrieval, and procedure-related major bleeding complications) and an increased risk of ischemic stroke and systemic embolism compared to warfarin.

The probable benefits of the device include a reduced risk of thromboembolism from the left atrial appendage and the ability for patients to discontinue of warfarin (following successful closure of the left atrial appendage orifice) resulting in a reduced risk of long-term bleeding complications (which may include a reduction in the risk of hemorrhagic stroke) associated with warfarin use.

In conclusion, given the available information above, the data show that for percutaneous, transcatheter closure of the left atrial appendage in patients meeting the criteria described in the indications for use statement, the probable benefits of the WATCHMAN device outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the WATCHMAN LAA Closure Technology to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc[1] scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

XIV. CDRH DECISION

CDRH issued an approval order on March 13, 2015. The final conditions of approval cited in the approval order are described below.

1. ***Continued Follow-up of IDE Cohorts*:** The study will consist of all IDE patients from PREVAIL, CAP, and CAP2 who are currently enrolled and alive.

The study objective is to characterize the safety and effectiveness of the WATCHMAN LAA Closure Technology annually through 5 years post-procedure. For continued follow-up of patients from CAP, the safety and effectiveness endpoints are listed in the protocol as follows: The primary effectiveness endpoint is the successful treatment of the patient without stroke (including ischemic or hemorrhagic), systemic embolism, and cardiovascular or unexplained death. The primary safety endpoint is treatment of the patient without the occurrence of life-threatening events as determined by the Clinical Events Committee, which would include events such as device embolization requiring retrieval, bleeding events such as pericardial effusion requiring drainage, cranial bleeding events due to any source, gastrointestinal bleeds requiring transfusion and any bleeding related to the device or procedure that necessitates an operation.

For continued follow-up of patients from PREVAIL and CAP2, the primary endpoints are listed in the protocol as follows: The first primary endpoint is the occurrence of the composite of stroke (including ischemic or hemorrhagic), systemic embolism, and cardiovascular or unexplained death. The second primary endpoint is the occurrence of ischemic stroke or systemic embolism, excluding the first 7 days post randomization. Additional outcomes which should be reported include complete LAA closure rate, effective LAA closure rate, warfarin discontinuation rate, warfarin or other oral anticoagulation resumption rate and reasons, and information regarding device thrombus (including event rate, treatment, and any associated adverse events).

All available patients in CAP will be followed semi-annually through 5 years. All available patients in PREVAIL and CAP2 will be followed at post-enrollment intervals of 45 days, 6 months, 12 months, semi-annually through 3 years, and thereafter annually through 5 years.

2. ***WATCHMAN New Enrollment Study***: The study will assess whether the rates of safety and effectiveness during the early commercialization of the WATCHMAN device in the United States are consistent with the premarket findings. This will be a prospective, single-arm study comprised of 1,000 participants implanted with the WATCHMAN device and consented to two years of clinical follow-up. The applicant has agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance (annually from years three through five years post-implant).

   Each of the following three primary endpoints must be met separately per the pre-specified performance goals in order to declare study success, where the upper bound of the 95% confidence interval for the event rates for the first, second, and third primary endpoints must be lower than 9.6%, 6.6% and 2.66%, respectively. The first primary endpoint is the occurrence of the composite of stroke (including ischemic or hemorrhagic), systemic embolism, and cardiovascular or unexplained death at 24 months from the time of enrollment. The second primary endpoint is the occurrence of ischemic stroke or systemic embolism at 24 months from the time of enrollment. The third primary endpoint is the occurrence of one of the following events between the time of implant and within seven days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or

procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications will not be included in the assessment of the third primary endpoint, but the rates of these events should be calculated. Secondary endpoints include the following to be collected in the prospective cohort study: (1) implant success rate, procedural safety, and effective closure of the orifice of the left atrial appendage; and (2) CMS claims-identified occurrence of all stroke (including ischemic or hemorrhagic).

Should the left atrial appendage closure (LAAC) National Cardiovascular Device Registry (NCDR) be used for post-approval data collection, pre-procedure, peri-procedure, post-procedure, discharge, 45-day, 12-month, and 24-month follow-up will be nested within the NCDR registry with linkage of the data to CMS claims as described above.

3. ***WATCHMAN Novel Surveillance***: The applicant will support and actively participate as a stakeholder in the left atrial appendage closure (LAAC) National Cardiovascular Device Registry (NCDR) registry and undertake such activities to ensure that surveillance occurs through 12 months post-implant within the registry for the WATCHMAN LAAC in at least 1,000 serially implanted patients not participating in the *New Enrollment Study.* The applicant has agreed to link the data to Centers for Medicare and Medicaid Services (CMS) database for long-term surveillance (annually through five years post-implant).

   This surveillance should monitor registry collected data (including: implant success rate, procedural safety, effective closure of the orifice of the left atrial appendage, and stroke [including ischemic or hemorrhagic] through one- year post-implant] and CMS claims identified occurrence of all stroke (including ischemic or hemorrhagic).

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1] January CT, Wann LS, Alpert JS, et. al., 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, Circulation, 2014; 130: e199-e267.

[2] FDA Guidance for Industry and Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment, August 2008.