FDA Executive Summary Memorandum

Prepared for the April 23, 2009 meeting of the
Circulatory System Devices Advisory Panel

P080022
WATCHMAN® LAA Closure Technology
Atritech, Inc.

2009-4434B1-01

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I. Introduction

The applicant, Atritech, Inc., has submitted a premarket approval application (PMA) to FDA requesting marketing approval for the WATCHMAN® LAA Closure Technology, hereinafter referred to as the WATCHMAN device. The device is a permanent implant placed in the left atrial appendage (LAA) in order to trap thrombi in order to reduce systemic embolic events, particularly stroke, in patients with atrial fibrillation.

Atrial fibrillation (AF) is a clinically significant arrhythmia with an estimated prevalence of approximately 1% and increased prevalence with age and underlying heart disease.[1] In addition to consideration of rate and rhythm control, the treatment of AF involves the prevention of systemic embolism in patients with chronic or paroxysmal AF since the incidence of stroke in these patients is estimated to be 3 to 5% per year.[2] The etiology of stroke is presumed, at least in part, related to left atrial appendage thromboembolism (based on clinical experience and nonrandomized clinical studies). The choice of therapy for the prevention of stroke (e.g., aspirin or warfarin) depends on the estimated risk of ischemic stroke and typically a risk stratification model (e.g., $CHADS_2$ – an acronym for congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and stroke or transient ischemic attack) is used to guide treatment. However, given the increased risk of major hemorrhage associated with anticoagulation therapy as well as the challenge in maintaining a therapeutic INR,[3] alternative therapies designed to prevent systemic embolism in AF patients are being explored. Specifically, in the current application, the WATCHMAN device has been investigated in the PROTECT AF trial to assess the potential for this device to aid in the prevention of thromboembolism as an alternative to warfarin therapy in atrial fibrillation patients.

The PMA application includes information regarding the PROTECT AF trial results, device design, manufacturing data, preclinical data (including animal study data), reports of prior clinical experience and postmarket approval data collection plans.

II. Regulatory History

The PMA has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration. A chronology of the key milestones with respect to this premarket approval application (PMA) application is provided below.

- **August 18, 2008** – FDA filed PMA P080022 for the WATCHMAN® device. The initial submission contained the analysis of the 600 patient-year cohort, as described in the approved statistical analysis plan. Expedited review status was granted since the

[1] Go AS. Hylek EM. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285(18):2370-5.

[2] Wolf PA, Kannel WB. Duration of atrial fibrillation and imminence of stroke: the Framingham study. Stroke 1983;14(5):664-7.

[3] Connolly SJ. Eikelboom J. Challenges of Establishing New Antithrombotic Therapies in AF. Circulation. 2007;116(4):449-455.

WATCHMAN device is intended to treat a life-threatening or irreversibly debilitating disease or condition (i.e., stroke) and the device potentially represents a breakthrough technology over available alternatives.

- **November 25, 2008** – FDA issued a major deficiency letter (attached) including numerous clinical and preclinical data concerns regarding the information provided in the PMA.
- **January 8, 2009** – Applicant submitted a response to the clinical and statistical questions from the FDA major deficiency letter; other questions related to nonclinical testing are still pending.
- **March 2, 2009** – Full report containing the supplemental analysis of the 900 patient-year data was provided to FDA.

III. Proposed Indications for Use

The following indication for use has been proposed for the WATCHMAN device:

"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."

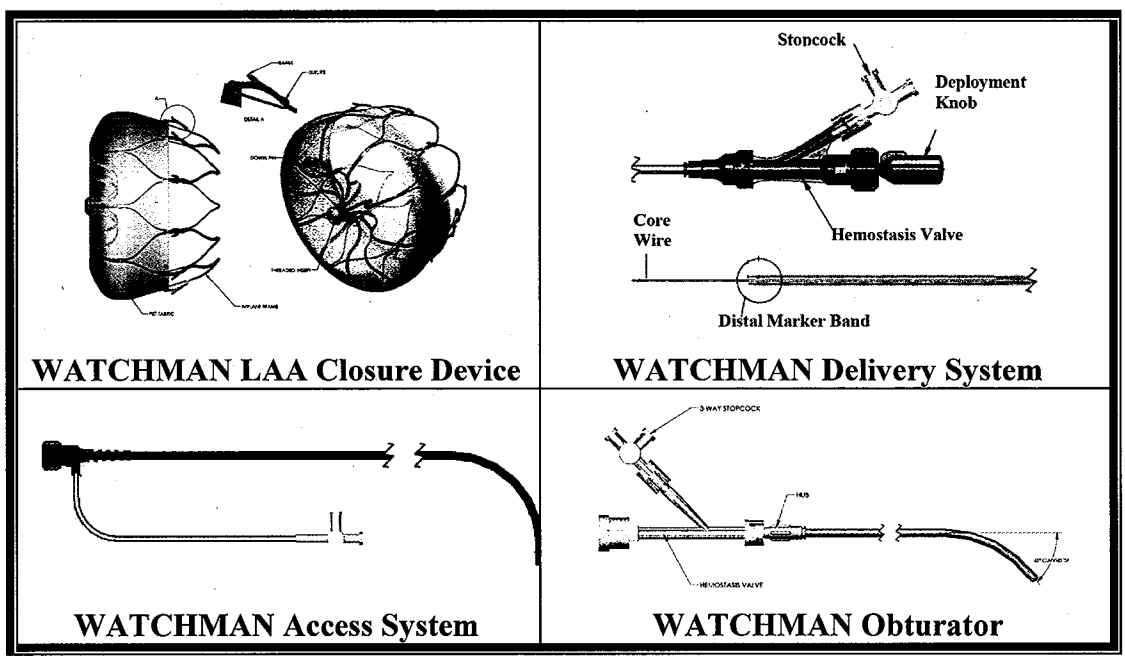
IV. Device Description

The device consists of four components: (1) the WATCHMAN LAA Closure Device; (2) the WATCHMAN Delivery System; (3) the WATCHMAN Access System; and the optional WATCHMAN Obturator. See Figure 1.

The WATCHMAN device is packaged preloaded into a 12F delivery system and is manufactured in five sizes corresponding to the maximum device diameter (21 mm, 24 mm, 27 mm, 30 mm, and 33 mm). The device size is intended to also correspond to the maximum LAA ostium width. Per the Instructions for Use (Tab 6 of the Panel Pack), device selection should be based on accurate LAA measurements obtained using fluoroscopy and transesophageal echocardiography (TEE) in multiple angles.

Following use of a standard transseptal access system to cross the atrial septum, the 12F Delivery System is placed through a 14F Access Sheath. The Access Sheath comes in three configurations, the single curve (90 degree angle), double curve and reverse curve distal tip. An optional Obturator is also available to facilitate Access Sheath positioning into the LAA. (Specific user instructions are not provided for choosing an appropriate Access Sheath tip or when use of the optional Obturator is appropriate; this information has been requested from the applicant.) Upon proper positioning, the device is deployed by unscrewing the core wire from the permanent implant microscrew attachment.

Figure 1: Device Components: This Figure includes images of the four device components including the WATCHMAN Implant, Delivery System, Access System and Obturator.



V. Bench Testing:

The applicant has provided a number of bench tests to evaluate the performance of the device and delivery system. A list of the tests performed to-date is included in Table 1. The permanently implanted LAA closure device that was studied in the clinical trial was designated Gen 2.5 and is the closure device version intended for marketing. The Gen 2.5 device also included a few modifications implemented during the course of the trial, the most significant of which was the introduction of the "short implant" that included a reduced device length. The change was part of an iterative design modification and also introduced in an effort to minimize the potential for pericardial perforation/effusion events. However, the final versions of the Delivery System, Access System and Obturator were not used in the clinical trial. Table 2 includes a summary of the generational changes, noting the version used in the pivotal clinical trial is highlighted in green and the version proposed for marketing depicted in dark red text.

Table 1: Bench Studies. This table includes a list of all the bench studies performed.

Implant
Implant Threaded Insert to NiTi Tube Joint
Core Wire Assembly Wire through Threaded Insert Tensile Strength
Implant Filtration
Implant Deployment and Recapture Force
Implant Mechanical Integrity
Individual Barb Mechanical Integrity
Implant Radial Force
Implant Diameter Recovery
Implant Dislodgement Force
MRI Field Interactions
Implant Corrosion Resistance
Implant Durability/Fatigue
Finite Element Analysis
MR Testing
Delivery System
Delivery System Tensile Strength
Snap Fit Luer Connection Compressive and Tensile Properties
Core Wire Torque Properties
Core Wire Assembly Torquer Bond Strength
Kink Resistance – Delivery System
Contrast Flow Rate – Delivery System
Leak Free Conduits - Delivery System
Corrosion Resistance – Delivery System
Access System and Dilator
WATCHMAN Access System – Tensile Testing
Kink Resistance – Access System
Contrast Flow Rate
Leak Free Conduits – Access System
Access System Distal Tip Deflection
Dilator Tensile Strength
Obturator
Leak Free Conduits - Obturator
Obturator Tensile Strength

Given the initial information provided, FDA is unable to determine whether the changes made to the Delivery System (designated Gen 4), Access System (designated Gen 4) and Obturator (designated Gen 2) warrant additional bench, animal and/or acute (i.e., peri-procedural) clinical studies to support approval of the final versions intended for marketing. Although the changes to the Access System and Obturator are unlikely to be clinically significant, it is unknown whether some changes to the delivery system could impact clinical performance (e.g., change in shaft configuration and elimination of proximal catheter braid). Further information has been requested of the sponsor regarding this issue and is pending.

Table 2: Device Design Generations. This table includes a summary of the changes that comprise the different design generations for the WATCHMAN implant, Delivery System, Access System and Obturator.

Implant	Delivery System	Access System	Obturator
Gen 1 (Pilot Study)	**Gen 1 (Pilot Study)**	**Gen 1 (Pilot Study)** Single and double curve	No Obturator was included in early generations
Gen 2 (Pilot Study) • Modified Barb Angle, Height and Tip Shape	**Gen 2 (Pilot Study)** • Changed catheter shaft materials • Shaft profile changed from stepped ID to single ID • Lengthened shaft by 0.34" • Hub/luer materials changed • Distal tip profile: added tri-cuts and marker bands	**Gen 2 (Pilot Study and Pivotal Study)** • Changed hub configuration from hemostasis seal to touhy borst • Changed hub lead in, body thread start, cap material • Changed dilator color and tip configuration • Introduced reverse double curve • Introduced soft tip, new tip material, vent holes and marker bands at distal tip • Introduced radius soft tip design	
Gen 2.5 (Pilot Study, Pivotal Study and PMA Subject Device • Modified the thread configuration on the implant insert • Introduced 33mm implant • Introduced "short implant" (21, 24, 27, 30, and 33 mm) • Modified short implant barb design	**Gen 2.5 (Pilot and Pivotal study)** • Modified core wire threads • Modified core wire taper profile • Added core wire jacket		**Gen 1 (Pivotal Study)** • Introduced Obturator
	Gen 4 (PMA Subject Device) • Changed catheter shaft configuration from constant ID to stepped ID • Eliminated braid in proximal section of catheter • Proximal Y-adapter and touhy changed to molded components • Added a rotational lock mechanism • Stopcock from 2 way to 3 way • Add removable deployment stop	**Gen 4 (PMA Subject Device)** • Change hub material	**Gen 2 (PMA Subject Device)** • Affixed stopcock and Y-adapter touhy to Obturator

In addition to the tests noted in Table 1 above, the applicant conducted biocompatibility testing, sterility testing, and shelf life testing including either the finished device or device components.

In summary, there are multiple outstanding nonclinical issues outlined to the applicant in our November 25, 2008 major deficiency letter. These include:

- Supporting evidence for applicability of results from tests conducted on prior device generations.
- Supporting evidence or new data to show that selection of device sizes used in testing is representative of the range of performance of the device.
- Clarification regarding the clinical potential and consequences of device "entanglement" during deployment as was seen in a fatigue device sample.
- More stringent testing regarding radiofrequency heating during MR imaging.
- Assessment of the potential for particulate matter to be released from the device.
- Numerous questions regarding the biocompatibility testing conducted, its adequacy, and the need for additional testing.
- Additional information regarding sterilization, specifically regarding bacterial endotoxin testing.

While additional testing, including clinical experience, may be needed to fully address the issues outlined above, the pivotal clinical trial conducted by the applicant would still be the primary dataset upon which a decision regarding marketing approval would be based. Any additional acute clinical data, if needed, would likely be confirmatory in nature only. FDA is continuing to work with the applicant to obtain the additional information needed to address these issues. Further information from the applicant may be available by the time of the Panel meeting.

VI. Animal Studies

The applicant conducted several animal studies to support the PMA application. Overall, 96 animals were studied. Following feasibility evaluation during the device development process, four pivotal animal studies were performed and are summarized in Table 3.

Table 3: Animal Studies Conducted. This table includes a summary of the animal test subjects and study goals for the four pivotal animal studies.

Implant	Test Subjects	Study Purpose
Gen 1	Canine: 14 animals; 72 hrs, 45 days, 180 days	Initial evaluation of ease of implantation, demonstrating that device is not thrombogenic, assessment of endothelial coverage and filter integrity post implantation
Gen 2	Canine: 10 animals; 3 days, 15 days, 33 days	Evaluate modified implant anchoring features and effects on adjacent tissue
Gen 2	Canine: 9 animals; 3 days, 49 days, 91 days	Evaluate tissue integration, stability of fixation and systemic embolization
Gen 2.5	Canine: 6 animals; 3 days, 47 days	Evaluate tissue response, particularly perforation; filter position

The device was extensively studied in a series of four GLP studies in 39 dogs at time points ranging from 72 hours to 182-days. The models included simulated transvenous access as well as thoracotomy in order to visualize the exterior surface of the atrium at placement. The initial two studies did not utilize antiplatelet therapy. The latter two studies utilized combination antiplatelet therapy (75 mg Plavix, 325 mg aspirin orally once daily).

Specific findings of interest in the series of animal studies included:

- Immediately following implantation, the device was visible through the epicardial surface.
- Endocardial thickening was noted at the site of iatrogenic septal defect.
- Early GLP studies utilizing dogs not treated with antiplatelet therapy showed a thick even thrombus on the free atrial device surface at acute time points. Dogs in the same study survived to longer time points, did not appear to experience clinically-relevant adverse events due to this finding.
- Chronic left atrial epicarditis without pericarditis was noted in early studies.
- Use of aspirin and clopidogrel in later GLP studies appeared to reduce both the quantity and organization of acute device-associated thrombus and also the thickness of the neointima that ultimately formed over the device.
- Other pathologic findings included endocardial thickening between the iatrogenic septal defect and the device, moderate LAA distension, and partial to complete sealing of appendage from the atrium.
- There was one case of distal tine penetration of the epicardium (i.e., perforation of the LAA myocardium). This event occurred with the Generation 2 device and appears to have been addressed by the final iterative design ("short" or Generation 2.5 device).
- The clot that intentionally forms within the lumen of the appendage begins as a fibrin-rich pyogranulomatous mass and organizes over time to a more dense fibrin thrombus that is walled off by the device from the circulation.
- There was no reported evidence in the GLP animal studies of device embolization or downstream embolic events.
- There were no device-associated adverse events or device-associated early mortality.

VII. Clinical Trial Design

A. Trial Name: PROTECT AF = WATCHMAN LAA Closure Technology for Embolic PROTECTion in Patients with Atrial Fibrillation

B. Objective: To demonstrate the safety and efficacy of the WATCHMAN device for the prevention of ischemic stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation and who are eligible for warfarin therapy.

C. Design: Prospective, multicenter, randomized controlled trial comparing device implantation plus short term (45-days) warfarin therapy (WATCHMAN) to warfarin therapy (Control).

D. Subjects and Investigational Sites: Rolling enrollment of up to 1,500 patients at 60 investigational sites (US and European).

E. Randomization Scheme: A 2:1 randomization ratio (Device: Control) was used with stratification by center.

F. Endpoints:

Primary Effectiveness Endpoint: Successful treatment of the randomized patient without stroke (including ischemic and hemorrhagic), cardiovascular death (cardiovascular and unexplained) and systemic embolism. The primary analysis is intent-to-treat (ITT).

Primary Safety Endpoint: 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. (Note that there was no hypothesis for the primary safety endpoint and, in its execution, focused on periprocedural events and longer term events related to bleeding or device embolization.)

Primary Technical Endpoint: Device success, defined as successful delivery and release of the WATCHMAN device into the LAA, including successful re-capture and retrieval if necessary.

Secondary Endpoints
There were no pre-specified hypotheses for secondary endpoints, so only descriptive statistics were to be reported for these endpoints.

1. WATCHMAN and Control Group:

    - Transient Ischemic Attack (TIA), defined as an acute focal neurological event lasting at least 5 minutes and up to 24 hours that is MR imaging negative. All TIAs were to be adjudicated by the CEC.
    - Other individual complication rates including, but not limited to MI and death.

2. WATCHMAN Group:
    - Technical Success defined as successful delivery and release into the LAA including successful recapture and retrieval if necessary.
    - Procedure Success defined as technical success and no serious adverse events related to the treatment or procedure within the hospital stay.
    - 30-day Major Complication Rate defined as death, stroke, MI or any other serious adverse events related to the treatment or procedure within the first 30 days or through hospital discharge (whichever is longer).
    - Individual complication rates including, but not limited to hematomas and pseudoaneurysms.

3. Control Group:
   - Non-therapeutic INR (INR > 3.0 INR or < 2.0) or stopped therapy.
   - Excessive anticoagulation INR > 4.0.
   - Bleeding complications: hematuria, rectal bleeding, epistaxis, bleeding from varicose veins, oral bleeding, prolonged bleeding from a laceration, or bruising-hematoma, hemothorax, red eye, thrombosis, or retroperitoneal bleeds.

G. Device Placement plus Short Term (45-day, window ≤ 60 days) Warfarin Therapy (WATCHMAN Arm): Permanent placement of the device into the LAA using a transseptal puncture technique. Patients were assessed at 45 days post-procedure and if a TEE demonstrated complete LAA occlusion, warfarin therapy could be discontinued. Continuation of warfarin was at the discretion of the treating physician. If warfarin was discontinued, patients remained on clopidogrel for 6 months and aspirin for at least the duration of the trial.

H. Anticoagulation Therapy (Control Arm): An inclusion criterion specified that all patients must either be on warfarin or candidates for warfarin therapy. It was planned that warfarin therapy would be initiated or that patients would remain on warfarin therapy (target INR = 2.0-3.0) for the duration of the trial.

I. Statistical Hypothesis for Evaluation of Primary Effectiveness Endpoint: A formal hypothesis was established only for the primary effectiveness endpoint. The other primary endpoints (primary safety endpoint and primary technical endpoints) were to be presented in terms of observed rates and confidence intervals only; no comparisons between groups were planned. FDA concurred that since safety and effectiveness are captured in the primary endpoint, a separate powered hypothesis for the safety endpoint was not essential. FDA did note, however, as a future PMA concern that the contributions of the individual composite endpoint components should be fully analyzed.

A Bayesian model was established to evaluate the primary endpoint. (See Appendix B for a brief summary of Bayesian statistics.) The number of events was assumed to follow a Poisson distribution with a parameter, λ (hazard rate). In this study design, λ was assumed to be a constant during any follow-up period. In the Bayesian analysis, a non-informative prior distribution (Γ (0.001, 0.001)) was assumed for λ, and there were no historical data borrowed from other studies.

A sequential analysis plan was established with initial evaluation after 600 patient years of follow-up, with subsequent evaluations after each additional 150 patient years, up to a maximum of 1,500 patient years of follow-up. At each evaluation, the posterior probabilities would be assessed within each criterion described below. The posterior probability was first assessed for futility, and then non-inferiority (and, if applicable, superiority). If neither futility (the applicant referred to this as "not non-inferior") nor non-inferiority was declared, an additional 150 patient years of follow-up would be collected before the next evaluation time point, up to a limit of 1,500 patient years of follow-up. If, after the maximum of 1,500 patient years of follow-up, the WATCHMAN was not established as "non-inferior," the device would be considered "not non-inferior."

The first interim analysis was performed after collection of 600 patient years of follow-up which included 282 patients (185:97 for device:control) with one year of follow-up. Among 282 patients who had one year of follow-up, 91 patients (60:31 for device:control) had two years of follow-up. The trial was formally stopped after this interim analysis because non-inferiority had been demonstrated according to the predefined stopping rules at 600 patient-years. Hence, the primary dataset submitted in the PMA and presented in this Executive Summary is based on the 600 patient-year follow-up, with additional supporting data from a supplemental 900 patient-year follow-up cohort.

Criterion for Futility ("Not Non-Inferiority"): Futility was declared if the posterior probability that the event rate for the device group is greater than or equal to the event rate for the control group was 0.95 or greater. If futility was declared, no assessment of non-inferiority or superiority was made. Stop for futility would occur if it was highly unlikely that a finding of non-inferiority would be achieved by 1,500 patient years.

Criterion for Non-inferiority: Non-inferiority was declared if the posterior probability that the event rate for the device group is less than 2 times the event rate for the control group was at least 0.975 and the preceding criterion for futility was not met. In addition, to demonstrate non-inferiority, the posterior probability that the event rate for the device group is less than the event rate for the control group must be at least 0.05.

Criterion for Superiority: Superiority was declared if the posterior probability that the event rate for the device group is less than the event rate for the control group was at least 0.95. The superiority test was to be performed only if non-inferiority could be established.

J. Follow up Schedule:

All enrolled patients in both groups were required to receive follow-up assessments to re-assess medical status and evaluate for the occurrence of adverse events. Assessments where made according to the schedule in Table 4.

Table 4: Patient Assessments. This table depicts the baseline and follow-up assessment for the WATCHMAN and Control Groups.

	Baseline	45-day	6 mo	9 mo	12 mo and annual	Semi-annual
WATCHMAN						
TEE	X	X	X		X	
INR*	X	X	monthly if continue warfarin	monthly if continue warfarin	monthly if continue warfarin	monthly if continue warfarin
CONTROL						
INR**	X	X	X monthly	X monthly	X monthly	X Monthly
ALL ENROLLED						
TTE	X					
Blood work	X					
HR, BP	X	X			X	
neurological assessment	X	X			X	
NIH stroke scale	X	X			X	
Barthel Index	X	X	X	X	X	X
Modified Rankin Scale	X	X	X	X	X	X
SF-12v2 Health Survey	X				X	
Brain Imaging (CT/MR) and stroke scales	X	as needed	as needed	as needed	as needed	as needed

* INR checks required every other week through 45-day visit; however, if WATCHMAN patients continue warfarin beyond this visit, INR checks should be done every other week through 6 months and monthly thereafter if required.
** INR should be obtained every other week for CONTROL patients from randomization until 6 months and monthly thereafter.

Annual office visits and semi-annual telephone follow-up are required for all patients up to 5 years, or until the study is terminated or sufficient information for regulatory authorities has been obtained.

K. Patient Selection Criteria:

Selected Inclusion Criteria

a) 18 years of age or older;
b) paroxysmal (with appropriate documentation) persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease);
c) eligible for long-term warfarin therapy;
d) eligible to come off warfarin therapy if the LAA is sealed, i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice;
e) calculated $CHADS_2$ score of 1 or greater;

Selected Exclusion Criteria

Clinical (pre-echocardiography) Exclusion Criteria

a) New York Heart Association Class IV Congestive Heart Failure (defined as: a patient with severe physical limitations, experiencing symptoms even while at rest);
b) recent MI (within 3 months);
c) patient had a single occurrence of AF;
d) ablation procedure planned within 30 days of potential WATCHMAN device implant;
e) resting heart rate >110 bpm;
f) patient had a transient case of AF [i.e., secondary to recent CABG (within 3 months), etc.];
g) symptomatic carotid disease (i.e., carotid stenosis ≥ 50% associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months);
h) prior embolic stroke or TIA within the last 30 days;
i) requires long-term warfarin therapy:
    - Secondary to conditions such as prior arterial embolism or other indications such as pulmonary embolism or deep vein thrombosis within the previous 6 months;
    - The patient is in a hypercoagulable state; exclude the patient if per medical record documentation, the patient meets any of the following criteria:
        1. Thrombosis occurring at a young age (i.e. less than 40 y/o);
        2. Idiopathic or recurrent VTE (venous thromboembolism);
        3. Thrombosis at an unusual site (cerebral veins, hepatic veins, renal veins, IVC, mesenteric veins);
        4. Family history of VTE or of inherited prothrombotic disorder;
        5. Recurrence/extension of thrombosis while adequately anti-coagulated;
    - The patient is contraindicated for warfarin therapy;
j) contraindicated for aspirin.

Echocardiographic Exclusion Criteria (as assessed via TTE and TEE)

a) LVEF <30%;
b) intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant;
c) high risk patent foramen ovale (PFO)
d) significant mitral valve stenosis (i.e., MV <1.5 cm^2);
e) existing pericardial effusion of >2 ±1 mm
f) complex atheroma with mobile plaque of the descending aorta and/or aortic arch.
g) cardiac tumor.

L. Key Definitions

Key definitions for the PROTECT AF pivotal trial are found in Appendix A.

VIII. Clinical Trial Results

A. Introduction

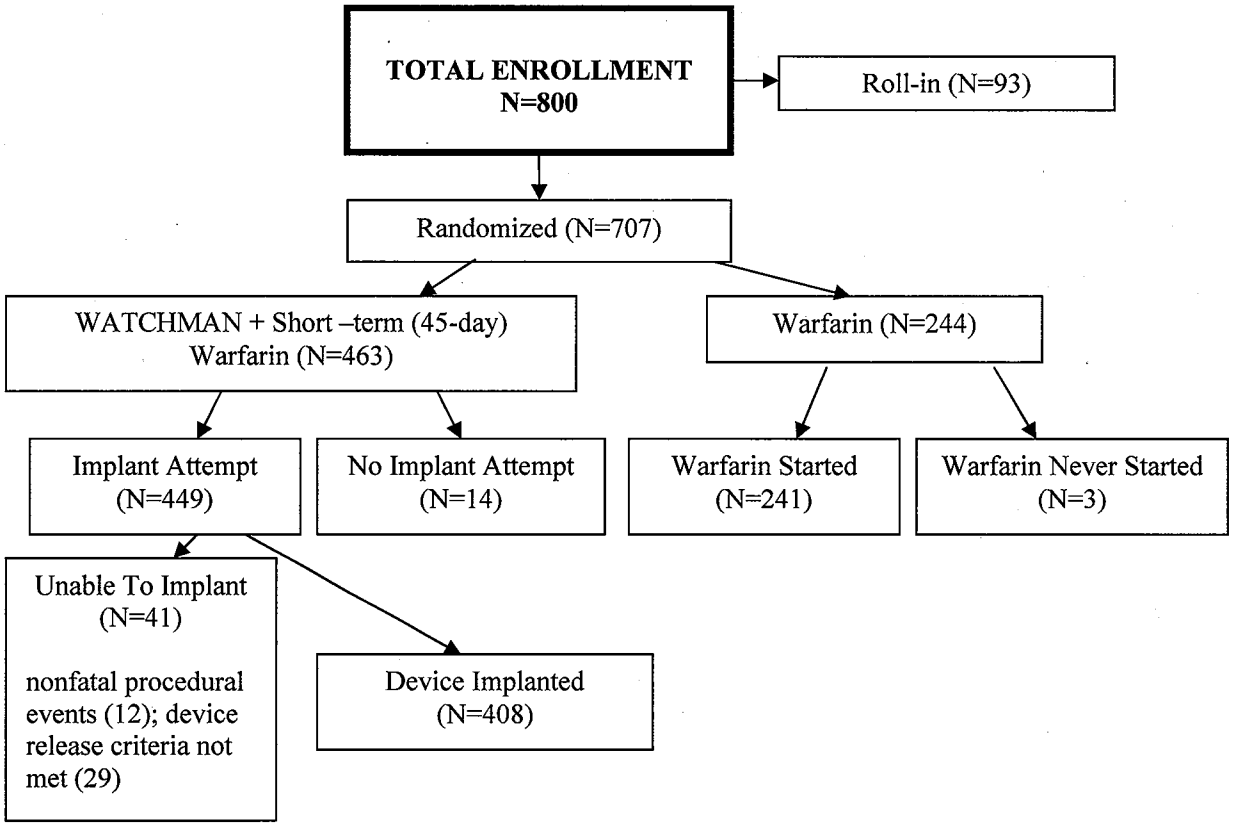
The pivotal trial results for the PROTECT AF trial including the evaluation of the WATCHMAN device plus short term (45-day, window ≤ 60 days) warfarin therapy compared to warfarin therapy will be presented and discussed. While reviewing this information, please consider the following issues:

- The trial design was intended to evaluate the WATCHMAN device plus 45 days of warfarin compared to standard warfarin treatment. The impact of the device alone (i.e., without concomitant warfarin therapy) is therefore only evaluable after the 45-day visit in those patients who actually discontinued warfarin.
- The trial was not designed with typical endpoints (i.e., one addressing effectiveness and one addressing safety). In this trial, the primary effectiveness endpoint captures the events that would also be considered significant safety events (i.e., stroke, death and systemic embolism). In the device arm, the safety endpoint is limited to periprocedural events and longer-term events related to bleeding or device embolization. Therefore, ischemic strokes that occurred in the device arm after hospital discharge were considered effectiveness events and were not counted as safety events.
- The primary effectiveness endpoint was to be evaluated as a non-inferiority hypothesis. However, the hypothesis was that the event rate in the device arm would be non-inferior to 2 times the event rate in the control arm. Therefore, the posterior probabilities reported from the Bayesian analysis do not assess equivalence of the two therapies, but instead whether the event rate in the device arm is less than 2 times that in the control arm. (Note that the non-inferiority criterion proposed by the applicant for this trial carried the inherent risk that the trial results would be difficult to interpret if the resultant device event rate is considered "high.")
- Warfarin use in this trial was a significant confounding issue for both the device and control arms. In the device arm, a number of patients remained on warfarin beyond 45 days, and in the control arm, a number of patients discontinued or interrupted warfarin therapy during follow-up. Maintenance of therapeutic INR was difficult in both arms as has been the case for similar trials.
- Although allowed per the protocol, concomitant aspirin and clopidogrel use in the device arm, confounds interpretation of results.

B. Patient Accountability

For the updated 900-patient-year dataset, 800 patients were enrolled in the trial at 59 centers (55 U.S. and 4 European). This total included 463 patients randomized to the WATCHMAN group, 244 patients randomized to the Control group and 93 roll-in patients. Patient accountability is summarized in Figure 2.

Figure 2: Patient Accountability. This figure represents the total number of patients enrolled in the trial and how many patients were randomized to the WATCHMAN and Control arms. For device patients, implant attempts are also depicted.



C. Patient Demographic and Baseline Characteristics

Baseline demographic analyses of both the 600 and 900 patient-year datasets do not indicate significant differences between the treatment and control groups (Table 5). Of note is the disproportionate number of male patients (~70%) compared to female patients (~30%) as well as the disproportionate number of Caucasian patients (~92%) compared to all other racial groups combined (~8%) included in both the WATCHMAN and Control groups. Although the risk of developing AF is estimated to be 1.5 times greater in men,[4] when one considers the higher number of elderly women versus men in the population, the prevalence of the disease begins to equalize. The prevalence of AF is also estimated to be higher in Caucasian than non-Caucasian patients;[5] however, the true difference is unclear. Nonetheless, the representation of gender and race in the PROTECT AF trial is consistent with trends in major trials evaluating atrial fibrillation that have also included large number of Caucasian men.

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[4] Benjamin EJ, Levy D, Vaziri S, et al. Independent risk factors for atrial fibrillation in a population-based cohort of the Framingham Heart Study. JAMA 1994;271:840-844

[5] Ruo B. Capra AM . et al. Racial Variation in the Prevalence of Atrial Fibrillation Among Patients with Heart Failure. J Am Coll Cardiol. 2004; 43: 429-435.

Table 5: Baseline Demographics based on 900-patient year analysis. This table includes a comparison of age, gender, race, height and weight between the WATCHMAN and Control Groups.

Characteristic	Device (N=463)	Control (N=244)	P-value
Age (years)	71.7 ± 8.8 (46.0, 95.0)	72.7 ± 9.2 (41.0, 95.0)	0.1800
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)	
Height	68.2 ± 4.2 (54.0 , 82.0)	68.4 ± 4.2 (59.0, 78.0)	0.6067
Weight	195.3 ± 44.4 (85.0, 376.0)	194.6 ± 43.1 (105.0, 312.0)	0.8339

Two sample t-tests or chi-square tests, as appropriate, were used to compare the baseline risk factors for the randomized groups (Table 6). Although many baseline risk factors in the control group were noted at a slightly higher frequency, there were no statistically significant differences between the treatment and control groups. The percentage of patients ≥ 75 years-old was initially statistically significantly higher in the control group for the 600-patient cohort (p-value = 0.0894), but the statistically significant difference did not persist in the 900 patient-year cohort. Note that the patient population is weighted towards lower risk patients (by $CHADS_2$ score) in this study (68% $CHADS_2$ 1/2 vs 5% $CHADS_2$ 5/6 in the device arm).

Table 6: Baseline Risk Factors based on 900-patient year analysis. This table includes a comparison of numerous baseline risk factors between the WATCHMAN and Control Groups.

Risk	Device (N=463) %	Control (N=244) %	P-value
$CHADS_2$ Score			0.3662
1	34.1	27.0	
2	33.9	36.1	
3	19.0	20.9	
4	8.0	9.8	
5	4.1	4.1	
6	0.9	2.0	
CHF	26.8	27.0	0.9392
History of HTN	89.0	90.2	0.6284
Age ≥ 75	41.0	47.1	0.1198
Diabetes	24.4	29.5	0.1423
Previous TIA/ischemic stroke	17.7	20.1	0.4404
AF pattern			0.7623
Paroxysmal	43.2	40.6	
Persistent	21.0	20.5	
Permanent	34.6	38.1	
unknown	1.3	0.8	
LVEF	57.3 ± 9.7	56.7 ± 10.1	0.4246

D. Primary Effectiveness Results

1. Intent-To-Treat (ITT) Analysis

The Intent-To-Treat (ITT) population was defined as all patients randomized to either the WATCHMAN or Control arm, regardless of treatment actually received. The primary analysis was stratified by $CHADS_2$ score.

The applicant has conducted the primary effectiveness analysis on the ITT Population for both the 600 patient-year and 900 patient-year cohorts (Table 7). Please note that the 600 patient-year cohort was submitted as the primary dataset as specified in the statistical plan and the applicant subsequently updated this dataset with the 900 patient-year cohort, the results of which are also provided below. Rates are calculated per 100 patient-years of follow-up.

Table 7: Primary Effectiveness Endpoint (ITT). This table depicts the Bayesian analysis primary effectiveness results for the 600 and 900 patient-year cohorts.

Device			Control			Rel Risk (RR*)	Posterior Prob.	
N pts	N Events / Total Pt-yrs	Rate**	N pts	N Events / Total Pt-yrs	Rate**	(95% CI*)	Non-inferiority	Superiority
454 600 pt-yr	18/409.3	4.4 (2.6, 6.7)	238	13/223.6	5.8 (3.0, 9.1)	0.76 (0.39, 1.67)	0.992	0.734
463 900 pt-yr	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

* CI is credible interval. RR is the relative risk of device over control.
** Rate = event rate per 100 patient years (calculated as 100*N events/total patient-years).

The applicant has concluded that the primary effectiveness endpoint (the event rate in the device arm being less than two times the control rate) was met, but the superiority hypothesis was not met. For the 900 patient-year data, their conclusion is based on a decreased primary efficacy event rate per 100 patient-years in the WATCHMAN group (3.4%) compared to the Control group (5.0%) yielding a relative risk (RR) of 0.68 correlating with a 32% lower efficacy event rate in the WATCHMAN arm compared to the Control arm. The 95% credible interval (CI) for the rate ratio is 0.37 to 1.41, implying that the upper bound of 1.41 is lower than the non-inferiority margin of 2.0. In this case, the posterior probability of non-inferiority (0.998) exceeds the pre-specified non-inferiority criterion (≥ 0.975). The Kaplan Meier curve and estimates for the Primary Effectiveness ITT analysis are included in Figure 3 and Table 8, respectively.

Of the 20 events in the device arm (900 patient-year cohort), 11 occurred in patients who had discontinued warfarin at 45 days, with 2 of the 11 patients having restarted warfarin at a later date. An additional 3 events occurred in patients who discontinued warfarin at a point beyond the 45-day visit. The remaining 6 events in the device arm occurred in patients who did not ultimately receive a device, or for whom no warfarin information was available. Of the 16 events in the control arm (900 patient-year cohort), 10 occurred in patients who were on warfarin, 5 occurred in patients who had discontinued or interrupted warfarin therapy and 1 occurred in a patient who had no information recorded regarding warfarin status.

Figure 3: Kaplan-Meier Curve for Primary Effectiveness Endpoint (ITT). This figure includes a depiction of the Event-Free Probability of a primary endpoint event for the WATCHMAN and Control patients over time.

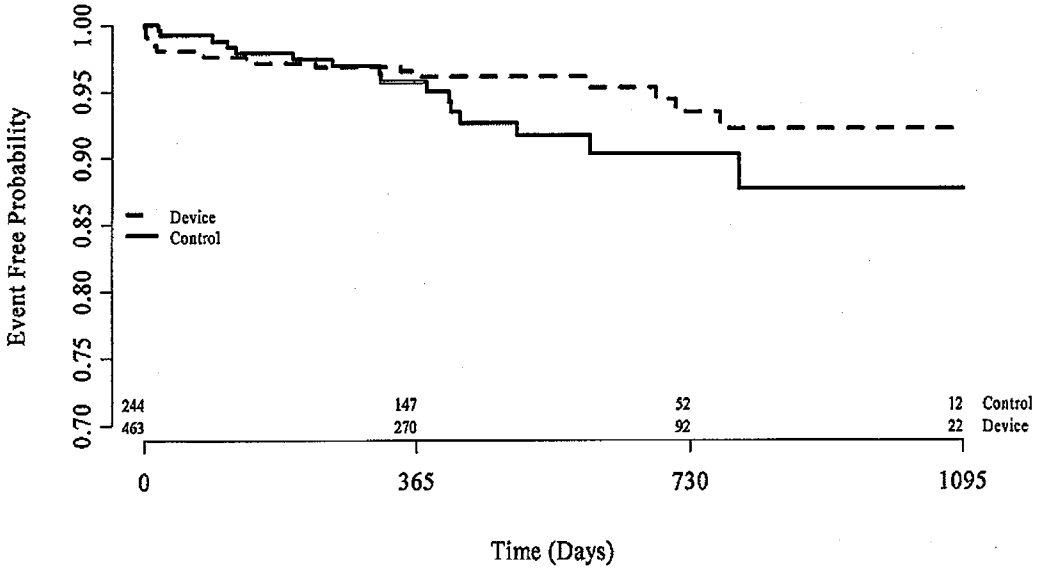

Table 8: Kaplan-Meier Estimates for Freedom from Primary Effectiveness Endpoint Event (ITT). This table includes an accounting of the number of primary effectiveness endpoint events that occurred during each time point for the WATCHMAN and Control patients.

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	7	7	98.5 (97.4, 99.6)	0	0	100.0 (100.0, 100.0)
45-days	2	9	98.0 (96.8, 99.3)	2	2	99.2 (98.0, 100.0)
6-months	4	13	97.1 (95.5, 98.6)	3	5	97.9 (96.0, 99.7)
1-year	2	15	96.4 (94.7 , 98.2)	4	9	95.7 (93.0, 98.5)
2-year	4	19	93.5 (90.0 ,96.9)	6	15	90.3 (85.2, 95.4)
3-year	1	20	92.1 (87.8 , 96.4)	1	16	87.7 (80.5, 94.8)

The rates of the individual components of the primary effectiveness endpoint were also analyzed (Table 9) revealing that the rates of ischemic strokes and systemic embolism were numerically higher, although not statistically significantly higher, in the WATCHMAN arm in both cohorts, but there were numerically fewer deaths and hemorrhagic strokes in the device arm compared to the control. Note that the absolute number of events is not directly comparable given the 2:1

device:control randomization ratio. Also note that these are ITT results and this is a time-to-event analysis; therefore, only the first event was counted and reported in Table 9. For example, if a patient had a non-fatal event and then died, only the non-fatal event is counted below. See Sections on Primary Safety Evaluation and Mortality below.

Table 9: Event Rates for Components of the Primary Effectiveness Endpoint (ITT). This table includes reporting of the percentage of randomized patients in both the WATCHMAN and Control groups who had stroke, systemic embolic events, or died.

Type	600-patient-year dataset				900-patient-year dataset			
	Device		Control		Device		Control	
	N Events	% of Randomized patients	N Events	% of Randomized patients	N Events	% of Randomized patients	N Events	% of Randomized patients
Stroke – Ischemic	13	2.9	4	1.7	14	3.0	5	2.0
Death (Cardiovascular or unexplained)	2	0.4	5	2.1	3	0.6	5	2.0
Stroke – Hemorrhagic	1	0.2	4	1.7	1	0.2	6	2.5
Systemic Embolism	2	0.4	0	0.0	2	0.4	0	0.0

Mortality

In total, there were 17 deaths in the WATCHMAN group and 15 deaths in the control group over the course of the trial; some of which are included in Table 9 if they were counted towards the primary effectiveness endpoint.

Of the 17 deaths in the WATCHMAN group, two were not counted as effectiveness events, but were linked to prior strokes that were captured as initial effectiveness events. One was a hemorrhagic stroke 15 days after implant when the patient had an INR of 5.8. The second was an ischemic stroke which occurred after randomization but before the device could be implanted.

The Clinical Events Committee (CEC) did not attribute any of the other deaths to the device. This lack of attribution to the device/procedure is difficult to interpret clinically, given the following narratives:

- One patient ([redacted]) had a right middle cerebral artery infarct presumed due to air embolism during the device implantation (with device recapture x 2) which resulted in profound disability (Modified Rankin = 5) and confinement to a nursing home until the patient died 8 months later. The cause of death was attributed to urosepsis and was not linked to a primary efficacy event (ischemic stroke). The applicant does not classify this as a fatal stroke related to the device. This death was not linked to the stroke.
- Another patient ([redacted]) had the device implanted and required two device recaptures. She was diagnosed with an ischemic stroke after the implant and had right arm weakness and trouble swallowing. She was discharged to a progressive care unit for rehabilitation

and treatment. She died 8 weeks later with CHF and renal failure. This death was not linked to the stroke.

Of the 15 deaths in the control group, 5 were linked to initial effectiveness events. These include:

- Patient [redacted] who died from "failure to thrive and pneumonia after stroke." This should be contrasted to the patient listed above whose death was not linked to a primary effectiveness endpoint stroke event.
- Another of the control deaths (patient [redacted]) was listed in Table 10-21 (page 68 of applicant's executive summary) as a death due to ventricular arrhythmia secondary to cardiovascular disease. However, the death summary in the PMA submission states that this patient was diagnosed with lung cancer 5 months after enrollment and died of an unknown cause 3 months after the cancer diagnosis. There was no mention of a cardiovascular cause.
- Another of the deaths [redacted] was attributed to a cardiovascular cause. The patient died in Nicaragua, but no medical records were available. The information came from a telephone call from a relative.
- Patient [redacted] died at home and was dead 30 minutes before EMS arrived. He did not have an autopsy. The death certificate was signed out as acute coronary insufficiency.

Strokes and Systemic Thromboembolism

This device was intended to reduce the risk of systemic and cerebral thromboembolism. However, in the 900 patient-year cohort, there were 16 episodes of thromboemboli in the WATCHMAN group, 7 of which occurred on the day of or within 30 days of the implant procedure.

An evaluation of any stroke (ischemic or hemorrhagic) reveals a lower number of strokes on a 100-patient year basis in the device arm, 2.6 (15/582.9 pt-yrs) compared to the control arm, 3.5 (n=11/318.1).

Assessment of Constant Hazard Rate Assumption

Because the Bayesian Poisson-Gamma model was used for the primary endpoint analysis, a constant hazard rate for each treatment arm was assumed (i.e., constant primary endpoint event rate over every follow-up interval). However, the data from the 600 patient-year and 900 patient-year cohorts indicated that for the device arm, such an assumption was not valid, with significant non-homogeneity of event rates in the device arm. Therefore, sole reliance on the planned statistical analysis may be problematic. Results of the applicant's and FDA's calculations for the 600 patient-year cohort may be found in Tables 10-1 and 10-2, respectively and for the 900 patient-year cohort in Tables 10-3 and 10-4, respectively. Please note that FDA's analyses are slightly different than the applicant's because FDA did not have access to the same SAS method as the applicant.

Table 10 - 1: Homogeneity of Primary Effectiveness Endpoint Event Rates (Events/Patient-years) Over 6 Month Intervals (ITT). This table includes event rates for the WATCHMAN and Control arms for each follow-up period

(600 patient-year dataset) (Applicant's calculation).

Group	0-6 m	6-12 m	12-18 m	18-24 m	24-30 m	P-value*
Device	7.47	0.84	1.65	5.58	5.72	0.0786
Control	4.25	6.25	11.27	4.87	0.00	0.5732

* P-values were calculated by the applicant via Monte Carlo estimates for a test of homogeneity of Poisson rates across strata separately for each treatment group.
Rates are calculated per 100 patient-years of follow-up during the intervals based on the date of randomization.

Table 10 - 2: Homogeneity of Primary Effectiveness Endpoint Event Rates (Events/Patient-years) Over 6 Month Intervals (ITT). This table includes event rates for the WATCHMAN and Control arms for each follow-up period.

(600 patient-year dataset) (FDA's calculation)

Group	0-6 m	6-12 m	12-18 m	18-24 m	24-30 m	P-value*
Device	7.47	0.84	1.65	5.58	5.72	0.045
Control	4.25	6.25	11.27	4.87	0.00	0.596

* P-values were calculated by FDA via SAS procedure Genmod for a test of homogeneity of Poisson rates across strata separately for each treatment group.
Rates are calculated per 100 patient-years of follow-up during the intervals based on the date of randomization.

Table 10 - 3: Homogeneity of Primary Effectiveness Endpoint Event Rates (Events/Patient-years) Over 6 Month Intervals (ITT). This table includes event rates for the WATCHMAN and Control arms for each follow-up period.

(900 patient-year dataset) (Applicant's calculation)

Group	0-6 m	6-12 m	12-18 m	18-24 m	24-30 m	P-value*
Device	6.37	1.22	0.93	5.21	3.13	0.0691
Control	4.36	4.40	9.08	3.17	5.92	0.7667

* P-values were calculated by the applicant via Monte Carlo estimates for a test of homogeneity of Poisson rates across strata separately for each treatment group.
Rates are calculated per 100 patient-years of follow-up during the intervals based on the date of randomization

Table 10 - 4: Homogeneity of Primary Effectiveness Endpoint Event Rates (Events/Patient-years) Over 6 Month Intervals (ITT). This table includes event rates for the WATCHMAN and Control arms for each follow-up period.

(900 patient-year dataset) (FDA's calculation)

Group	0-6 m	6-12 m	12-18 m	18-24 m	24-30 m	P-value*
Device	6.37	1.22	0.93	5.21	3.13	0.034
Control	4.36	4.40	9.08	3.17	5.92	0.599

* P-values were calculated by FDA via SAS procedure Genmod for a test of homogeneity of Poisson rates across strata separately for each treatment group.

Rates are calculated per 100 patient-years of follow-up during the intervals based on the date of randomization.

Several additional statistical analyses were consequently performed to assess the performance of the WATCHMAN in terms of the primary effectiveness endpoint. Because a non-constant hazard rate was observed, the applicant also performed the pre-specified Bayesian piecewise proportional hazards model with (or without) adjustment for $CHADS_2$ score to calculate the 95% credible interval for the hazard ratio of the primary endpoint (Table 11).

Table 11: Hazard Ratio of Primary Effectiveness Endpoint (ITT). This table reports the hazard ratio and credible interval for proportional and piecewise hazards models.

Model	Hazard Ratio (Device/Control)	95% Credible Interval
Bayesian Proportional Hazards Model	0.81	(0.37, 1.60)
Bayesian Proportional Hazards Model, stratified by $CHADS_2$	0.83	(0.37, 1.64)
Bayesian Piecewise Hazards Model	0.83	(0.38, 1.65)
Bayesian Piecewise Hazards Model with $CHADS_2$ Adjustment	0.88	(0.40, 1.73)

The Bayesian Piecewise Hazards Model (with CHADS2 adjustment) can be used to assess the primary endpoint with respect to hazard ratio, which remains less than 1.0, slightly in favor of the device arm. While such an analysis is supportive of the applicant's conclusions, it cannot be used to fully assess the impact of a nonconstant hazard rate on the calculated posterior probabilities provided by the original Poisson-Gamma Model.

An alternative approach for further examination of the primary endpoint is to perform a post-hoc Frequentist analysis. This approach is useful since the prior distribution assumed in the original Bayesian model was a noninformative one and therefore, one would assume reasonable consistency between the Bayesian and Frequentist results. Although the Frequentist approach also relies on an assumption of a constant hazard rate, the results of this analysis do, in fact, suggest that the post-hoc Frequentist calculations and conclusions are generally supportive of the original inferences provided by the Bayesian model, i.e., the ITT primary effectiveness event rate of the device arm is statistically significantly less than two times the control event rate (p=0.004) (Table 12).

Table 12: Primary Effectiveness Endpoint ITT analysis using Frequentist approach. This table depicts the Frequentist analysis of the primary effectiveness results for the 600 and 900-patient year cohorts.

	Device			Control		RR	RR* adjusted for CHADS2 (95% CI*)	P-value for non-inferiority	P- value for Superiority
N pts	N Events / Total Pt-yrs	Rate**	N pts	N Events / Total Pt-yrs	Rate**				
454 600 pt-yrs	18/409.3	4.4	238	13/223.62	5.8	0.76	0.79 (0.38, 1.76)	0.013	0.266
463 900 pt-yrs	20/582.3	3.4	244	16/318.04	5.0	0.68	0.71 (0.36, 1.46)	0.004	0.166

* CI is credible interval. RR is the relative risk of device over control.
** Rate = event rate per 100 patient years (calculated as 100*N events/total patient-years).

2. Per Protocol Analysis

The applicant prespecified a per-protocol analysis that excluded device patients who did not receive the device or who did not discontinue warfarin therapy, and control patients for which there was no evidence of warfarin use at either baseline or 45 days. Although not pre-specified, the applicant calculated time-to-event from the date of warfarin discontinuation for the device arm; for the control arm, time-to-event was calculated from date of randomization.

The applicant has performed the per-protocol analysis on both the 600 and 900 patient-year cohorts. In the device arm, excluded patients 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.

Interpretation of the per-protocol analysis is complicated by: (1) inclusion of all patients with the device implanted and who initially stopped warfarin, no matter whether warfarin was stopped after the 45-day visit and/or re-initiated; and (2) inclusion of only the events that occurred after warfarin was stopped initially, thus excluding all events occurring during the procedure and before initial warfarin treatment was stopped. This analysis biases the results towards the device group because of the exclusion of a large proportion of the device adverse events and the introduction of selection bias.

3. Post-Procedure analysis

The protocol included an additional pre-specified secondary analysis referred to as the "post-procedure" analysis. This analysis excludes any patient with an adverse event that occurred either before or on the date of device implant. The clinical evaluation of this additional analysis is difficult since it differentially excludes adverse events in only the test arm. The FDA does not view this analysis as clinically meaningful.

4. Confounding factors in evaluation of effectiveness

Warfarin Discontinuation

Warfarin use varied among the device and control groups and many device patients continued warfarin therapy after the intended short term 45-day window. Reasons for continuation of initial warfarin therapy included 12% (55/442) of patients who did not have the device successfully implanted and an additional combined 14 % (62/442) of patients who remained on therapy (> 60 days) for reasons such as: flow around the device at 45 days, physician preference , device explant or embolization, TEE not done, and thrombus on the device.. (Note that the sponsor reports 52 patients who did not discontinue warfarin when a different SAS variable is used for the analysis.)

Table 13: Warfarin Discontinuation from Date of Implantation – Device arm (FDA's calculation). This table depicts reasons for discontinuation of warfarin in the device arm and the number of patients in each category.

	Warfarin Use Unknown		Warfarin Use Discontinued Pos-Device Implantation				
Group	Not Implanted	No Information	≤ 60 days	60 days ~ 225 days	225 days ~ 410 days	410 days ~ 775 days	Total
Device 900 pt-yrs	55	21	325	51	6	5	463

In the 900 patient years dataset, for the 55 patients without the device implanted and 21 patients without any warfarin discontinuation information, the warfarin restart information is not available (Table 13). However, for the remaining 387 patients, of the 325 patients who discontinued warfarin at or before 60 days, 32 later restarted therapy, and among the 62 patients who did not discontinue initial warfarin therapy until after 60 days, 4 later restarted therapy.

In the control arm, 65/238 (27.3%) of patients had warfarin therapy discontinued or interrupted during the study (Table 14).

Table 14: Warfarin Discontinuation – Control arm (FDA's calculation). This table depicts reasons for discontinuation of warfarin in the control arm and the number of patients in each category.

Group	No warfarin information recorded in CRF	Discontinued/interrupted warfarin	Stayed on warfarin*	Total
Control 600 pt-yrs	2	65	171	238
Control 900 pt-yrs	3	84	157	244

* Regardless of INR status

To evaluate the impact of warfarin discontinuation in device patients, FDA calculated the primary effectiveness event rates by warfarin discontinuation status at the 45 day visit, calculated from the implantation date for both the 600 and 900-patient-year cohorts (Tables 15-1 and 15-2). In the 600 patient-year cohort, the event rate appears slightly numerically higher in the patient cohort who discontinued warfarin at 45-day visit compared to the patient cohort who continued warfarin at 45-day visit, but due to the small sample size, a statistically significant difference is not able to be detected. In the 900 patient-year cohort, the event rate in those patients who continued warfarin becomes slightly higher than that in patients who discontinued warfarin at 45 days. The differences between cohorts may be due to the differential follow-up and the differences in hazard rates discussed above.

Table 15 - 1. Device Primary Effectiveness Endpoint by warfarin status. This table depicts the primary endpoint adverse event rate for patients who continued and discontinued warfarin by warfarin discontinuation status at the 45 Day Visit (≤ 60 days after implantation) (for patients who had warfarin discontinuation information recorded) (600 patient years dataset, FDA's calculation)

Warfarin Status at 45 day visit	# of Patients	# of Events / Patient years	Event Rate*
Discontinued	306	9/306.565	2.94
Continued	56	2/72.266	2.77

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

Table 15 - 2. Device Primary Effectiveness Endpoint by warfarin status. This table depicts the primary endpoint adverse event rate for patients who continued and discontinued warfarin by warfarin discontinuation status at the 45 Day Visit (≤ 60 days after implantation) (for patients who had warfarin discontinuation information recorded) (900 patient years dataset, FDA's calculation)

Warfarin Status at 45 day visit	# of Patients	# of Events / Patient years	Event Rate*
Discontinued	325	11/449.24	2.45
Continued	62	3/98.59	3.04

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

Table 16 is provided below to evaluate the impact of warfarin therapy on the incidence of ischemic strokes and systemic embolism. Of the 16 total events, 6 ischemic strokes and 1 systemic embolism occurred on the day of or within 30 days of the procedure; 3 patients were on warfarin at the time of the event, but INRs were subtherapeutic. Post-procedure (all beyond 60 days post-implant) 6 ischemic strokes and 1 systemic embolism occurred in patients off warfarin and 1 ischemic stroke occurred in a patient on warfarin due to flow in the LAA. Finally, one ischemic stroke occurred in a patient after randomization but prior to implantation (device not implanted). Both cases of systemic embolism were retinal arterial occlusions.

Table 16. Device Ischemic Strokes and Systemic Emboli categorized by procedure-related and warfarin status. This tables depicts the number of pre-procedure events, events temporally related to the procedure, and events not temporally related to the procedure, including which events occurred on and off warfarin.

	Pre-procedure	Temporally Related to Procedure	Not Temporally Related to Procedure	
			Off Warfarin	On Warfarin
Ischemic Stroke (n=14)	1	6	6	1
Systemic Embolism (n=2)		1	1	

Total Duration of Warfarin Therapy

The applicant has provided an analysis of the percent of follow-up time that patients in both arms were on warfarin medication. This analysis only includes those patients who successfully received the device. Table 17 below displays summary statistics of the percentage of time on warfarin therapy by randomized group; this was calculated by dividing the total amount of time on warfarin for each treatment group divided by the total amount of follow-up time. Even excluding those patients who did not receive a device, and therefore remained on warfarin, patients with the device remained on warfarin for 19-23% of the follow-up time, potentially confounding the effectiveness analyses.

Table 17: Percent of Follow-Up Time on Warfarin. This table includes the medication-years and the percentage of follow-up time on warfarin for both the 600 and 900-patient year cohorts.

	Medication-Years		Percent of follow-up time on warfarin
	on warfarin	total	
600 patient-years			
Device	93.3	401.7	23%
Control	201.3	225.0	89%
900 patient-years			
Device	107.7	578.2	19%
Control	279.8	320.3	87%

Level of Anticoagulation

Table 18 below provides an indication of the percent of time patients in both arms were adequately anticoagulated. In both arms, patients taking warfarin therapy had INR measurements between 2.0 and 3.0 only about half of the time. The extent of interruption of warfarin therapy and the difficulty achieving and maintaining a therapeutic INR is consistent with that found in other studies of warfarin therapy.

Table 18: Percent of Time with INR 2.0-3.0. This table includes the mean, median, maximum and minimum patient-years for which patients were within therapeutic INR range.

(based on fraction of observed measurement)

Group	Mean ± SD	Median (Interquartile Range)	Min	Max
600-Patient-Years				
WATCHMAN	46.6 ± 27.0	50.0 (25.0 – 66.7)	0	100
Control	52.3 ± 23.1	54.3 (35.6 – 66.7)	0	100
900-Patient-Years				
WATCHMAN	46.3 ± 26.1	50.0 (27.3 – 66.7)	0	100
Control	54.2 ± 19.9	55.6 (40.5 – 68.4)	0	100

Antiplatelet Therapy

Patients in both arms could be on aspirin and/or clopidogrel therapy at the discretion of the treating physician. In addition, per the protocol, patients in the device arm were to be on aspirin through the duration of the study and clopidogrel through six months if they discontinued warfarin. The percentage of follow-up time that patients were on clopidogrel was higher in the device group compared to the control group (51% versus 16%). Similarly, the percentage of follow-up time that patients were on aspirin was higher in the device group (91% versus 54%). Data are not available on the number of events occurring with or without one or two antiplatelet medications. Some control patients who had endpoint events were on a combination of warfarin, clopidogrel, and/or aspirin.

It is difficult to account for the confounding presence of antiplatelet drugs both as a protection for ischemic cardiovascular accident (CVA) and as a contributor to bleeding events, including hemorrhagic CVA. Other stroke trials, such as WARSS,[4] have shown the protective effect of antiplatelet medications.

E. Primary Safety Evaluation

1. Intent-To-Treat (ITT) Analysis

As stated above, the primary safety endpoint for the device captured peri-procedural events. The endpoint included events such as device embolization requiring retrieval, esophageal perforation due to the TEE, 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 necessitated an operation. No hypothesis was associated with the primary safety endpoint.

[4] Mohr et al., A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001;345(20):1444-51.

Applicant Analysis

In general, the primary safety rate was 8.7% per 100 patient-years for the device compared to 4.2% for the control (Table 19) and application of the same Bayesian techniques used for the efficacy endpoint suggests that this difference is significant. However, because the safety endpoint includes peri-procedural events, one would expect more events in the device arm. Interpretation of the safety endpoint is also confounded by the way in which events were counted in that some events were counted for the efficacy endpoint only, some were counted for the safety endpoint only and some were counted for both. The Kaplan Meier curve and estimates for the Primary Safety Endpoint ITT analysis are included in Figure 4 and Table 20, respectively.

Table 19: Primary Safety Endpoint (ITT). This table depicts the Bayesian analysis primary safety results for the 600 and 900-patient year cohorts.

	Device			Control		RR*
N pts	N Events / Total Pt-yrs	Rate**	N pts	N Events / Total Pt-yrs	Rate**	(95% CI*)
454 600-pt-yr	45/386.4	11.6 (8.5, 15.3)	238	9/220.4	4.1 (1.9, 7.2)	2.85 (1.48, 6.43)
463 900-pt-yr	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)

* CI is credible interval. RR is the relative risk of device over control.
** Rate = event rate per 100 patient years (calculated as 100*N events/total patient-years).

Figure 4: Kaplan-Meier Curve for Primary Safety Endpoint (ITT). This figure includes a depiction of the Event-Free Probability of a primary safety endpoint event for the WATCHMAN and Control patients over time.

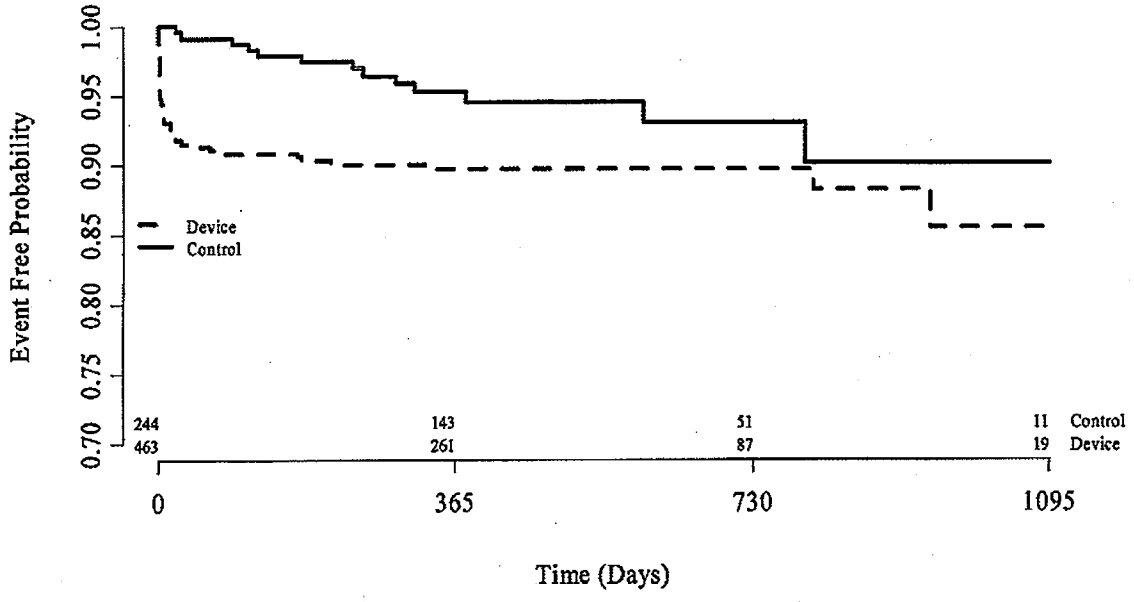

Table 20: Kaplan-Meier Estimates for Freedom from Primary Safety Endpoint Event (ITT). This table includes an accounting of the number of primary per-procedural safety endpoint events that occurred during each time point for the WATCHMAN and Control patients.

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%)	N Events	N Cumulative Events	Event Free Rate (%)
7-days	32	32	93.1 (90.7, 95.4)	0	0	100.0 (100.0, 100.0)
45-days	7	39	91.5 (89.0, 94.1)	2	2	99.2 (98.0, 100.0)
6-months	5	44	90.3 (87.6, 93.0)	4	6	97.4 (95.4, 99.5)
1-year	2	46	89.7 (86.9, 92.6)	4	10	95.2 (92.3, 98.2)
2-year	0	46	89.7 (86.9, 92.6)	2	12	93.0 (88.8, 97.3)
3-year	2	48	85.5 (78.9, 92.1)	1	13	90.1 (83.2, 97.1)

The applicant has presented the safety events by type (Table 21). Please note that these are ITT results. In this time-to-event analysis, only the first event was counted. The majority of primary safety events in the device group (27/48, 56%) occurred on the day of the procedure. These 27 events consisted of 17 serious effusions, 5 ischemic strokes, 1 device embolization and 4 other events. Of the 5 ischemic strokes, 3 were related to air embolism during the procedure. Ischemic strokes that occurred following the procedure (8 events) were not counted as safety events, but instead included in the effectiveness endpoint (Table 9). The hemorrhagic stroke in the device group (also captured as an effectiveness event, Table 9) was a spontaneous bleed which occurred 15 days post implant while the patient was still on warfarin therapy. Of the remaining 21 events, 9 occurred within 7 days of the procedure and 12 occurred more than 7 days post procedure.

Safety events in the control group occurred later and on a continuing basis. There were 6 hemorrhagic strokes in the control group (captured as effectiveness events, Table 9), 4 of which resulted in death. Warfarin was taken by 4/6 patients and the warfarin status is unknown in 2/6.

Table 21: Safety events by type (ITT analysis - 900 patient-year cohort). This table includes the number of patients in the WATCHMAN and Control arms with different types of safety events.

Type	Device N events	Device % of randomized pts	Control N events	Control % of randomized pts
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

* Serious pericardial effusion was defined as one that required either pericardiocentesis or surgery.
** Subdural hematoma was reported as cranial bleed.

FDA Analysis

The applicant has conducted the pre-specified ITT analysis, that is, calculating time-to-event based on date of randomization in both arms; however, the delay between randomization and implantation in some patients can increase the total patient-years used as the denominator. FDA has performed an ITT analysis using date of implantation in the device arm to calculate time to event. In this analysis, the relative risks reported by the applicant increase slightly but not significantly.

FDA also developed Table 22 to assess the potential impact of only counting the first event that occurred in a patient. In both cohorts, there were 7 device patients with 2 safety events and 1 device patient with 3 events. In the 600 patient-year cohort, 1 control patient had 2 safety events and 1 control patient had 3 events. In the 900 patient-year cohort, 3 control patients had 2 events, and 1 control patient had 3 events.

Table 22: Number of Patients with Multiple Safety Events. This table includes the number of patients in the WATCHMAN and control cohorts who had 1, 2 and 3 events for both the 600 and 900-patient year analysis.

Randomization group	600 patient years data (ITT) Number of safety events 1 event	2 events	3 events	Total # of patients
WATCHMAN	37	7	1	45
Control	7	1	1	9
Randomization group	**900 patient years data (ITT) Number of safety events 1 event**	**2 events**	**3 events**	**Total # of patients**
WATCHMAN	40	7	1	48
Control	9	3	1	13

2. Per-Protocol Analysis

The applicant prespecified a per-protocol analysis that excluded device patients who did not receive the device or who did not discontinue warfarin therapy and control patients for which there was no evidence of warfarin use at either baseline or 45 days. For the device arm, time-to-event was calculated from the date of warfarin discontinuation; for the control arm, time-to-event was calculated from date of randomization. Similar to the primary effectiveness per-protocol analysis, the analysis is difficult to interpret since: (1) certain events (such as ischemic stroke) were not counted as safety events in the device arm if they occurred following the procedure; (2) the analysis specifically excluded the events that happened prior to warfarin discontinuation (time-to-event was calculated from date of warfarin discontinuation in the device arm); and (3) the analysis broke randomization between treatment groups and introduced selection bias.

3. Confounding factors in the evaluation of safety

Warfarin discontinuation

FDA calculated the primary safety event rates for the device arm by warfarin discontinuation status at the 45-day visit, calculated from the implantation date for both the 600 and 900 patient-year cohorts (Tables 25-1 and 25-2). The event rate is numerically, but not statistically significantly, higher in the patients who discontinued warfarin at the 45-day visit.

Table 25 - 1: Device Primary Safety Endpoint

by Warfarin Discontinuation Status at the 45 Day Visit (≤ 60 days after implantation)
(for patients who had warfarin discontinuation information recorded)
(600 patient years dataset, FDA's calculation)

Warfarin Status at 45 day visit	# of Patients	# of Events / Patient years	Event Rate*
Discontinued	306	19/295.0	6.4
Continued	56	3/68.9	4.4

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

Table 25 - 2: Device Primary Safety Endpoint

by Warfarin Discontinuation Status at the 45 Day Visit (≤ 60 days after implantation)
(for patients who had warfarin discontinuation information recorded)
(900 patient years dataset, FDA's calculation)

Warfarin Status at 45 day visit	# of Patients	# of Events / Patient years	Event Rate*
Discontinued	325	22/434.1	5.1
Continued	62	4/94.9	4.2

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

Level of anticoagulation

In the 900 patient-year cohort, a substantial portion of patients in the control arm were excessively anticoagulated (INR ≥ 4.0) at least once during follow-up (86/202, 42.6%). The number of measurements during which the patient was excessively anticoagulated was also determined to be 4.1% (162/3948). In the control group, 9 patients were reported to have "any bleeding event" and 1 patient was reported to have had a "serious bleeding event" as adjudicated by the CEC.

5. Other Safety Considerations

Thrombus was identified on the device in 15 (3.8%) patients who had the device implanted, one of whom had a cerebral ischemia endpoint event. Routine brain imaging was not performed so the true incidence of subclinical cerebral infarcts is not known. Subclinical systemic embolism could not be detected in this study. In the PMA application, only 2 of these 15 events were reported as "serious."

Device embolization occurred in 3 patients, two of whom were asymptomatic and the device displacement was only found on TEE at 45 days. One of the two devices discovered embolized was removed by percutaneous snare and the second was initially left in the abdominal aorta and

has since been successfully surgically removed. The third embolization occurred during the procedure and required aortic valve replacement because of injury to the valve.

The WATCHMAN was explanted in two patients. One patient had an uneventful implantation but returned on post implant day #4 with a large pericardial effusion and was septic. She developed GI bleeding. She had the device surgically explanted 2 weeks later for presumed infection which was complicated by an ischemic CVA. The second patient had perforation of the LAA by the device during implantation and required an emergency open operation for device removal and atrial repair.

6. Device Recapture and Malfunctions

The applicant reports a 90.9% (408/449) implant procedure success rate. Not counted in this measure are the number of device recaptures. If release criteria were not met, the device was recaptured, removed, replaced and another attempt was made to place the device. Approximately 58% (261/449) of devices were adequately placed on the first attempt and 42% required one or more recaptures with approximately 4% (17/449) recaptured four or more times. The applicant indicated that the number of recaptures decreased as the trial progressed. (See Learning Curve Analysis Section below). In two cases, recaptured "short implant" device barbs were noted to be missing without known associated clinical sequelae. Use of the "short implant" was suspended at that time until a device redesign could address the issue. The barb design was changed and the "short implant" was subsequently reintroduced into the trial without known further events.

Device malfunctions were recorded in 23 patients when there was a problem with the packaging, breakage or failure of the device to perform as intended.

F. Learning Curve Analysis

In order to assess operator experience/learning, the applicant evaluated the incidence of pericardial effusions by enrollment date and site. In evaluating the 29 serious pericardial effusions that occurred in both roll-in and randomized patients with respect to enrollment date, there were more effusions in the first half of enrolled patients (17) compared to the second half of enrolled patients (12).

In evaluating pericardial effusions with respect to site, the pre-specified statistical analysis plan included planned comparison between the first 3 enrolled patients at each site ("early") to patients enrolled thereafter ("late"). Of the 29 serious pericardial effusions, 11 were experienced "early" (7.2%, 11/153) and 18 were experienced "late" (4.7%, 18/380). This non-statistically significant trend ($p = 0.29$) of a comparatively higher rate in "early" patients holds when evaluating the incidence of all pericardial effusions (serious and not serious) as well as all procedure and device related pericardial effusions.

A combined analysis was also performed wherein the "early" and "late" enrolled patients were analyzed with respect to the overall number of patients enrolled in the first half of the trial compared to the second half of the trial. In general, effusion rates were higher in the first half of enrolled patients compared to the second half of enrolled patients for both "early" and "late"

patients. Findings suggest that pericardial event rates were more influenced by learning over the course of the trial compared to learning at the site level.

Furthermore, the number of device recaptures in the first half of the study (1.8) decreased in the second half of the study (1.5) and the "late" patients (4+ implants at a site) had a lower number of recaptures compared to "early" patients with the majority of "late" patients having zero recaptures (61%) compared to the "early" patients (49%). These findings suggest that the need to recapture the device multiple times before adequately deploying the device showed learning both over the course of the trial and at the site level.

G. Summary and Conclusions

Fundamentally, this trial was designed to compare device + 45 days of warfarin as a treatment strategy compared to warfarin therapy alone. The clinical context of determining effectiveness for the WATCHMAN is to evaluate whether the data support stopping warfarin after satisfactory implantation of the WATCHMAN. That is, does this device without long-term warfarin provide equivalent protection against thromboembolic events to the atrial fibrillation patient compared to the use of warfarin? This clinical decision has to be weighed against the risks associated with the device as well as the risks and difficulties associated with warfarin.

Despite a favorable statistical conclusion with respect to the primary statistical analysis of effectiveness in the PROTECT AF trial, there are several confounding issues to be considered when formulating an assessment of the results of this trial:

1. The <u>limitations of the prespecified analyses plans</u> (Intent-to-Treat and Per-Protocol) should be considered. Because of the confounding factors of continued warfarin administration in some WATCHMAN patients and the failure to take or the discontinuation of warfarin in some patients in the control group, the problem of clinical interpretation of the results of the ITT non-inferiority analysis is evident.

2. Likewise, the per-protocol (PP) analysis has limitations. For the WATCHMAN arm, the pre-specified PP analysis includes any patients with the device implanted and who stopped warfarin, no matter whether he/she stopped beyond 45-day visit or whether he/she restarted warfarin later. The PP analysis only includes events that occurred after warfarin was stopped initially, thus excluding all events occurring during the procedure and before initial warfarin treatment was stopped.

   For the control arm, the PP analysis includes any patient who has taken warfarin at any time, whether or not they spent most of their time off warfarin. All events from the time of randomization were counted within the PP analysis cohort. Since the device arm PP analysis only counts events occurring after warfarin was stopped, this would be expected to favor the device arm.

3. A <u>non-inferiority hypothesis</u> was used for this trial because one could argue that a single permanent implant would be preferable to the use of long-term warfarin. This contrasts to most device vs. medical therapy studies, which are typically designed to demonstrate

device superiority. The non-inferiority margin (e.g., the equivalence delta or relative risk) was chosen by the applicant to be two times the control endpoint event rate. One has to consider the size of this margin and the types of events that comprise the primary effectiveness endpoint when evaluating the clinical significance of the calculated posterior probabilities.

4. The primary analysis was based on the assumption of a constant hazard rate across the follow-up period for each treatment arm. However, it turned out that this assumption was not valid for the device group. Hence, sole reliance on the statistical results from the primary analysis which assumes a Bayesian Poisson-Gamma model may be problematic.

5. This trial enrolled a select group of patients with atrial fibrillation (30+ inclusion/ exclusion criteria for trial enrollment). These criteria (such as exclusions for NYHA Class IV, recent stroke or MI, carotid disease, EF <30%, etc.) tended to exclude the patients at higher risk of poor outcomes. This is evidenced by the fact that 66% of the patients were in $CHADS_2$ Class 1/2 and only 5% were Class 5/6. The clinical utility of the device should be examined in the context of the risk in the patient group studied.

6. Of the WATCHMAN patients who had ischemic strokes after the peri-procedural period, seven times as many had strokes off warfarin (n=7) than on warfarin (n=1).

7. Warfarin use varied among groups. Warfarin was continued after 45 days in the 12% of patients who could not have the device successfully implanted. Another 14% of the patients who had the device implanted continued warfarin after the 45 day visit for various reasons including flow around the device, physician preference, TEE not done, and thrombus on the device. We do not know the warfarin status in another 4.5%. WATCHMAN patients who successfully received the device were on warfarin for 19-23% of their follow-up time. This affects interpretation of the ITT analyses and possibly introduces selection bias into the PP analyses.

   Flow around the occluder occurred in 7% of the WATCHMAN patients at the 45 day visit; these patients remained on warfarin.

   Some believe that discontinuing warfarin can produce a hypercoagulable state. Two of the efficacy endpoint events in the WATCHMAN group occurred within 60 days of discontinuing warfarin.

   In the control group, 28% of the patients either did not have warfarin started or had it stopped during the study. Control patients were off warfarin for 10% of their total followup time.

   All 5 of the ischemic strokes in the control group occurred either when the INR was subtherapeutic (n=2, INR < 2) or when we have no data on INR within 30 days of the event (n=3).

Of the 6 control patients with hemorrhagic stroke, only 2 had INRs in the therapeutic range recorded within 30 days of the event. There were 40% of the control patients who had at least one INR > 4.0 during the study, while 26% of the WATCHMAN patients did.

8. Antiplatelet drug administration may confound the results of the trial. It is difficult to account for the influence of antiplatelet drugs as protection for ischemic CVA and as well as a contributor to bleeding events, including hemorrhagic CVA.

   Patients who received the device and were able to discontinue warfarin, were required per protocol to receive clopidogrel for 6 months and aspirin for the remainder of the study

   Of the 6 control patients with hemorrhagic stroke, 2 were on ASA + warfarin, 1 was on ASA + clopidogrel + warfarin, and we do not know the antiplatelet drug status in the remaining three.

9. The primary effectiveness endpoint was a composite (CV death, unexplained death, ischemic stroke, hemorrhagic stroke, and systemic embolism). This composite was not hierarchically weighted; therefore, the components have to be examined individually as well as in the context of concomitant medications. It is also important to note that only the initial event was counted towards the primary endpoint.

   This device was intended to reduce the risk of systemic and cerebral thromboembolism. However, in the 900 patient-year cohort, there were 16 (3.0%) episodes of thromboemboli in the WATCHMAN group, 7 of which were temporally related to the procedure; 3 of these patients were on warfarin, but levels were subtherapeutic. In the control patients, 6 (2.4%) had ischemic strokes.

   An evaluation of any stroke (ischemic or hemorrhagic) reveals a lower rate of strokes (n=15, 3.2%) in the device arm than in the control arm (n=11, 4.5%).

10. In the present study, the primary effectiveness endpoint contains safety events. The primary safety endpoint was a composite of bleeding, peri-procedural, and device embolization serious adverse events, some of which were already counted as part of the effectiveness endpoint. The primary safety endpoint was not rigorously defined, it did not have a hypothesis, and the events were not hierarchically weighted. The incidence of individual events should be examined as well as the incidence of each serious adverse event.

11. Thrombus was identified on the device in 15 (3.8%) patients who had the device implanted, one of whom had a cerebral ischemia endpoint event. Device embolization occurred in 3 patients, two of which were asymptomatic and the device displacement was only found on TEE at 45 days. The third embolization occurred during the procedure and required aortic valve replacement because of injury to the valve. The WATCHMAN was surgically explanted in two patients.

12. Placement of this device requires skill at transseptal puncture and manipulating this device into a thin LAA. Acute pericardial effusion (perforation) after attempted device placement was adjudicated as related to the device or procedure in 6.6% of the patients, of which 5.0% of attempted device placements required either catheter or surgical drainage of the pericardial space after the myocardial perforation. There were numerically more serious effusions in the first half of enrolled patients compared to the second half of enrolled patients.

13. This is a permanently implanted device used to treat a chronic condition. It is necessary to establish the durability of the results with this device. We have effectiveness event data on 22% of the implanted patients at 2 years and in the data provided to-date, the hazard rate is not constant over time. Therefore, the expected timecourse of events for both device and control patients is not known.

The advisory panel members will be asked to specifically comment on the above points both via the panel questions and during the open discussion periods.

IX. Post-Approval Study Considerations

Should FDA approve this PMA, several questions remain unanswered which might be addressed in an appropriate post-approval study (PAS).

1. The data from the PMA study provide information on acute and mid-term outcomes. Longer term data to assess safety and the possible effect of implantation of WATCHMAN LAA Closure Device on mortality, stroke, systemic thromboembolism, arteriovenous fistula, device migration and erosion, device infection, and ability to discontinue warfarin therapy might be beneficial.
2. The PMA trial included centers with experience in clinical trials and investigational devices. The generalizability of these safety and effectiveness results to less experienced centers and operators is of interest.
3. The impact of the learning curve with the device on the overall safety remains unclear at this point. There is a question if the safety profile will vary depending on the experience of the operator.

The applicant proposed postmarket plan consists of two parts: (1) Post-Approval Physician Education and Training; and (2) Post-Approval Registries Proposal.

1. The proposed Post-Approval Physician Education and Training consists of formal training and educational activities.

2. The applicant proposed two PAS designed to provide additional corroborative safety and effectiveness data for the WATCHMAN®LAA Closure Technology in patients with non-valvular atrial fibrillation who require treatment for potential thrombus formation. The first PAS proposed to follow the PROTECT AF WATCHMAN patients (US and OUS) annually

for 5 years. The applicant proposes to follow patients in who the device was successfully deployed. The applicant does not describe if patients randomized to warfarin or those in whom the device was not successfully deployed will be followed for 5 years. The primary safety endpoint will be the occurrence of life-threatening events at 5-years, including device embolization requiring retrieval and bleeding events (e.g. pericardial effusion requiring drainage, cranial bleeding, events, gastrointestinal bleeding requiring transfusion, and any bleeding related to the device or procedure that necessitates an operation). The primary effectiveness endpoint will be the occurrence of stroke (ischemic and hemorrhagic), cardiovascular death, or systemic embolism at 5-years.

3. The second PAS is a new prospective registry of 300 patients treated with the WATCHMAN LAA Closure device. The applicant proposed to monitor procedural and device related complications occurring in these patients through 45 days. The proposed study will include up to 200 patients enrolled in the Continued Access PROTECT AF Registry (IDE #G020312) and a minimum of 100 patiens enrolled in 10 new (non-PROTECT AF) centers, who do not have prior experience with the WATCHMAN device. The primary endpoint proposed was serious procedure and device related events in patients with a successful implantation at 45 days. The applicant also proposed to describe the successful delivery and release of the WATCHMAN device in the LAA and freedoms from life-threatening events (e.g. pericardial effusion requiring drainage, cranial bleeding, events, gastrointestinal bleeding requiring transfusion, and any bleeding related to the device or procedure that necessitates an operation) and other complications (e.g. MI, TIA and death).

FDA is continuing to work with the applicant on PAS protocols for: (a) the extended follow-up of the premarket cohort (b) evaluation of device performance in general conditions of use, (c) identifying clinically important events to be assessed, (d) the evaluation of the impact of the learning curve and operator experience on the safety profile of the device, and (e) methods for evaluating the effectiveness of the training program for new operators.

The Panel will be asked to comment on potential PAS study plans, including hypotheses, controls, clinical important events, length and of follow-up, and the impact of physician experience on safety.

X. Conclusions

The data presented in the PMA characterize the safety and effectiveness of the WATCHMAN® LAA Closure Technology when used to treat patients with non-valvular atrial fibrillation. The Advisory Panel will be asked to fully assess the significance of these results and comment on the utility of the WATCHMAN® System for the prevention of stroke and systemic embolism in these patients.

Appendix A – Key Definitions

Adverse event (AE): At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this protocol, an adverse event is any undesirable clinical occurrence in a subject. Adverse events will be categorized as mild, moderate and severe/serious.

Serious Adverse Event (SAE): Any untoward medical occurrence that is any Adverse Event that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with, the WATCHMAN device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with the WATCHMAN device that relates to the rights, safety, or welfare of subjects.

Arrhythmias: An alteration in rhythm of the heartbeat that requires treatment with a device or anti-arrhythmic medication.

Atrial Fibrillation:

Lone Atrial Fibrillation: Atrial fibrillation in a structurally normal heart not caused by an underlying heart disease.

Non-valvular Atrial Fibrillation: Atrial fibrillation in the absence of rheumatic mitral valvular heart disease.

Paroxysmal Atrial Fibrillation: An intermittent form of atrial fibrillation that is characterized by a sudden onset and abrupt cessation of this rhythm. Spontaneous termination may occur in < 7 days and most often in < 48 hours. Medical documentation is required.

Persistent Atrial Fibrillation: Atrial fibrillation that is not self-terminating, lasting > 2 days, and termination using pharmacologic therapy or electrical cardioversion may be required. Persistent AF may be the first presentation of the arrhythmia or may be preceded by recurrent episodes of paroxysmal AF.

Permanent Atrial Fibrillation: Atrial fibrillation that has been present for at least 2 days and fails to terminate using cardioversion, or is terminated but relapses within 24 hours.

Bleeding Complication: Rectal bleeding, hematuria, epistaxis, bleeding from varicose veins, oral bleeding and prolonged bleeding from a laceration, bruising-hematoma, hemothorax, red eye and thrombosis.

Cardiac perforation (myocardial perforation): A Cardiac Perforation is an effusion >1cm that causes hemodynamic change which requires intervention and/or closure of the hole by surgical intervention and is classified as a SERIOUS ADVERSE EVENT/Safety endpoint.

Cardiac tamponade: A cardiac tamponade is a pericardial effusion that requires drainage and classified as a SERIOUS ADVERSE EVENT/Safety endpoint.

CHADS2 scale: A classification scheme to stratify patients by their risk of future stroke. A patient is assigned a score from 1 to 6 based on the following factors:

1 point for each of:

- Recent CHF
- History of Hypertension
- Age at least 75 years
- Diabetes

2 points for having had a prior stroke or TIA

Death: Deaths will be recorded on a patient data form with a detailed description of the circumstances surrounding the patient's death documented. Autopsy results and explanation of the device will be obtained whenever possible. Deaths will also be sub-categorized as peri-procedural(<30days of procedure) and late-term (>31 days after the procedure)

Device Failure: A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

Device Malfunction: A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

Device Erosion: Device erosion is tissue wear resulting from mechanical loading as evidenced by device protrusion.

Device Embolization: An obstruction or occlusion by a device that has been dislodged from the LAA and is introduced into the circulatory system potentially occluding vessels and / or organs by occluding its blood supply.

Excessive anticoagulation event: Any INR>4.0mg will constitute an excessive anticoagulation event as described in the warfarin package insert.

INR Therapeutic range - INR range of 2.0-3.0.

Pericardial effusion (hemodynamically insignificant): A Pericardial Effusion is increased fluid within the pericardial sac that does not cause circulatory compromise and does not require drainage. It will be classified as NON-SERIOUS ADVERSE EVENT / not a safety endpoint

unless it requires prolonged hospitalization and/or progresses to tamponade or perforation requiring intervention or transfusion.

Stroke

Ischemic Stroke: Sudden onset of a focal neurological deficit with symptoms and/or signs
persisting more than 24 hours or symptoms less than 24 hours confirmed by CT or MRI, including a full neurological exam by a Neurologist.

Hemorrhagic Stroke: Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage, including full neurological exam by a Neurologist.

Systemic Embolism: Abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation).
In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

Transient ischemic attack (TIA): Acute focal neurological event (including focal motor deficit aphasia, difficulty walking, hemi sensory deficit, amaurosis fugax, blindness, or focal visual deficit) lasting at least 5 minutes and up to 24 hours that is MR imaging negative, including full neurological exam by a Neurologist. All TIAs will be adjudicated for seriousness and causality by the CEC.

Appendix B – What is Bayesian Statistics?

Bayesian statistics is an approach for learning from evidence as it accumulates. The Bayesian approach uses Bayes' Theorem to combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available.

When good prior information on clinical use of a device exists, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial. However, the Bayesian approach is useful even in the absence of prior information. For example, the approach can accommodate adaptive trials (e.g., interim analyses or change to sample size) and even some unplanned, but necessary trial modifications. Other potential uses include adjustment for missing data, sensitivity analysis, multiple comparisons, and optimal decision making.

Prior Distribution

As an illustration, suppose that the Greek letter $\boldsymbol{\theta}$ represents a parameter in a clinical trial. The initial knowledge about $\boldsymbol{\theta}$ prior to data collection is represented by the prior distribution for $\boldsymbol{\theta}$, which we denote in symbols as $P(\boldsymbol{\theta})$. Suppose $\boldsymbol{\theta}$ is the rate of a serious adverse event. Its possible values lie between 0 and 1. The prior distribution might give preference to lower values of $\boldsymbol{\theta}$ (see Figure 1). The probability that $\boldsymbol{\theta}$ takes on any particular set of values is determined by the area under the curve for those values. So the prior probability that the adverse event rate $\boldsymbol{\theta}$ is greater than 0.4 (the shaded area) is about 0.38.

An *informative* prior distribution gives preferences to some values of the quantity of interest as being more likely than others (See Figure 1). Lack of preference among the values or lack of information can be represented through a *non-informative* prior distribution (e.g., a uniform prior which indicates no preference for any value of $\boldsymbol{\theta}$).

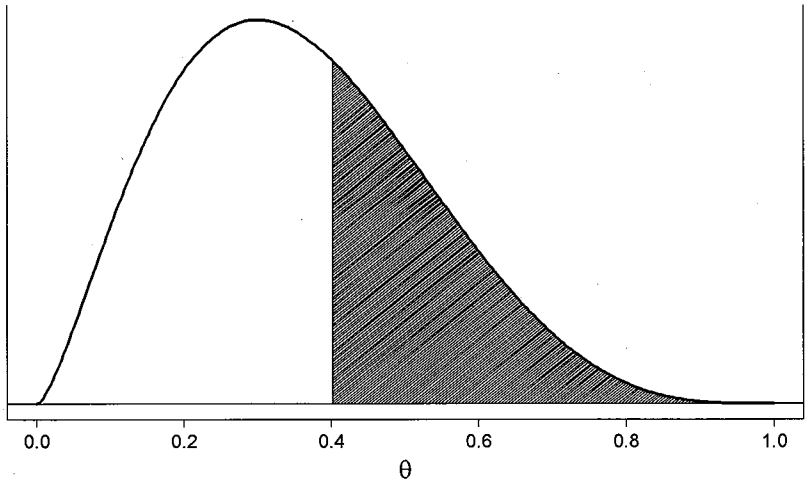

Figure 1. Example of a unimodal, right-skewed prior distribution for a serious adverse event rate, denoted by θ. The prior probability that θ is greater than 0.4 (the shaded area) is about 0.38.

Likelihood of the Observed Data
Now suppose outcomes have been obtained from a clinical trial. The likelihood function is a mathematical representation of the relationships between observed outcomes and the parameter $\boldsymbol{\theta}$. The likelihood function can be expressed in symbols by P(data $|\boldsymbol{\theta}$), which is the conditional probability of observing the data given a specific value of the parameter $\boldsymbol{\theta}$, for each possible value of $\boldsymbol{\theta}$.

Posterior Distribution
The final objective is to obtain the posterior distribution, the probabilities of the possible values of the parameter $\boldsymbol{\theta}$ conditional on the observed data, which can be denoted in symbols as P($\boldsymbol{\theta}$| data). Bayes' theorem is used to update the prior distribution for $\boldsymbol{\theta}$, P($\boldsymbol{\theta}$), via the likelihood, P(data|$\boldsymbol{\theta}$), to obtain the posterior distribution for $\boldsymbol{\theta}$, P($\boldsymbol{\theta}$|data). At the conclusion of the trial, the information about $\boldsymbol{\theta}$ is summarized by this posterior distribution, and Bayesian inferences are based on it.

As an example, Figure 2 shows the posterior distribution that would be obtained if we started with the prior shown in Figure 1 and observed data with 1 adverse event in 10 patients. Since the adverse event rate observed in these patients is 0.10, the distribution has shifted further to the left (that is, it now favors even lower values for $\boldsymbol{\theta}$). The posterior probability that $\boldsymbol{\theta}$ is greater than 0.4 (the shaded area) is about 0.04. The probability that the adverse event rate is greater than 0.4 has been reduced from about 0.38 (the prior probability) to about 0.04 (the posterior probability) by the favorable trial results.

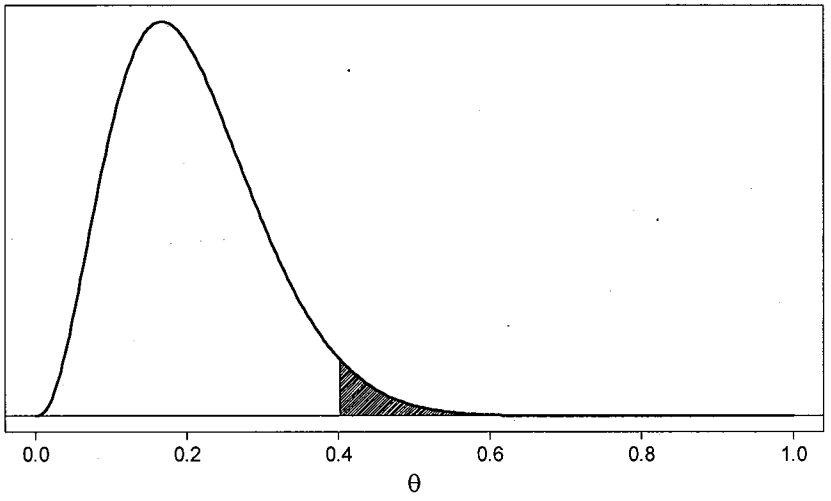

Figure 2. Example of a unimodal, right-skewed posterior distribution for a serious adverse event rate, denoted by θ, after observing one adverse event in 10 patients and updating the prior probability in Figure 1. The posterior probability that θ is greater than 0.4 (the shaded area) is about 0.04.

The posterior distribution that has been obtained today may serve as a prior distribution when more data are gathered. The more information that is accrued, the less uncertainty there may be about the posterior distribution for $\boldsymbol{\theta}$. If enough data are collected, the relative importance of the prior distribution will be negligible compared to the likelihood.

Bayesian inferences are based on the posterior distribution. For example, a Bayesian decision procedure might rule out a set of parameter values if the posterior probability of the parameter values (given the observed data) is small.

A pre-specified decision rule is used to demonstrate hypotheses that define safety and effectiveness with reasonable assurance. For Bayesian trials, one common type of decision rule considers that a hypothesis has been demonstrated (with reasonable assurance) if its posterior probability is large enough (e.g., 95 or 99 percent).

Predictive Distribution

The Bayesian approach allows for the derivation of a special type of posterior probability; namely, the probability of unobserved outcomes (future or missing) given what has already been observed. This probability is called the *predictive probability*. Collectively, the probabilities for all possible values of the unobserved outcome are called the predictive distribution. Predictive distributions have many uses, including determining when to stop a trial (based on predicting outcomes for patients not yet observed) or adjusting trial results for missing data (imputation).

These uses are discussed in more detail below in **Analyzing a Bayesian Clinical Trial**.

Exchangeability

Exchangeability is a fundamental concept underlying statistical inference. It can be of particular importance in Bayesian trials. Formally, we would say that units (patients or trials) are considered *exchangeable* if the probability of observing any particular set of observations on those units is invariant to any re-ordering of the units.

- **Exchangeability of patients**

  In a clinical trial, patients within the trial are usually assumed to be exchangeable. Under exchangeability, patient outcomes are not expected to depend on the order in which the patients were enrolled, the order in which the outcomes are observed, or any other re-indexing or re-numbering of the patients. If patients in the trial are exchangeable with patients in the population from which they were sampled (e.g., the intended use population), then inferences can be made about the population on the basis of data observed on the trial patients. Thus, the concept of a *representative sample* can be expressed in terms of exchangeability.

- **Exchangeability of trials**

  For a Bayesian clinical trial, another level of exchangeability might be assumed. Namely, the trial can be assumed to be exchangeable with other previous trials when the previous trials are considered to be good prior information. The assumption of trial exchangeability enables the current trial to "borrow strength" from the previous trials, while acknowledging that the trials are not identical in all respects. Thus, exchangeability is important in the development of realistic models for combining trial data with prior information.

Bayesian Adaptive Designs

Adaptive designs use accumulating data to decide how to modify certain aspects of a trial according to a pre-specified plan without undermining the validity and integrity of the trial.

Adaptive trial designs have the potential to provide optimal statistical inference and to improve quality, speed and efficiency of decision making.

An adaptive Bayesian clinical trial can involve interim looks to adapt the sample size (to stop or to continue patient accrual) or interim looks for the purpose of possibly stopping the trial early either for success, futility, or harm.

A purely Bayesian approach would allow for continuous design adaptation as the trial take place. However, in order to maintain the integrity of the trial while minimizing operational biases, the Bayesian adaptive trial should be adaptive *by design*.

Analyzing a Bayesian Clinical Trial

The results, conclusions, and interpretation of a Bayesian analysis all rely on the posterior distribution. Consequently, results and conclusions for a Bayesian trial are based only on the posterior distribution.

Hypothesis testing

For Bayesian hypothesis testing, one can use the posterior distribution to calculate the probability that a particular hypothesis is true, given the observed data.

Interval estimation

Bayesian interval estimates are based on the posterior distribution and are called *credible intervals*. If the posterior probability that an endpoint lies in an interval is 0.95, then this interval is called a 95 percent *credible interval*.

Predictive probabilities

Uses of predictive probabilities include the following:

Deciding when to stop a trial

One can use a predictive probability at an interim point as the rule for stopping the trial. If the predictive probability that the trial will be successful is sufficiently high (based on results at the interim point), the trial may be stopped and declared successful.

Exchangeability is a key issue here: these predictions are reasonable only if you can assume the patients who have not been observed are exchangeable with the patients who have. This assumption is difficult to formally evaluate but may be more plausible in some instances (e.g., administrative censoring) than others (e.g., high patient drop-out).

Predicting outcomes for future patients

One may also calculate the predictive probability of the outcome of a future patient, given the observed outcomes of the patients in a clinical trial, provided the current patient is exchangeable with the patients in the trial.

Predicting (imputing) missing data

One may use predictive probabilities to predict (or *impute*) missing data, and trial results can be adjusted accordingly. The adjustment depends on the assumption that patients with missing outcomes follow the same statistical model as patients with observed outcomes. This means the missing patients are exchangeable with the non-missing patients, or that data are *missing at random*.

Predicting a clinical outcome from earlier measurements

If patients have measurements of the same outcome at earlier and later follow-up visits, one can make predictions for the later follow-up visit (even before the follow-up time has elapsed).

Interim analyses

Bayesian interim analyses typically involve the following applications:

Applying posterior probability

One method stops the trial early if the posterior probability of a hypothesis at the interim look is large enough. In other words, the same Bayesian hypothesis test is repeated during the course of the trial.

Applying predictive distribution

Another method calculates at interim stages the probability that the hypothesis test will be successful at the end of accrual and follow-up. This method uses the Bayesian predictive distribution for patients yet to be measured. If the predictive probability of success is sufficiently high, the trial may stop early. If the predictive probability is very low, the trial may stop early for futility.