Summary of Safety and Effectiveness

1 General Information

Device Generic Name:	WATCHMAN® LAA Closure Technology
Device Trade Name:	WATCHMAN® LAA Closure Device (Implant) WATCHMAN® Delivery System WATCHMAN® Access System WATCHMAN® Obturator (Optional Accessory)
Applicant's Name and Address:	ATRITECH Inc. 3750 Annapolis Lane N., Suite #105 Plymouth, MN 55447
Date(s) of Panel Recommendation:	TBD
Premarket Approval Application (PMA) Number:	TBD
Date of Notice of Approval to Applicant:	TBD

2008-4434161-05

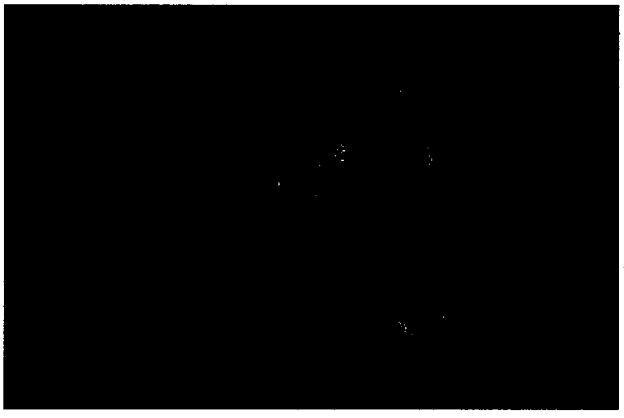
2 Indications for Use

The WATCHMAN® Left Atrial Appendage (LAA) Closure Technology is intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation. The WATCHMAN LAA Closure Technology is designed to prevent embolization of thrombi that may form in the LAA, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism.

3 Device Description

The WATCHMAN LAA Closure Device (**Figure 3-1**) is designed to be permanently implanted at or slightly distal to the ostium (opening) of the LAA.

Figure 3-1. WATCHMAN LAA Closure Device *in situ*



WATCHMAN LAA Closure Technology consists of:

- WATCHMAN® LAA Closure Device (also referred to as "WATCHMAN Device" and "Device")
- WATCHMAN® Delivery System (consisting of Delivery Catheter and loaded Device)
- WATCHMAN® Access System (consisting of Access Sheath and Dilator)
- WATCHMAN® Obturator (Optional Accessory)

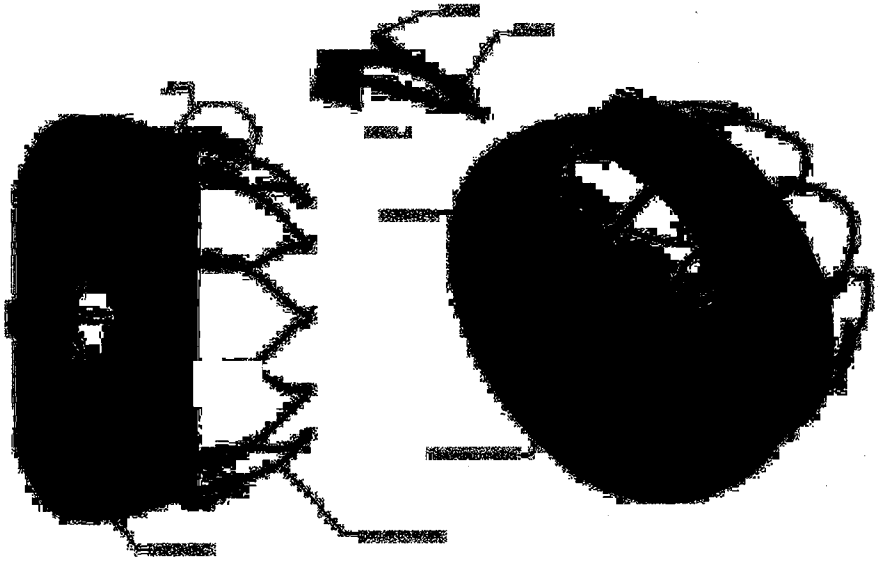
The WATCHMAN LAA Closure Device, which is constrained within the Delivery System, is a self-expanding nitinol structure with a membrane on the proximal face. The Access System and Delivery Catheter provide femoral venous access and a means to cross into the left atrium via the intra-atrial septum. The Obturator, an optional accessory, provides a smooth transition from the WATCHMAN Access Sheath to a pigtail catheter, facilitating atraumatic entry into the distal segment of the LAA.

3.1 WATCHMAN LAA Closure Device

The WATCHMAN LAA Closure Device (**Figure 3-2**) is the implantable component of WATCHMAN LAA Closure Technology. The Device is composed of:

- A laser-cut nitinol frame that is formed to an umbrella-like shape and electropolished. Fixation barbs 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 suture and to the top of the frame with a threaded insert.
- A threaded insert, which 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 3-2. WATCHMAN LAA Closure Device

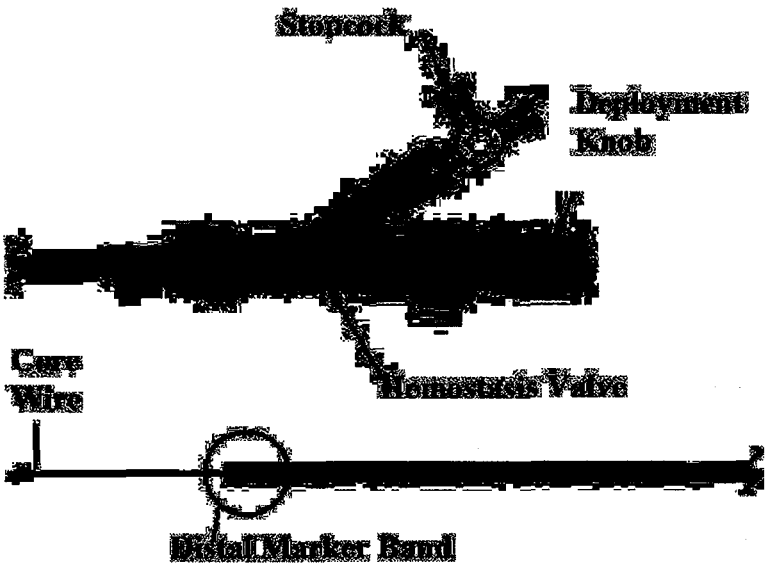


The WATCHMAN Device is available in five sizes: 21, 24, 27, 30 and 33 mm.

3.2 WATCHMAN Delivery System

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

Figure 3-3. Delivery Catheter



A threaded core wire provides the mechanism for deployment and recapture or release 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 counter clockwise, 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, a 3-way stopcock, and a rotational lock mechanism to prevent inadvertent core wire rotation while the Device remains in a loaded position within the Delivery Catheter.

3.3 WATCHMAN Access System

The WATCHMAN Access System includes an Access Sheath (**Figure 3-4**) 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 Touhy-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 marker bands for *in situ* visualization and vent holes for contrast distribution.

Figure 3-4. Access Sheath

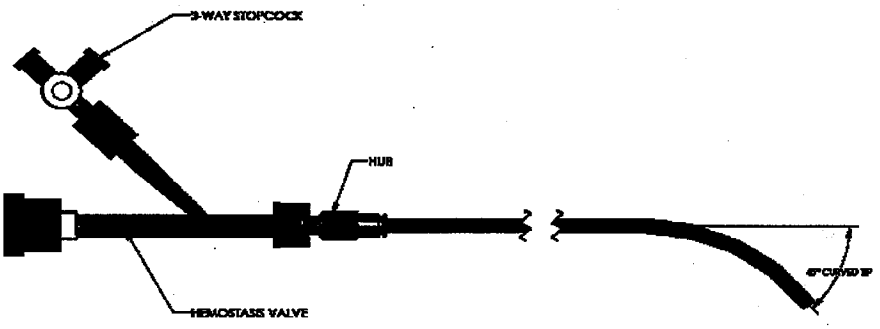
The Dilator is composed of a polymer shaft with a proximal flush port hub and standard luer taper and threads. The distal tip of the Dilator is tapered for septal crossing and curved to an approximate 90 degree angle. The hub is designed for snap fit connection to the Access Sheath hemostasis valve.

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

3.4 WATCHMAN Obturator (Optional Accessory)

The WATCHMAN Obturator (**Figure 3-5**) is a 12 Fr catheter. The proximal portion of the Obturator has a luer fitting with an attached Y adapter hemostasis valve and a 3-way stopcock. The Obturator fits within the Access Sheath; the proximal end of the Obturator has a snap fit hub for connection to the Access Sheath hemostasis valve. Overall length of the Obturator is 85 cm and the distal tip, which contains a marker band for *in situ* visualization, is curved to a 45 degree angle. The Obturator will accommodate up to a 6 Fr pigtail catheter.

Figure 3-5. WATCHMAN Obturator



4 Contraindications, Warnings and Precautions

4.1 Contraindications

WATCHMAN LAA Closure Technology is contraindicated when:

- Intracardiac thrombus is visualized by TEE.

- An atrial septal 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 IFU).
- All the customary contraindications for other percutaneous catheterization interventions, e.g., patient size (i.e., too small for TEE probe, catheter size, etc.) or condition (i.e., active infection, bleeding disorder, untreated ulcer or any other contraindication to anticoagulation therapy, etc.).

4.2 Warnings and Precautions

Implantation of the WATCHMAN LAA Closure Device should only be performed by physicians trained in percutaneous and transseptal procedures who have completed the WATCHMAN training program.

- **The LAA is a thin walled structure. Use caution when accessing the LAA and deploying the Device.**
- The WATCHMAN Access and Delivery Systems are sterile and intended for single use only. Do not reuse or resterilize.
- If sterile barrier has been compromised in any way, or WATCHMAN Access System, Obturator or Deliver System appear damaged DO NOT USE.
- Careful consideration should be given to use the Device in pregnant and/or breastfeeding women due to the risk of significant exposure to x-rays and the use of strong anticoagulation medication.
- Device selection should be based on accurate LAA measurements obtained using fluoroscopy and TEE in multiple angles (e.g. 0°, 45°, 90°, 135°).
- Aspirin should be started one day prior to scheduled procedure and continued daily.
- Patients should be fully heparinized throughout the procedure with an active clotting time (ACT) of 200 - 300 seconds after transseptal puncture.
- Fluoro and TEE should be used when implanting the Device.
- Do not release (unscrew) the Device unless release criteria are satisfied.
- Potential for Device embolization exists with cardioversion < 30 days following Device implantation, verify Device position post cardioversion.

- Post- procedure warfarin therapy is required in ALL patients receiving a Device per institution's protocol. Patients should remain on warfarin for a minimum of 45 days post implant (INR 2.0-3.0). At 45 days post implant perform Device assessment with TEE. Cessation of warfarin is at physician discretion. Patients ceasing warfarin should begin clopidogrel 75mg daily for 6 months post-implant and remain on one adult aspirin indefinitely.
- Prescribe appropriate endocarditis prophylaxis for 6 months following device implantation. The decision to continue endocarditis prophylaxis beyond 6 months is at physician discretion.

5 Alternative Practices and Procedures

An alternative to device closure of the LAA is open-heart surgery. Cardiac surgery that is required for closure of the LAA is commonly done following or in tandem with a MAZE procedure for atrial fibrillation and is a major procedure that may require cardiopulmonary bypass.

6 Marketing History

The WATCHMAN LAA Closure Technology has not been marketed in the United States. The WATCHMAN Access System and Delivery System received the CE Mark in October 2005. The WATCHMAN has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the Device.

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7 Potential Adverse Effects of the Device on Health

Adverse events reported in the WATCHMAN group during the clinical study were adjudicated by the Clinical Events Committee. A total of seventeen deaths were reported, five of which were related to efficacy endpoints (stroke, cardiovascular causes or systemic embolism). No deaths were due to device or procedure-related causes. Those events adjudicated as "study-related" (serious and non-serious) were as follows in descending order of frequency:

- Pericardial Effusion-Serious
- Stroke - Ischemic
- Device Thrombus
- Bruising - Hematoma
- Rectal Bleeding
- Hematuria
- Pseudoaneurysm
- Arrhythmia
- Bleeding From Varicose Veins
- Major Bleed Requiring Transfusion
- Pleural Effusion
- Transient Ischemic Attack (TIA)
- Allergic Reaction To Contrast Media
- Pulmonary Edema
- Thrombosis
- Gastrointestinal Bleeding
- Death
- Pericardial Effusion
- Epistaxis
- Device Embolization
- Infection
- Anemia Requiring Transfusion
- AV Fistula
- Cranial Bleed
- Oral Bleeding
- Systemic Embolization
- Air Embolism
- Inability To Move Or Retrieve Device
- Stroke - Hemorrhagic
- Vasovagal Reactions

Some additional adverse events that may be expected in catheterization procedures include:

- Pneumothorax
- Pulmonary Vein Obstruction
- Valvular or Vascular Damage

8 Summary of Preclinical Studies

8.1 Bench Testing

Atritech performed an extensive series of mechanical and functional testing to demonstrate that the WATCHMAN LAA Closure Device, Delivery System, Access System, and Obturator met design input requirements and engineering specifications. The results show that all requirements were met, thus supporting the integrity and reliability of the WATCHMAN LAA Closure Technology.

A summary of the WATCHMAN bench testing is provided in **Table 8-1**.

Table 8-1. Summary of WATCHMAN Bench Testing

Implant Threaded Insert to NiTi Tube Joint	Pass
Core Wire Assembly Wire through Threaded Insert Tensile Strength	Pass
Implant Filtration	Pass
Implant Deployment and Recapture Force	Pass
Implant Mechanical Integrity	Pass
Individual Barb Mechanical Integrity	Pass
Implant Radial Force	Pass
Implant Diameter Recovery	Pass
Implant Dislodgement Force	Pass
MRI Field Interactions	Pass
Implant Corrosion Resistance	Pass
Implant Durability/Fatigue (Test articles were cycled up to the equivalent of 10 years of use or 400,000,000 cycles corresponding to 76 heartbeats per minute for ten years)	Pass
Finite Element Analysis (for characterization)	N/A
Delivery System Tensile Strength	Pass
Snap Fit Luer Connection Compressive and Tensile Properties	Pass
Core Wire Torque Properties	Pass
Core Wire Assembly Torquer Bond Strength	Pass
Kink Resistance – Delivery System	Pass
Contrast Flow Rate – Delivery System	Pass
Leak Free Conduits - Delivery System	Pass
Corrosion Resistance – Delivery System	Pass

WATCHMAN Access System – Tensile Testing	Pass
Kink Resistance – Access System	Pass
Contrast Flow Rate	Pass
Leak Free Conduits – Access System	Pass
Access System Distal Tip Deflection	Pass
Dilator Tensile Strength	Pass
Leak Free Conduits - Obturator	Pass
Obturator Tensile Strength	Pass

8.2 Magnetic Resonance Imaging (MRI) Information

The WATCHMAN LAA Closure Device was determined to be MR-conditional (International, Designation: F2503-05. Standard Practice for Marking Medical Devices and Other Items for Safety in the MR Environment. ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, Pennsylvania, 19428, 2005).

A patient with the Device can be scanned safely, immediately after placement and thereafter under the following conditions: Static magnetic field of 3-Tesla or less Spatial gradient field of 720-Gauss/cm or less Max MR system reported SAR of 3-W/kg for 15min of scanning.

In non-clinical testing, the Device produced a temperature rise of < 0.5°C at a max MR system-reported SAR of 3-W/kg as assessed by calorimetry for 15min of MR scanning in a 3-Tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare, Milwaukee, WI).

MR image quality may be compromised if the area of interest is relatively close to the Device. Optimization of MR imaging parameters is recommended.

8.3 Biocompatibility Tests

The safety of the WATCHMAN LAA Closure Technology has been evaluated in a series of biocompatibility/toxicity studies on the WATCHMAN LAA Closure Device, Delivery System, Access System, and Obturator. According to ISO 10993, the WATCHMAN Delivery System, Access System, and Obturator are classified as blood contacting, externally communicating device with limited, less than 24 hour exposure. The WATCHMAN LAA Closure Device is classified as a blood contacting, permanent duration implant.

All studies were conducted in compliance with U.S. Food and Drug Administration regulations set forth in 21 CFR Part 58 - *Good Laboratory Practice for Non Clinical Laboratory Studies.*

These test results in accordance with ISO 10993 demonstrate that the WATCHMAN LAA Closure Technology including the WATCHMAN LAA Closure Device, Delivery Catheter, Access System and

Obturator are biocompatible for its intended use. A summary of the biocompatibility testing is provided in **Table 8-2**.

Table 8-2. Summary of Biocompatibility Testing

Cytotoxicity (ISO 10993-5)	Pass
Irritation (ISO 10993-10)	Pass
Sensitization (ISO 10993-10)	Pass
Acute Systemic Toxicity (ISO 10993-11)	Pass
Pyrogenicity (ISO 10993-11)	Pass
Genotoxicity (ISO 10993-3)	Pass
Implant / Chronic Toxicity	Pass
Hemocompatibility (ISO 10993-4)	Pass
USP Physico-Chemical Test (USP<25>)	Pass
Lee & White	Pass
UPTT	Pass
Carcinogenicity	Assessed
Cytotoxicity (ISO 10993-5) L-929 MEM Elution	Pass
Irritation (ISO 10993-10) Intracutaneous Injection	Pass
Sensitization (ISO 10993-10) Murine Local Lymph Node Assay	Pass
Acute Systemic Toxicity (ISO 10993-11) Systemic Injection	Pass
Pyrogenicity (ISO 10993-11) Material Mediated/Rabbit Pyrogen	Pass
In-vitro Hemocompatibility (ISO 10993-4) Direct and Indirect Methods	Pass
Cytotoxicity (ISO 10993-5)	Pass
Irritation (ISO 10993-10)	Pass
Sensitization (ISO 10993-10)	Pass
Acute Systemic Toxicity (ISO 10993-11)	Pass
Pyrogenicity (ISO 10993-11)	Pass
Hemocompatibility (ISO 10993-4)	Pass
Cytotoxicity (ISO 10993-5)	Pass
Irritation (ISO 10993-10)	Assessed
Sensitization (ISO 10993-10)	Assessed
Acute Systemic Toxicity (ISO 10993-11)	Assessed
Pyrogenicity (ISO 10993-11)	Assessed
Hemocompatibility (ISO 10993-4)	Pass

8.4 Packaging, Sterilization & Shelf Life Testing

The WATCHMAN LAA Closure Technology packaging was evaluated to demonstrate that the package design adequately protects the product during storage and distribution. Based upon these results, the WATCHMAN Delivery System and Access System are labeled with a 3 year shelf life and the WATCHMAN Obturator is labeled with a 2 year shelf life.

The WATCHMAN LAA Closure Technology products are single-use devices that are provided sterile (via ethylene oxide) to the user. WATCHMAN LAA Closure Technology products are sterilized using a validated 100% gaseous ethylene oxide (EO) mixed load sterilization process that provides a Sterility Assurance Level (SAL) of $\leq 10^{-6}$.

8.5 Animal Testing

Atritech conducted several animal studies in canines to evaluate the procedural and device effects associated with various device designs and implant variables. A total of 96 animals were tested as part of Atritech development, design and safety testing processes. Four GLP studies were conducted to assess the safety of the device, and for design verification.

The study results indicate that the WATCHMAN LAA Closure Technology intended for commercialization can be safely and effectively implanted into the LAA. The results indicate that the device promotes endothelial overgrowth and completely seals the LAA from the left atrium within 45 days. The studies have also shown that there are no visible strut fractures, and that the device has caused no clinically significant effects on adjacent tissues. The results also show an acceptable healing response, with no evidence of risk associated with thrombus formation. Procedural methods and retrievability of the device were shown to be simple, repeatable and safe.

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9 Summary of Clinical Studies

The purpose of the PROTECT AF study was to determine whether the WATCHMAN LAA Closure Device is a safe and effective alternative to long term warfarin therapy.

9.1 Study Objective

The objective of the PROTECT AF study was to demonstrate that the WATCHMAN LAA Closure Device is safe and effective in patients with non-valvular atrial fibrillation who require anticoagulation therapy for potential thrombus formation.

9.2 Study Design

The PROTECT AF study was designed to demonstrate that the WATCHMAN LAA Closure Technology and specifically the WATCHMAN LAA Closure Device can be used safely and effectively in patients with non-valvular atrial fibrillation who require anticoagulation therapy for potential thrombus formation. A documented history of paroxysmal, persistent or permanent atrial fibrillation was required for every patient.

The investigation of the WATCHMAN LAA Closure Technology was a multi-center prospective randomized design comparing the WATCHMAN Device to a Control group of long-term warfarin therapy. A 2:1 randomization allocation ratio (two devices to one control) was used with stratification by center.

9.3 Patient Accountability and Follow-up

Patient enrollment in the PROTECT AF study commenced in February 2005 and ended randomization in June 2008. A total of 800 patients were enrolled in the study at 59 centers (55 U.S., 4 European). This total included 93 roll-in patients and 707 randomized patients (463 patients to the Device group and 244 to the warfarin Control) group with a total 900 patient-years of follow-up for the primary efficacy endpoint as of database cutoff. A 2:1 randomization allocation ratio was implemented across investigational centers in the randomized cohort. Upon completion of enrollment in the PROTECT AF study, continued access to the WATCHMAN device was allowed to a subset of the PROTECT AF investigators through a study entitled Continued Access PROTECT AF Registry (CAP Registry) which started enrollment in August 2008.

Table 9-1 provides an accounting of follow-up compliance achieved in the PROTECT AF study. Expected visits are based on visit windows defined in the protocol.

Due to the cumulative patient-year design of the statistical plan, achieving maximum follow-up compliance for all required visits was of significant importance. As a result, very few patients were lost to follow-up in the study and approximately 98% follow-up was achieved in both groups.

Table 9-1. Follow-up Visit Attendance

	Attended/ Expected (%)	Attended/ Expected (%)
45 day	432/438 (98.6)	235/239 (98.3)
6 month	389/391 (99.5)	220/221 (99.5)
9 month	336/344 (97.7)	190/192 (99.0)
12 month	288/295 (97.6)	151/154 (98.1)
18 month	203/205 (99.0)	104/104 (100.0)
24 month	103/106 (97.2)	53/56 (94.6)
30 month	59/61 (96.7)	32/32 (100.0)
36 month	25/26 (96.2)	12/13 (92.3)

9.4 Baseline Demographics

Table 9-2 summarizes the patient baseline demographic information of the randomized cohort. Baseline demographics demonstrate that patients in the two treatment groups were comparable.

Table 9-2. Patient Baseline Demographics

Age (years)	71.7 ± 8.8 463 (46.0, 95.0)	72.7 ± 9.2 244 (41.0, 95.0)	0.1800
Height (inches)	68.2 ± 4.2 462 (54.0, 82.0)	68.4 ± 4.2 244 (59.0, 78.0)	0.6067
Weight (lbs)	195.3 ± 44.4 463 (85.0, 376.0)	194.6 ± 43.1 244 (105.0, 312.0)	0.8339
Gender			0.9276
Female	137/463 (29.6)	73/244 (29.9)	
Male	326/463 (70.4)	171/244 (70.1)	
Race/Ethnicity			0.7788
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)	

Values presented are mean±standard deviation, n (minimum, maximum) or number of patients/total number of patients (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

Baseline risk factors for enrolled patients are summarized in **Table 9-3**. There were no statistically significant differences in risk factors between groups.

Table 9-3. Patient Risk Profile

$CHADS_2$ score			0.3662
1	158/463 (34.1)	66/244 (27.0)	
2	157/463 (33.9)	88/244 (36.1)	
3	88/463 (19.0)	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)	
CHF	124/463 (26.8)	66/244 (27.0)	0.9392
History of hypertension	412/463 (89.0)	220/244 (90.2)	0.6284
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
AF Pattern			0.7623
Paroxysmal	200/463 (43.2)	99/244 (40.6)	
Persistent	97/463 (21.0)	50/244 (20.5)	
Permanent	160/463 (34.6)	93/244 (38.1)	
Unknown	6/463 (1.3)	2/244 (0.8)	
LVEF %	57.3 ± 9.7	56.7 ± 10.1	0.4246
	460 (30.0, 82.0)	239 (30.0, 86.0)	

Values presented are mean±standard deviation, n (minimum, maximum) or number of patients/total number of patients (%) as appropriate. P-values are from two sample t-tests or chi-square tests as appropriate comparing the randomized groups.

Inclusion in the PROTECT AF study required a $CHADS_2$ score of ≥ 1. To calculate a patient's $CHADS_2$ score, one point is assigned each for the presence of congestive heart failure, history of hypertension, age 75 years or older, and diabetes, and two points assigned for prior stroke or TIA.

Over 80% of patients in both treatment groups were enrolled with a $CHADS_2$ score of 3 or lower out of a possible score of 6. The mean (standard deviation) of the $CHADS_2$ score was 2.2 (1.2) and 2.3 (1.2) for the Device and Control groups respectively.

Paroxysmal AF, defined as an intermittent form of atrial fibrillation that is characterized by a sudden onset and abrupt cessation of this rhythm, was the presenting rhythm in 42% of subjects. The second most common AF pattern reported was permanent AF, defined as ongoing atrial fibrillation that fails to terminate using cardioversion, or is terminated but reoccurs, which accounted for 36% of patients in the study.

9.5 Primary Efficacy Results

9.5.1 Intent-to-Treat

Results for the primary efficacy endpoint comprised of stroke, death (cardiovascular or unexplained) and systemic embolism are displayed in **Table 9-4**.

Table 9-4. Primary Efficacy Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**		**Non-inferiority**	**Superiority**
463	20/582.3	3.4 (2.1, 5.2)	244	16/318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837

N = number Pts = patients Pt-yrs = patient-years CI = 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.

The primary efficacy event rate was 3.4 events per 100 patient years for the Device group and 5.0 events per 100 patient years for the Control group. These rates yielded a relative risk, or rate ratio, of 0.68, a 32% lower rate of efficacy events in the Device group than in the Control group. The 95% credible interval for the rate ratio was (0.37, 1.41). The value of the upper bound for the rate ratio (1.41) is 0.59 lower than the pre-specified non-inferiority margin of 2.0. The posterior probability of non-inferiority of 0.998 exceeds the pre-specified non-inferiority criterion meeting the statistical objective in the PROTECT AF study.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are provided in **Figure 9-1** and **Table 9-5**.

Figure 9-1. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Intent-to-Treat)

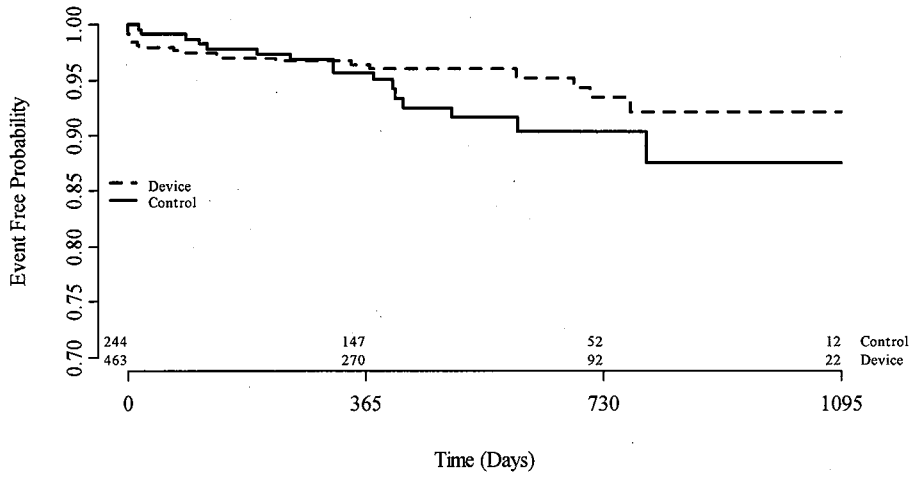

Table 9-5. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	7	7	98.5	0	0	100.0
45-days	2	9	98.0	2	2	99.2
6-months	4	13	97.1	3	5	97.9
1-year	2	15	96.4	4	9	95.7
2-year	4	19	93.5	6	15	90.3
3-year	1	20	92.1	1	16	87.7

The largest portion of the primary efficacy events for the Device group (7/20, 35%) occurred within 7-days of randomization, with 1 of these events (a stroke) occurring after randomization but prior to implant and 5 other events (also strokes) occurring on the day of implant procedure. For the reasons described below, these 5 procedural events were also, and more appropriately, characterized as safety events. At 3 years, the Device group had a Kaplan Meier estimated event rate of 7.9% compared to a 12.3% event rate in the Control group, a 36% lower relative rate for the Device group.

Table 9-6 summarizes the specific efficacy events which comprise the primary efficacy endpoint.

Table 9-6. Primary Efficacy Events by Type (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	% of Randomized Patients	N Events	% of Randomized Patients
Stroke - Ischemic	14	3.0	5	2.0
Death (Cardiovascular or Unexplained)	3	0.6	5	2.0
Stroke - Hemorrhagic	1	0.2	6	2.5
Systemic Embolism	2	0.4	0	0.0

While 14 patients in the Device group experienced ischemic stroke, it is important to note that these events include 1 patient who experienced a stroke after randomization but before a device was implanted and 5 patients with ischemic stroke occurring on the day of the procedure due to air embolism and excessive sedation. Without these 6 events, the Device ischemic stroke rate (8/463, 1.7%) is comparable to the Control rate.

The rate of cardiovascular or unexplained death and hemorrhagic stroke is lower in the Device group. The rate of systemic embolism is comparable between groups.

9.5.2 Post Procedure

A pre-specified analysis was performed removing patients who were randomized to the device but for whom no implant was attempted or who experienced events during the procedure. Fourteen patients were removed including 1 patient who experienced a stroke before a device was implanted and 13 patients who were unable to be implanted during the allotted time following randomization. Additionally, 5 patients were removed from this analysis who experienced strokes during the procedure (as noted above) which were adjudicated as both primary efficacy and safety events. As these 5 events occurred on the date of the implant and were primarily safety related, they were removed from the post procedure analysis (in part, to avoid double counting of the events as both efficacy and safety). Results of the primary efficacy endpoint once these 19 patients were removed are displayed in **Table 9-7**.

Table 9-7. Primary Efficacy Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-Inferiority	Superiority
444	14/572.3	2.4 (1.4, 4.0)	244	16/318.0	5.0 (2.8, 7.6)	0.49 (0.24, 1.06)	>0.999	0.965

The primary efficacy event rate was 2.4 events per 100 patient years for the Device group and 5.0 events per 100 patient years for the Control group. These rates yielded a relative risk, or rate ratio, of 0.49, a 51% lower rate of efficacy events in the Device group. The 95% credible interval for the rate ratio was (0.24, 1.06). The probability of superiority of 0.965 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 9-2** and **Table 9-8**.

Figure 9-2. Kaplan-Meier Curve: Freedom from Primary Efficacy Event (Post Procedure)

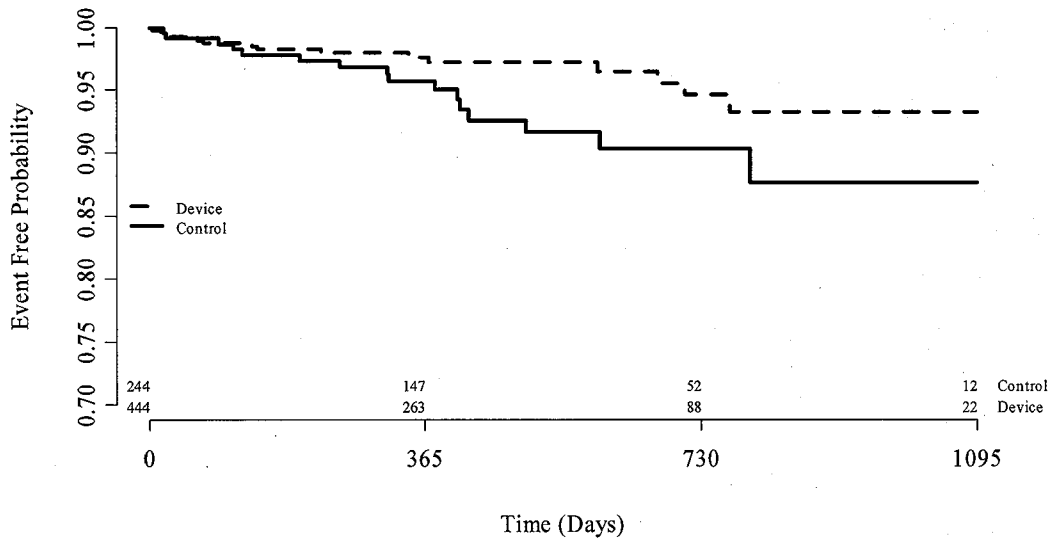

Table 9-8. Kaplan-Meier Estimates: Freedom from Primary Efficacy Event (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.8	0	0	100.0
45-days	2	3	99.3	2	2	99.2
6-months	4	7	98.3	3	5	97.9
1-year	2	9	97.7	4	9	95.7
2-year	4	13	94.6	6	15	90.3
3-year	1	14	93.2	1	16	87.7

At 3 years, the Device group had a Kaplan Meier estimated post procedure efficacy event rate of 6.8% compared to a 12.3% post procedure efficacy event rate in the Control group, a 45% lower relative rate for the Device group.

9.5.3 Per Protocol

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis attempts to compare effectiveness in patients who successfully received their assigned treatment. Excluded patients from the Device group were those in whom either no implant was attempted, those in whom the device was not successfully implanted, and those who did not stop warfarin therapy. Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. Time to event was calculated from the date of first warfarin cessation for. Results for the primary efficacy endpoint for this analysis population are displayed in **Table 9-9**.

Table 9-9. Primary Efficacy Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-Inferiority	Superiority
387	10/484.4	2.1 (1.0, 3.7)	241	15/317.5	4.7 (2.6, 7.2)	0.44 (0.20, 1.03)	>0.999	0.971

The primary efficacy rate was 2.1 events per 100 patient years for the Device group and 4.7 events per 100 patient years for the Control group. This yielded a rate ratio, or relative risk, of 0.44, a 56% lower rate of efficacy events in the Device group. The 95% credible interval for the rate ratio based on the Bayesian model was (0.20, 1.03). The probability of superiority of 0.971 was greater than the pre-specified superiority criterion demonstrating statistically superior efficacy event rates in the Device group.

Results from Kaplan-Meier analyses for the primary efficacy endpoint are given in **Figure 9-3** and **Table 9-10.**

Figure 9-3. Kaplan-Meier Curve: Freedom from Primary Efficacy (Per-Protocol)

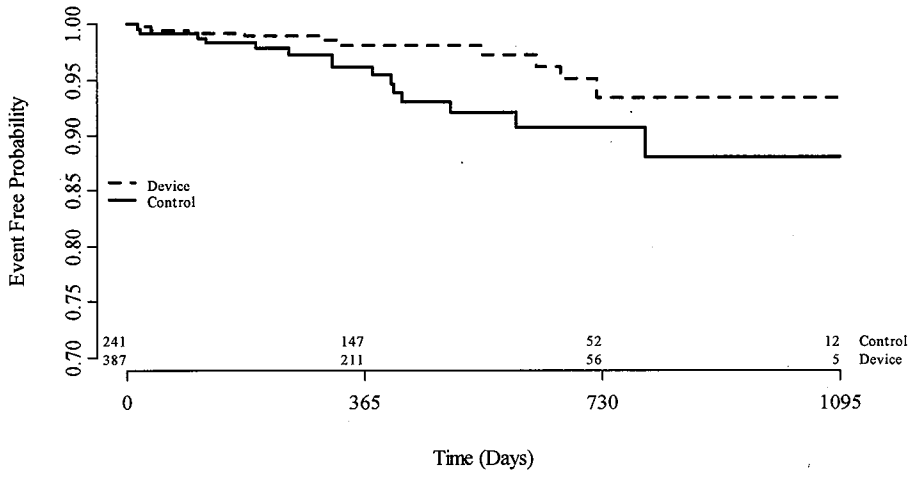

Table 9-10. Kaplan-Meier Estimates: Freedom from Primary Efficacy (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	0	0	100.0	0	0	100.0
45-days	2	2	99.5	2	2	99.2
6-months	1	3	99.2	2	4	98.3
1-year	3	6	98.1	4	8	96.1
2-year	4	10	93.4	6	14	90.7
3-year	0	10	93.4	1	15	88.0

At 3 years, the Device group had a Kaplan Meier estimated per-protocol primary efficacy event rate of 6.6% compared to a 12.0% per-protocol efficacy event rate in the Control group, a 45% lower relative rate for the Device group.

9.5.4 Stroke (Intent-to-Treat)

As the largest contributor to the primary efficacy endpoint, an intent-to-treat analysis was completed. This analysis, including a comparison of rates via the primary Bayesian Model, Kaplan-Meier figures and survival estimates, is provided in **Table 9-11**, **Figure 9-4** and **Table 9-12**, respectively.

Table 9-11. Stroke - Bayesian Model Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**	**N Pts**	**N Events/ Total Pt-Yrs**	**Rate (95% CI)**		**Non-inferiority**	**Superiority**
463	15/582.9	2.6 (1.5, 4.1)	244	11/318.1	3.5 (1.7, 5.7)	0.74 (0.36, 1.75)	0.988	0.731

The stroke rate was 2.6 events per 100 patient years for the Device group and 3.5 events per 100 patient years for the Control group. This yielded a relative risk, or rate ratio, of 0.74, a 26% lower stroke rate in the Device group. The 95% credible interval for the rate ratio was (0.36, 1.75). The posterior probability of non-inferiority of 0.988 exceeds the pre-specified non-inferiority criterion.

Figure 9-4. Kaplan-Meier Curve: Freedom from Stroke (Intent-to-Treat)

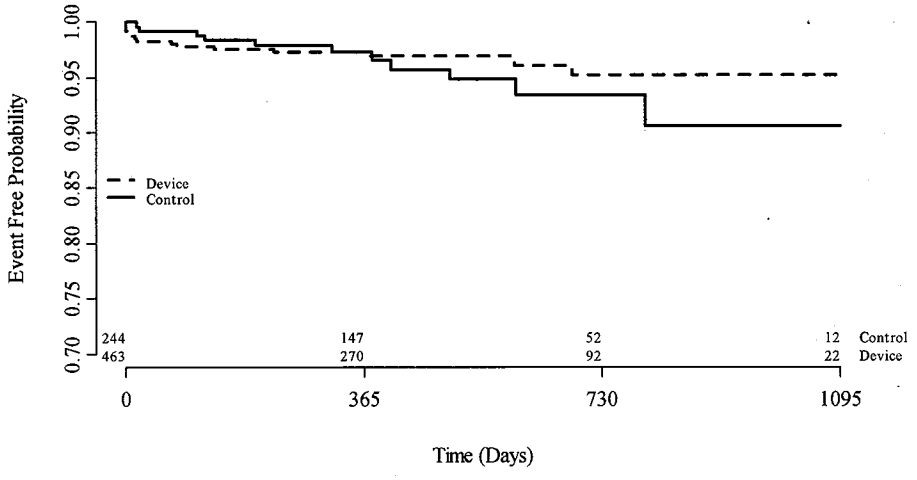

Table 9-12. Kaplan-Meier Estimates: Freedom from Stroke (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	6	6	98.7	0	0	100.0
45-days	2	8	98.3	2	2	99.2
6-months	3	11	97.5	2	4	98.3
1-year	1	12	97.2	2	6	97.2
2-year	3	15	95.2	4	10	93.4
3-year	0	15	95.2	1	11	90.6

The largest portion of the strokes for the Device group (6/15, 40%) occurred within 7 days of randomization; however, these strokes occurred on or before the day of the procedure and are not reflective of the long term efficacy of the device. At 3 years, the Device group had a Kaplan Meier estimated stroke event rate of 4.8% compared to a 9.4% stroke rate in the Control group, a 49% lower relative rate for the Device group.

Under a post procedure analysis of the stroke endpoint, the stroke rate was 1.6 events per 100 patient years for the Device group and 3.5 events per 100 patient years for the Control group. As described above, 6 strokes occurred either after randomization but before a device was implanted (1 patient) or on the day of the procedure due to the safety complications of air embolism and excessive sedation (5 patients). The post procedure analysis yielded a relative risk, or rate ratio, of 0.45, a 55% lower stroke rate in the Device group. The 95% credible interval for the rate ratio was (0.19, 1.17).

9.6 All Cause Mortality (Intent-to-Treat)

Analysis of all cause mortality, including a comparison of rates via the primary Bayesian Model, Kaplan-Meier figures and survival estimates, is provided in **Table 9-13**, **Figure 9-5** and **Table 9-14**, respectively.

Table 9-13. All Cause Mortality - Bayesian Model Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)		Non-inferiority	Superiority
463	17/593.6	2.9 (1.7, 4.4)	244	15/320.3	4.7 (2.5, 7.1)	0.61 (0.32, 1.31)	0.999	0.889

The mortality rate was 2.9 events per 100 patient years for the Device group and 4.7 events per 100 patient years for the Control group. This yielded a relative risk, or rate ratio, of 0.61, a 39% lower rate of

death in the Device group. The 95% credible interval for the rate ratio was (0.32, 1.31). The posterior probability of non-inferiority of 0.999 exceeds the pre-specified non-inferiority criterion.

Figure 9-5. Kaplan-Meier Curve: Freedom from All Cause Mortality (Intent-to-Treat)

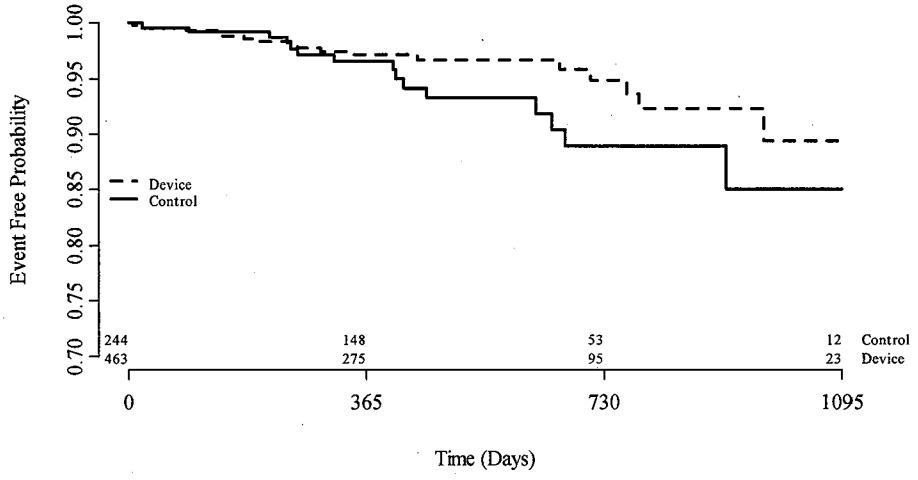

Table 9-14. Kaplan-Meier Estimates: Freedom from All Cause Mortality (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	0	0	100.0	0	0	100.0
45-days	2	2	99.6	1	1	99.6
6-months	4	6	98.6	1	2	99.2
1-year	5	11	97.1	5	7	96.6
2-year	3	14	94.9	7	14	88.9
3-year	3	17	89.4	1	15	85.0

The estimated all cause mortality rates were similar between groups through 1 year, and thereafter mortality in the Device group tended to be less frequent than that in the Control group. At 3 years, the Device group had a Kaplan Meier estimated all cause mortality event rate of 10.6% compared to a 15.0% all cause mortality rate in the Control group, a 29% lower relative rate for the Device group.

No deaths were due to device or procedure-related causes. Two strokes in the Device group were fatal compared to five strokes in the Control group. Neither of the fatal strokes in the Device group was attributed to the device as one occurred before device implant and the other stroke was adjudicated as a hemorrhagic stroke while the patient was still on warfarin. Four of the five fatal strokes in the Control

group were hemorrhagic strokes while the patient was receiving warfarin therapy and one stroke was ischemic.

9.7 Primary Safety Results

9.7.1 Intent-to-Treat

Results for the primary safety endpoint are displayed in **Table 9-15**. In contrast to the primary efficacy endpoint, there was no pre-specified hypothesis for the primary safety endpoint. Credible intervals are calculated from the same Bayesian model used for the primary efficacy endpoint.

Table 9-15. Primary Safety Results (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
463	48/554.2	8.7 (6.4, 11.3)	244	13/312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)

The primary safety rate was 8.7 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group. This yielded a rate ratio, or relative risk, of 2.08. The 95% credible interval for the rate ratio based on the Bayesian model was (1.18, 4.13).

Results from Kaplan-Meier analyses for the primary safety endpoint are provided in **Figure 9-6** and **Table 9-16**.

Figure 9-6. Kaplan-Meier Curve: Freedom from Primary Safety Event (Intent-to-Treat)

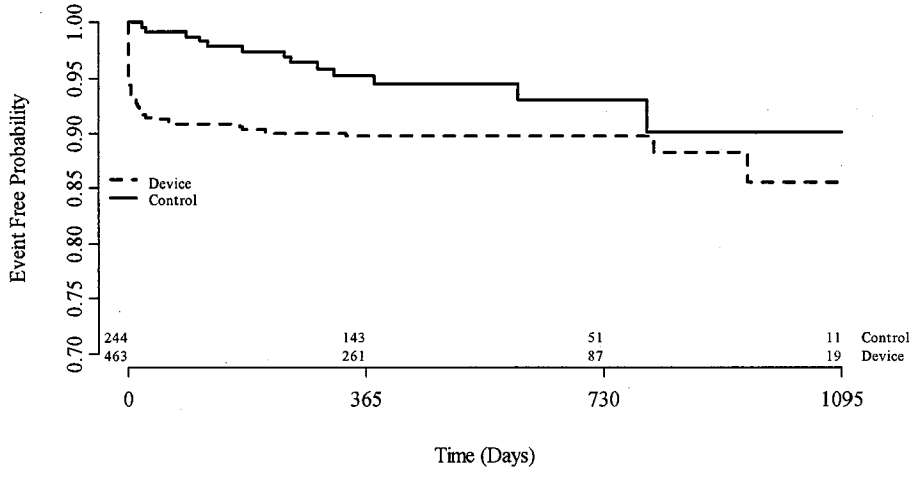

Table 9-16. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	32	32	93.1	0	0	100.0
45-days	7	39	91.5	2	2	99.2
6-months	5	44	90.3	4	6	97.4
1-year	2	46	89.7	4	10	95.2
2-year	0	46	89.7	2	12	93.0
3-year	2	48	85.5	1	13	90.1

The majority of primary safety events in the Device group (27/48, 56%) occurred on the day of implant. The observed trend in long term warfarin events in the Control group would be expected to continue beyond 3 years as data for 3-5 year event rates in the SPAF trials has previously demonstrated an increase in events over time.

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Table 9-17 summarizes the types of primary safety events by randomized group.

Table 9-17. Primary Safety Events by Type (Intent-to-Treat)

Randomization Allocation (2 Device: 1 Control)

	N Events	% of Randomized Patients	N Events	% of Randomized Patients
Pericardial Effusion - Serious	22	4.8	0	0.0
Gastrointestinal Bleeding	10	2.2	6	2.5
Stroke - Ischemic	5	1.1	0	0.0
Stroke - Hemorrhagic	1	0.2	6	2.5
Device Embolization	3	0.6	0	0.0
Esophageal Tear	1	0.2	0	0.0
Cranial Bleed	2	0.4	0	0.0
Major Bleed Requiring Transfusion	2	0.4	0	0.0
Arrhythmias	1	0.2	0	0.0
Bruising - Hematoma	1	0.2	0	0.0
Anemia Requiring Transfusion	0	0.0	1	0.4

A higher rate of early primary safety events in the Device group compared to the Control group is not unexpected due to the nature of the implant procedure. Ischemic and hemorrhagic stroke events have been categorized as both a safety and efficacy event as described above. The 5 ischemic strokes in the Device group were due to procedure complications including air embolism and excessive sedation which resulted in extended median hospitalization of 7 days and no deaths. The 22 pericardial effusions required physician intervention (15 were treated percutaneously with fluid drainage with a median hospitalization of 4 days and 7 required surgical intervention with a median hospitalization of 6 days).

9.7.2 Post Procedure

A pre-specified analysis was performed removing patients who were randomized to the device but for whom no implant was attempted or who experienced events during the procedure. Fourteen patients were removed who were unable to be implanted during the allotted time following randomization. Additionally, 5 patients were removed from this analysis who experienced strokes during the procedure (as noted above) which were adjudicated as both primary efficacy and safety events and 22 patients were removed who experienced procedural events including pericardial effusions. This analysis is intended to provide an alternate way to assess post procedural, long term safety which is an issue with warfarin, by evaluating the risk / benefit profile after the acute procedure risks with the device. As such, these 27

patients with procedure events were removed from this analysis. Results of the primary safety endpoint results are displayed in **Table 9-18**.

Table 9-18. Primary Safety Results (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
422	21/544.1	3.9 (2.4, 5.8)	244	13/312.0	4.2 (2.2, 6.7)	0.93 (0.48, 1.97)

The primary safety rate was 3.9 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group. This yielded a rate ratio, or relative risk, of 0.93. The 95% credible interval for the rate ratio based on the Bayesian model was (0.48, 1.97).

Figure 9-7 and **Table 9-19** display results from a Kaplan-Meier analysis of the primary safety events.

Figure 9-7. Kaplan-Meier Curve: Freedom from Primary Safety Event (Post Procedure)

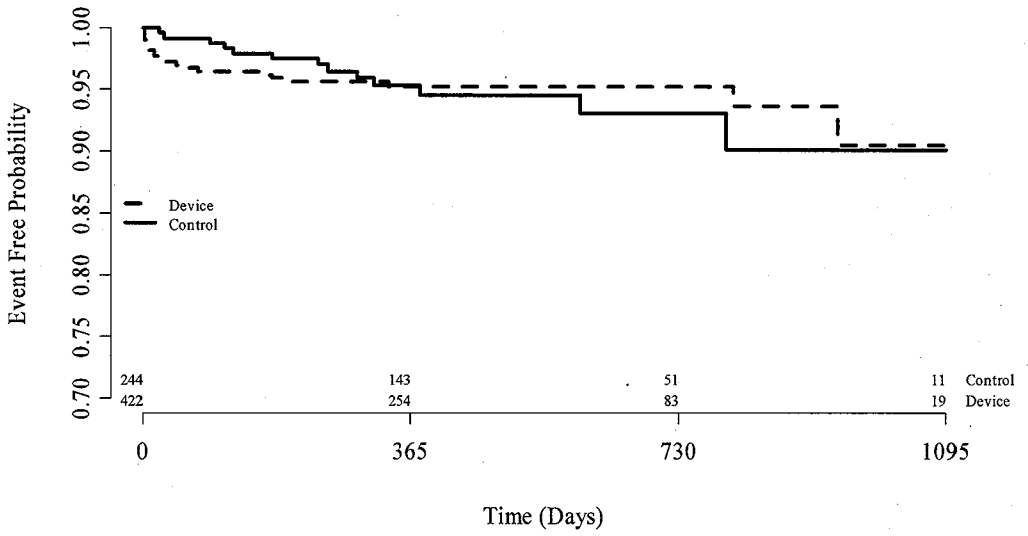

Table 9-19. Kaplan-Meier Estimates: Freedom from Primary Safety Event (Post Procedure)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	8	8	98.1	0	0	100.0
45-days	5	13	96.9	2	2	99.2
6-months	4	17	95.8	4	6	97.4
1-year	2	19	95.2	4	10	95.2
2-year	0	19	95.2	2	12	93.0
3-year	2	21	90.5	1	13	90.1

Under the post procedure analysis, at 3 years, the Device group had a Kaplan Meier estimated post procedure primary safety event rate of 9.5% compared to a 9.9% post procedure safety event rate in the Control group. After the first 7 days, the safety profile of the Device group with a primary safety event rate of 7.6% is slightly better than the 9.9% rate in the Control group.

9.7.3 Per Protocol

A pre-specified analysis was performed for those randomized Device patients who were successfully implanted with the device and who were then able to discontinue warfarin therapy and for those Control patients who were taking warfarin therapy at baseline or 45-days. This analysis attempts to compare safety in patients who successfully received their assigned treatment. Excluded patients from the Device group were those in whom either no implant was attempted, those in whom the device was not successfully implanted, and those who did not stop warfarin therapy. Control group patients were excluded where there was no evidence that warfarin was taken at baseline or at the 45-day visit. Time to event was calculated from the date of first warfarin cessation for Device patients. Results for the primary safety endpoint for this analysis population are displayed in **Table 9-20**.

Table 9-20. Primary Safety Results (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	N Pts	N Events/ Total Pt-Yrs	Rate (95% CI)	
387	8/483.9	1.7 (0.7, 3.1)	241	13/311.4	4.2 (2.2, 6.7)	0.40 (0.16, 0.96)

The primary safety rate was 1.7 events per 100 patient years for the Device group and 4.2 events per 100 patient years for the Control group. This yielded a rate ratio, or relative risk, of 0.40. The 95% credible interval for the rate ratio based on the Bayesian model was (0.16, 0.96).

Results from Kaplan-Meier analyses for the primary safety endpoint are provided in **Figure 9-8** and **Table 9-21**.

Figure 9-8. Kaplan-Meier Curve: Freedom from Primary Safety (Per-Protocol)

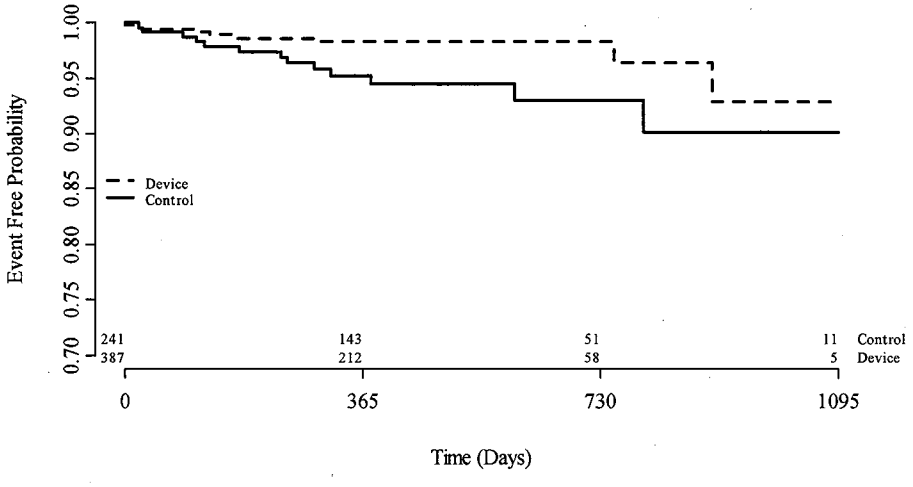

Table 9-21. Kaplan-Meier Estimates: Freedom from Primary Safety (Per-Protocol)

Randomization Allocation (2 Device: 1 Control)

	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	1	1	99.7	0	0	100.0
45-days	1	2	99.5	2	2	99.2
6-months	3	5	98.6	4	6	97.4
1-year	1	6	98.3	4	10	95.2
2-year	0	6	98.3	2	12	93.0
3-year	2	8	92.9	1	13	90.1

At 3 years, the Device group had a Kaplan Meier estimated per-protocol safety event rate of 7.1% compared to an 9.9% per-protocol safety event rate in the Control group, a 28% lower relative rate for the Device group.

9.8 Technical/Procedure Success

Technical Success was defined as successful delivery and release into the LAA including successful recapture and retrieval if necessary. Procedure Success was defined as technical success and no serious adverse events related to the treatment or procedure within the hospital stay. Results of each are reported in **Table 9-22.**

Table 9-22. Technical/Procedure Success

Technical Success	408/449 (90.9)
Procedure Success	375/449 (83.5)

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10 Conclusion

The PROTECT AF study, involving 707 randomized patients treated with either the WATCHMAN Device or standard warfarin therapy in a 2:1 randomized ratio, was performed to evaluate the safety and effectiveness of the WATCHMAN LAA Closure Technology. The primary analyses support a statistically significant finding of non-inferiority for the Device group relative to the Control group for the primary efficacy endpoint, and this finding was consistent across a wide range of secondary analyses.

The PROTECT AF study results support the following statements:

- The WATCHMAN LAA Device was associated with a 32% reduction in primary efficacy endpoint events (stroke, cardiovascular death, and systemic embolism) compared to patients on a standard warfarin regimen under the ITT analysis.
- The WATCHMAN LAA Device was successfully implanted in a significant majority (91%) of patients in whom an implant was attempted.
- After successful implant of the WATCHMAN Device, 87% of patients were able to discontinue warfarin therapy after 45 days. This percentage increased as follow-up continued (e.g. 93% after 6 months).
- In a modified intent-to-treat analysis (post procedure), the efficacy of the WATCHMAN device was statistically superior to warfarin therapy. This analysis removed 6 patients with events which are not reflective of the long term efficacy of the device, namely: 1 patient who experienced a stroke after randomization but before a device was implanted and 5 patients with ischemic stroke occurring on the day of the procedure due to air embolism and excessive sedation. These events are not reflective of the long term efficacy of the device.
- When comparing the effectiveness in patients who successfully received their assigned treatment (per protocol), the WATCHMAN device was statistically superior with a 56% lower relative rate of primary efficacy events in the Device group.
- In analyzing the stroke endpoint, the Device group experienced 15 strokes (14 ischemic and 1 hemorrhagic) for an event rate of 2.6% per 100 patient-years and the Control group had 11 strokes (5 ischemic and 6 hemorrhagic) for an event rate of 3.5% per 100 patient-years. As described above, 6 of the 15 Device group strokes were either pre-procedure or were due to air embolism or excessive sedation during the procedure. No hemorrhagic strokes occurred in the Device group once patients discontinued warfarin.
- Regarding safety, the Device group experienced a two times higher rate of events than the Control group; however once the initial procedure risk passed, the safety profile of the Device was slightly better. On average the procedure complications associated with the Device increased the median hospital stay of patients by 5 days. In addition, no deaths were device or procedure related.

The clinical study results demonstrate an overall positive risk/benefit profile for Device patients even with the risk of procedural complications. Clinicians who served on the Steering Committee during the PROTECT AF study believe this study provides quantitative evidence to represent the risk/benefit of the WATCHMAN procedure as a compelling alternative to warfarin therapy.

These data demonstrate that the WATCHMAN LAA Closure Technology is a safe and effective alternative to warfarin therapy in patients with non-valvular atrial fibrillation, thereby preventing the occurrence of ischemic stroke and systemic thromboembolism and reducing the occurrence of warfarin complications of hemorrhagic stroke and major bleeding events.

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11 Panel Recommendation

At an advisory meeting held on _____, the Circulatory System Devices recommended that WATCHMAN® LAA Closure Technology be approved subject to the submission to, and approval by, the Center for Devices and Radiological Health (CDRH) the following:

12 CDRH Decision

CDRH concurred with the Circulatory System Devices Panel recommendation of _____, and conveyed the Conditions of Approval in a facsimile dated _____.

FDA issued an approval order on _____. The applicant's manufacturing facility was inspected on _____ and contract sterilization facility was inspected on _____. These facilities were found to be in compliance with the device Good Manufacturing Practice regulations.

13 Approval Specifications

Indications for Use: See the Instructions for Use

Hazards to Health from use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use

Post approval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at address _____.