FDA Executive Summary

Prepared for the
October 8, 2014 meeting of the
Circulatory System Devices Panel

P130013

Boston Scientific WATCHMAN® Left Atrial Appendage Closure Therapy

INTRODUCTION

This is the FDA Executive Summary for a first-of-a-kind transcatheter left atrial appendage closure device, the Boston Scientific WATCHMAN Left Atrial Appendage Closure (LAAC) Therapy (WATCHMAN device), indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism.

This PMA submission was previously presented to the Circulatory Systems Devices Panel on December 11, 2013. The Panel voted 13 to 1 in favor of device safety, effectiveness, and a positive benefit-risk profile. However, in February 2014, FDA received updated follow-up data from the PREVAIL trial that showed additional ischemic strokes in WATCHMAN subjects. The updated total number of ischemic strokes in PREVAIL WATCHMAN subjects raises new questions about the effectiveness of the device and impacts benefit-risk considerations.

The updated datasets from the PREVAIL and PROTECT AF trials are the subject of this Advisory Panel meeting. This memorandum will summarize the FDA's review of the data received since the previous panel meeting, highlighting areas for which we are seeking the Panel's expertise and recommendations. Panel input is especially important in addressing the question of whether a new analysis of the totality of the data has substantially changed the assessment of the benefit-risk profile of the WATCHMAN device.

At the conclusion of the Panel's review and discussion of the new information, the Agency will ask for recommendations regarding whether or not the data demonstrate a reasonable assurance of the safety and effectiveness of the WATCHMAN device, and whether the probable benefits of the device outweigh the probable risks. It is critical that Advisory Panel members review the totality of data in making these determinations as each component of the dataset has strengths and limitations.

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1 PROPOSED INTENDED USE AND INDICATIONS FOR USE

The sponsor has proposed the following intended use and indications for use:

Intended Use

"The WATCHMAN LAAC Device is a percutaneous, transcatheter closure device intended for non-surgical closure of the left atrial appendage. In considering the use of the WATCHMAN LAAC Device, the benefits and risks of the device and the rationale for an alternative to chronic warfarin therapy should be taken into account."

Indications For Use

"The WATCHMAN LAAC Device is indicated to prevent thromboembolism from the left atrial appendage. The device may be considered for patients with non-valvular atrial fibrillation who, based on $CHADS_2$ or CHA_2DS_2-VASc scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism."

FDA Comment: The indications for use and intended use language were developed collaboratively by FDA and the sponsor following the December 11, 2013 panel meeting.

2 DEVICE DESCRIPTION

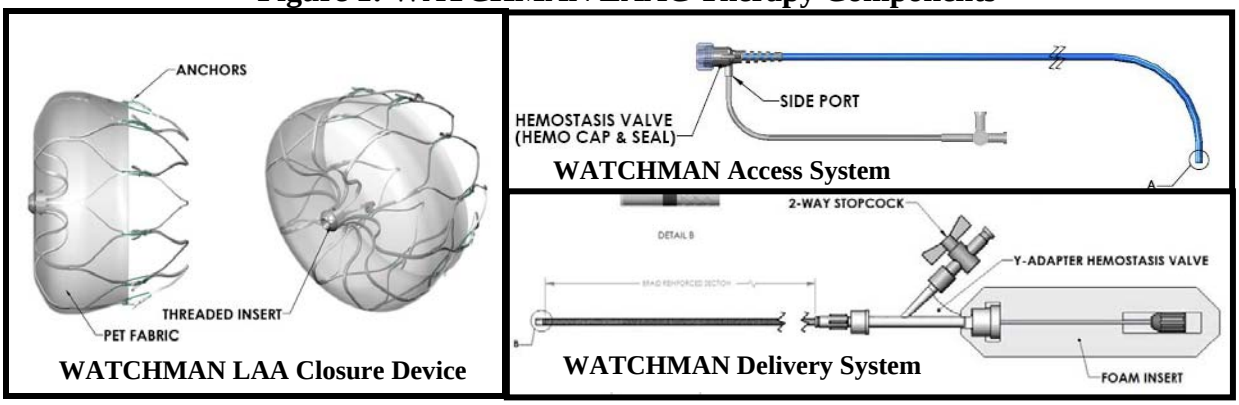
The WATCHMAN device consists of three components: (1) the WATCHMAN LAA Closure Device; (2) the WATCHMAN Delivery System, and (3) the WATCHMAN Access System (see Figure 1).

The WATCHMAN LAA Closure Device is a self-expanding nitinol structure covered by a porous polyethylene terephthalate (PET) membrane on the proximal face. The Access System and Delivery System allow for femoral venous access and provide a means to cross into the left atrium via the inter-atrial septum.

The WATCHMAN LAA Closure Device is packaged preloaded into the WATCHMAN 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 correspond to the maximum LAA ostium diameter. Per the Instructions for Use, device selection should be based on accurate LAA measurements obtained using fluoroscopy and transesophageal echocardiography (TEE) from multiple angles.

Following use of a standard transseptal access system to cross the atrial septum, the 12 French (Fr) Delivery System is placed through a 14 Fr Access Sheath. The Access Sheath comes in three configurations: the single curve (90 degree angle), double curve, and anterior curve distal tip. Upon proper positioning, the device is deployed by unscrewing the core wire from the permanent implant microscrew attachment.

Figure 1: WATCHMAN LAAC Therapy Components



3 BACKGROUND INFORMATION AND REGULATORY HISTORY

Atrial fibrillation (AF) is a clinically important arrhythmia with an estimated prevalence of approximately 1% in the U.S., and the development of AF is associated with increased age and the presence of underlying heart disease.[1] In addition to interventions targeted to heart rate and rhythm control, the treatment of AF involves the prevention of ischemic stroke and systemic embolism in patients with paroxysmal, persistent, or permanent AF. The etiology of stroke, with an estimated incidence of 3 to 5% per year[2] is presumed, in most part, to be related to the embolization of left atrial appendage thrombus. In clinical practice, the $CHADS_2$ and CHA_2DS_2-VASc[3] scoring systems provide risk stratification data on the likelihood of stroke or systemic embolism and are used to guide the use of anticoagulation therapy.

In patients eligible for anticoagulation therapy, warfarin has been the historical standard of care. The effectiveness of warfarin to prevent ischemic stroke and systemic embolism is directly related to maintaining a therapeutic INR. A subtherapeutic INR increases the risk of ischemic stroke, and a supratherapeutic INR is associated with an increased risk of major bleeding complications. Achieving a therapeutic INR can be difficult in some patients as it requires patient compliance with regular monitoring and is affected by diet and concomitant medication use. Over the last three years, three novel anticoagulants (NOACs: dabigatran, rivaroxaban, and apixaban) have been approved by FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Each of the NOACs has a different benefit-risk profile versus warfarin as shown in large global randomized trials.[4,5,6] For example, dabigatran

[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] Lip GY, Nieuwlaat R, Pisters R. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. Chest. 137 2010:263-272.
[4] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151

(150 mg twice per day) and apixaban were shown to be superior, and rivaroxaban was shown to be non-inferior, to warfarin for the endpoint of stroke and systemic embolism. Both dabigatran and apixaban were associated with a reduction of the rate of hemorrhagic stroke vs. warfarin, and apixaban was associated with a reduced rate of major bleeding vs. warfarin (major bleeding rates were similar to warfarin with dabigatran and rivaroxaban). However, the NOACs are costly, require compliance with once or twice per day dosing, and there is no readily available agent to reverse their anticoagulant effect. Physician experience with these new anticoagulants is progressing, but it remains relatively limited vs. warfarin. A data analysis from the American College of Cardiology's PINNACLE Registry showed that of patients receiving oral anticoagulation for atrial fibrillation, 87.4% were treated with warfarin in 2011 and 12.6% were prescribed one of the NOACs.[7] In a province-wide analysis of prescribing patterns in Ontario between October 2010 and September 2012, prescriptions for NOACs increased >20-fold, but still comprised only 21.1% of all anticoagulation therapy prescriptions.[8] The use of the NOACs in the U.S. is increasing, and a recent study of patients being started on anticoagulation showed that the NOACs accounted for 62% of new prescriptions.[9] However, warfarin remains a widely used and acceptable therapy to reduce the risk of ischemic stroke and systemic embolism in patients with non-valvular AF.

It is generally recognized that oral anticoagulation therapy to reduce the risk of ischemic stroke and systemic embolism is under-utilized in the U.S. due to concerns about bleeding complications. Because of the challenges in maintaining a stable therapeutic INR in some warfarin patients, as well as individual physician and patient preference to avoid anticoagulation therapy altogether,[10] alternatives to anticoagulation have been developed.

The WATCHMAN device was originally manufactured by Atritech, Inc., and Boston Scientific acquired Atritech, Inc., in March 2011. Under Investigational Device Exemption (IDE) G020312, the PILOT feasibility study was conditionally approved on September 12, 2003 and the PROTECT AF pivotal trial was conditionally approved on November 3, 2004. PROTECT AF was designed as a prospective, randomized, controlled, multicenter clinical trial to evaluate the safety and effectiveness of the WATCHMAN device.

The results from the PROTECT AF trial were submitted to the FDA as part of PMA P080022, which was presented to the Circulatory System Devices Panel on April 23, 2009 (see Appendix A of the December 2013 panel executive summary for a summary of the PROTECT AF trial

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[5] Patel MR, Mahaffey KW Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-891.

[6] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-992.

[7] PINNACLE-AF Registry Suggests Slow Uptake of New Anticoagulants. *Medscape*. August 17, 2012.

[8] Xu Y, et al. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. CMAJ Open 2013; 1(3): E115-E119.

[9] Desai NR, et al. Patterns of Initiation of Oral Anticoagulants in Patients with Atrial Fibrillation - Quality and Cost Implications. Am J Med 2014 (in press, available at http://www.sciencedirect.com/science/article/pii/S0002934314003994#)

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

design and previous primary endpoint results). Based on the data from the PROTECT AF trial, the Panel concluded that the short-term effectiveness of the WATCHMAN device had been demonstrated. However, the Panel believed that there was insufficient evidence to support long-term device effectiveness. Although the Panel voted 7 to 5 in favor of "Approval with Conditions," P080022 was deemed Not Approvable by the FDA.

In the Not Approvable letter issued on March 10, 2010, FDA cited the following concerns:

- Concomitant antithrombotic medication use varied in both study arms, which confounded the interpretation of device efficacy independent of adjunctive antithrombotic therapy;
- A substantial portion of both control and WATCHMAN patients did not receive their assigned treatment, and the majority of WATCHMAN patients who did not receive their assigned treatment received the control treatment;
- The hemorrhagic stroke rate in the control arm was higher than expected, which contributed to difficulty in interpreting the primary endpoint; and
- There were device safety issues, including device thrombus, pericardial perforations, and need for device explantation.

The Not Approvable letter also stated that additional follow-up from the PROTECT AF trial and the CAP registry would not be sufficient to address these issues, and FDA recommended collection of additional data in a new trial. For further discussion of the specific limitations of PROTECT AF, please see the December 2013 panel executive summary (Section 3, pages 9 to 12).

Following the April 2009 panel meeting, FDA worked interactively with the sponsor on the design of a new trial to gather additional safety and effectiveness data on the WATCHMAN device to address the concerns raised in the original PMA submission. In July 2010, FDA conditionally approved the PREVAIL trial, which is a prospective, randomized, controlled, multicenter clinical trial that utilizes a Bayesian design. FDA recognized that while the original data from the PROTECT AF trial were not adequate to provide a reasonable assurance of device safety and effectiveness, there was value in the information captured in PROTECT AF. Therefore, the PREVAIL study was designed to both borrow strength from PROTECT AF by incorporating a portion of the PROTECT AF data into a Bayesian statistical analysis plan and address some of the limitations of the PROTECT AF trial.

PMA P130013 was filed on June 10, 2013 and included the initial results of the PREVAIL clinical trial and additional follow-up from the PROTECT AF trial and CAP registry. Like the original PMA submission of the PROTECT AF trial, the PREVAIL trial PMA submission was granted priority review status, since the WATCHMAN device is intended to treat a life-threatening or irreversibly debilitating disease or condition (i.e., stroke), and the device represents a potential breakthrough technology for patients with non-valvular atrial fibrillation, a clinically significant and common medical condition.

PMA P130013 was presented to the Circulatory System Devices Panel on December 11, 2013. The PREVAIL trial was discussed, as well as additional long-term follow-up data from the PROTECT AF trial and the CAP registry. (Please see Sections 5 and 6, pages 14 to 30 of the December 2013 panel executive summary for a comprehensive discussion of the PREVAIL

study design and previous primary endpoint results.) Included herein is a summary of the PREVAIL trial design.

PREVAIL was a prospective, multicenter, randomized (2:1) study comparing WATCHMAN device implantation plus short term (45-days) warfarin therapy to warfarin therapy (Control group). PREVAIL enrolled subjects with non-valvular atrial fibrillation who were eligible for warfarin. Although the design of PREVAIL was similar to PROTECT AF, there were several key differences, including limiting inclusion to subjects with a $CHADS_2$ score ≥ 2 (or $CHADS_2$ =1 with additional stroke risk factors), exclusion of patients indicated for chronic clopidogrel therapy, and a commitment by the sponsor for enhanced monitoring to ensure adequate warfarin compliance and improved INR control.

- First Primary Endpoint: The occurrence of stroke (including ischemic and hemorrhagic stroke), cardiovascular death (cardiovascular and unexplained), and systemic embolism (18 month rates). Non-inferiority for the first primary endpoint would be met if the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio was less than 1.75.

- Second Primary Endpoint: The occurrence of late ischemic stroke and systemic embolism [8 days post-randomization and onward (i.e., excluding the first 7 days post-randomization), 18 month rates]. Non-inferiority for the second primary endpoint would be met if the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate ratio was less than 2.0 **or** the upper bound of the equitailed 2-sided 95% credible interval for the 18-month rate difference was less than 0.0275.

- Third Primary Endpoint: The occurrence of all-cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair, occurring between the time of randomization and within 7 days of the procedure or by hospital discharge, whichever was later. Success for this endpoint was considered to have been achieved if the upper bound of the one-sided 95% credible interval of the percentage of subjects experiencing an event in the WATCHMAN group was less than the performance goal of 2.67%.

PREVAIL was designed with a non-inferiority Bayesian statistical analysis that borrowed data from PROTECT AF, which was discounted 50% for the first and second primary endpoint analyses and was not discounted for the third primary endpoint analysis. Because PREVAIL used a more restrictive $CHADS_2$ inclusion criterion compared to PROTECT AF, the prior data borrowed from PROTECT AF included only subjects who would have met the PREVAIL $CHADS_2$ inclusion criterion.

The PREVAIL trial enrolled 407 subjects, 269 randomized to the WATCHMAN Group and 138 to the Control group (2:1 WATCHMAN:Control randomization).

PREVAIL co-primary endpoint results

- The first primary endpoint event rate was 0.64 in the WATCHMAN group and 0.63 in the control group. The rate ratio was 1.07 with a 95% credible interval of 0.57 to 1.89. Because the upper bound of the 95% credible interval was greater than 1.75, non-inferiority *was not met* for this endpoint.

- The second primary endpoint event rate was 0.0253 in the WATCHMAN group and 0.0200 in the control group. The rate ratio was 1.6 with a 95% credible interval of 0.5 to 4.2. The rate difference was 0.0053 with a 95% credible interval of -0.0190 to 0.0273. Even though the upper bound of the 95% credible interval of the rate ratio was greater than 2.0, non-inferiority *was met* for this endpoint because the upper bound of the 95% credible interval of the risk difference was less than 0.0275.

- Third primary endpoint events occurred in 2.2% (6/269) of WATCHMAN subjects. The upper bound of the 95% credible interval was 2.652%, *which met* the performance goal of 2.67%.

FDA Comment: It is important to recognize that the PREVAIL dataset above that was reviewed at the December 2013 panel meeting was locked in January 2013. The mean duration of PREVAIL subject follow-up from the time of randomization was 11.8 ± 5.8 months and only 28% of subjects had reached or passed the 18-month follow-up window.

The December 2013 Advisory Panel concluded that:

- The peri-procedural safety concerns that were observed in the PROTECT AF trial were adequately addressed by the peri-procedural results reported in the PREVAIL trial and CAP registry.
- The new PREVAIL data on ischemic stroke rates numerically favored the Control group, but the long-term follow-up from PROTECT AF provided support for the WATCHMAN device safety and effectiveness.
- Bleeding rates were consistent with other interventional procedures.
- The WATCHMAN device is a clinically reasonable alternative to warfarin for some patients.

The Panel voted 13 to 1 that the WATCHMAN device demonstrated a reasonable assurance of safety and effectiveness, and that the benefits of the device outweighed the risks for the proposed indication for use.

Following the December 2013 panel meeting, FDA and the sponsor worked interactively on device labeling, the post-approval study, and addressing any outstanding issues raised in the review of the PMA.

4 NEW PREVAIL EVENTS

During the initial PMA review, FDA noted that there were unadjudicated events (including an ischemic stroke in one additional WATCHMAN subject) that occurred after the dataset lock in January 2013. On August 15, 2013, FDA requested that the sponsor provide an updated analysis

of the PREVAIL data. The sponsor responded on September 5, 2013 that they would conduct an updated analysis, which would be provided *prior to* the December 2013 Panel meeting. However, this update was inadvertently not provided, and on January 3, 2014 FDA asked again for the updated PREVAIL analysis including adjudication of all new events.

On February 18, 2014, FDA received an updated PREVAIL dataset from the sponsor. This dataset was *locked on January 30, 2014* and included an additional one year of subject follow-up compared with the dataset presented at the December 2013 panel meeting. In addition to the 6 ischemic strokes (5 in the WATCHMAN group and 1 in the Control group) included in the PREVAIL dataset that was discussed at the December 2013 panel meeting, the updated January 2014 dataset included 6 additional ischemic strokes, all of which occurred in the WATCHMAN device group, corresponding to a total of 11 ischemic strokes in the WATCHMAN group vs. 1 in the Control group (2:1 randomization, WATCHMAN:Control). The sponsor subsequently provided a second updated analysis, representing a new dataset *locked on June 28, 2014*. In the June 2014 dataset, all PREVAIL subjects had reached or surpassed 18-months follow-up from randomization with mean follow-up duration of 25.9 ± 9.7 months (vs. only 28% of subjects at or beyond 18-months follow-up with mean follow-up duration of 11.8 ± 5.8 months for the January 2013 dataset presented at the December 2013 Panel meeting). Between the January and June 2014 dataset locks, there were 2 additional ischemic strokes in the WATCHMAN group corresponding to a total of 13 ischemic strokes in the WATCHMAN group vs. 1 in the Control group (2:1 randomization, WATCHMAN:Control).

FDA Comment: Because the new ischemic strokes, all of which occurred in subjects who were more than one year post-WATCHMAN implant, raised concerns regarding the effectiveness of the device, FDA worked interactively with the sponsor to clarify the circumstances surrounding these new ischemic strokes. Responses to FDA's questions were provided on May 2, 2014. In addition, enrollment in the CAP2 registry was suspended pending a complete analysis of the potential ischemic stroke signal in PREVAIL. The updated PREVAIL, CAP, and CAP2 data under review by the present Advisory Panel represents data locks as of June 28, 2014 (PREVAIL), June 25, 2014 (CAP), and July 2, 2014 (CAP2).

Table 1 shows primary endpoint events and event rates in PREVAIL subjects that were presented at the December 2013 panel meeting (January 2013 dataset) and the new events and event rates as of the June 2014 data set. Compared to the January 2013 dataset, the updated June 2014 dataset included:

- Eight additional ischemic strokes in WATCHMAN subjects vs. no additional ischemic strokes in the Control group
- One additional hemorrhagic stroke and 1 additional cardiovascular or unexplained death in the WATCHMAN group
- Two additional hemorrhagic strokes and 3 additional cardiovascular or unexplained deaths in the Control group

In total, as of June 2014, there were 24 primary endpoint events in the device group and 9 events in the control group. Of the 24 events in the device group, there were 13 ischemic strokes, 2 hemorrhagic strokes, 1 systemic embolism, and 8 cardiovascular or unexplained deaths. In the

control group, there were 1 ischemic stroke, 2 hemorrhagic strokes, and 6 cardiovascular or unexplained deaths.

Of the 13 ischemic strokes in the device group, 1 occurred 4 days after implantation, 2 occurred within 6 months of implantation, and the other 10 occurred > 1year post-implantation. The systemic embolism event occurred approximately 10 months post-implant.

Among the 8 deaths adjudicated as meeting the first primary endpoint definition in the WATCHMAN group, there were 6 sudden cardiac deaths and two deaths secondary to acute myocardial infarction. In the control group, there were 5 sudden cardiac deaths and 1 death attributed to chronic systolic heart failure. None of the deaths was causally linked to the WATCHMAN device, implantation procedure, or anticoagulant therapy.

Table 1: PREVAIL-only Endpoint Events and Event Rates (Sponsor and FDA analyses)

Dataset Date	Endpoint Event	WATCHMAN		Control	
		N Events /Total Pt-yrs	Rate (95% CI*)	N Events /Total Pt-yrs	Rate (95% CI*)
January 2013	Stroke-Ischemic	5/257.1	1.94 (0.63, 4.54)	1/140.1	0.71 (0.02, 3.98)
	Stroke-Hemorrhagic	1/259.0	0.39 (0.01, 2.15)	0/140.8	0.00 (0.00, 2.62)
	Systemic Embolism	1/259.6	0.39 (0.01, 2.15)	0/140.8	0.00 (0.00, 2.62)
	Death (Cardiovascular or Unexplained)	7/259.7	2.70 (1.08, 5.55)	3/140.8	2.13 (0.44, 6.23)
June 2014	Stroke-Ischemic	13/564.9	2.30 (1.23, 3.94)	1/298.1	0.34 (0.01, 1.87)
	Stroke-Hemorrhagic	2/577.3	0.35 (0.04, 1.25)	2/300.1	0.67 (0.08, 2.41)
	Systemic Embolism	1/576.9	0.17 (0.004, 0.97)	0/300.2	0.00 (0.00, 1.23)
	Death (Cardiovascular or Unexplained)	8/578.1	1.38 (0.60, 2.73)	6/300.2	2.00 (0.73, 4.35)

*The 95% CI calculations are performed assuming Poisson distribution.
Randomization allocation (2 Device: 1 Control), initial event only. One control hemorrhagic stroke resulted in a death not captured in the table above.

FDA Comment: As of the updated PREVAIL June 2014 dataset:

- There has been a further divergence in the rate of ischemic stroke and systemic embolism in PREVAIL, significantly favoring the Control group.
  - The ischemic stroke rate ratio, control vs. device, is 0.15, p-value=0.044 (FDA analysis)
  - The ischemic stroke or systemic embolism rate ratio, control vs. device, is 0.14, p-

value=0.027 (FDA analysis)

- Hemorrhagic strokes were infrequent (two events in each treatment group), rate ratio, control vs. device, is 1.92, p-value=0.61 (FDA analysis)
- The rate of cardiovascular or unexplained death numerically favored the device group (rate ratio, control vs. device, is 1.45, p-value=0.575, FDA analysis), but none of the deaths was causally linked to the WATCHMAN device, implantation procedure, or anticoagulant therapy.

FDA clinical evaluation of the ischemic stroke signal in PREVAIL

The number of new ischemic strokes in the WATCHMAN group and the increased ischemic stroke rate from 1.94 to 2.30 with increased duration of follow-up (396.2 pt-yrs in the January 2013 dataset vs. 860.3 pt-yrs in the June 2014 dataset) raise questions about the long-term effectiveness of the WATCHMAN device for protecting patients from ischemic stroke.

Clinical narratives were reviewed to see if there were any mitigating factors that might help explain the increasing number of effectiveness endpoint events observed in PREVAIL.

- There were 14 effectiveness events in the WATCHMAN group consisting of 13 ischemic strokes and one systemic embolism event.
    - Only one of these events was related to the device implant procedure; in this ischemic stroke case, the WATCHMAN device embolized and became entrapped in the mitral valve apparatus leading to open surgical removal. The subject developed left ventricular dysfunction, requiring prolonged bypass time and vasopressor use post-operatively.
    - The remaining 13 effectiveness events (12 ischemic strokes and 1 systemic embolism event) occurred at a mean of 15 ± 8 months post device implantation (range 2 to 26 months).
    - Anti-thrombotic medications in the remaining 13 subjects were as follows:
        - 8 subjects were on aspirin alone (per the PREVAIL protocol)
            - 1 subject (an 85-year old man) was found to have cardiolipin and beta-2 glycoprotein antibodies, which are of uncertain significance in the elderly
        - 3 subjects were on aspirin plus clopidogrel
        - 1 subject was on warfarin, which was started 1 month prior to the ischemic stroke to treat a DVT. Importantly, a TEE at the time of the ischemic stroke showed a device-related thrombus. The subject (a 70-year old man) was subsequently found to have Factor V Leiden mutation, which has not been shown to be a risk factor for stroke in patients with atrial fibrillation.[11].
        - 1 subject had a TIA 11 months post-device implantation and was switched from aspirin to apixaban. The apixaban was stopped prior to the ischemic stroke.

[11] Berge E, et al. The Factor V Leiden, Prothrombin Gene 20210GA, Methylenetetrahydrofolate Reductase 677CT and Platelet Glycoprotein IIIa 1565TC Mutations in Patients With Acute Ischemic Stroke and Atrial Fibrillation. Stroke. 2007;38:1069-1071.

One PREVAIL Control subject experienced an ischemic stroke, which occurred at a time when the INR was sub-therapeutic after warfarin was interrupted for knee surgery.

FDA Comment: The number of new ischemic strokes and the increased ischemic stroke rate in the WATCHMAN group of PREVAIL raise questions about the long-term effectiveness of the WATCHMAN device to protect patients from ischemic stroke. A review of the ischemic stroke event narratives found no mitigating circumstances that could otherwise address the device effectiveness concerns.

5 UPDATED PREVAIL PRIMARY ENDPOINTS

Summarized below are the first two[12] PREVAIL primary endpoint results based on two datasets:

- The January 16, 2013 dataset presented at December 2013 panel meeting;
- The June 28, 2014 dataset representing the most up-to-date data available.

FDA Comment: At the December 2013 Panel meeting, FDA noted that PREVAIL subject follow-up post-randomization in the PREVAIL study was limited to 11.8 ± 5.8 months, and only 113 of 407 (28%) randomized subjects had reached or passed the window for their 18-month follow-up visit. FDA also noted that because follow-up from the PREVAIL study was limited, the prior information incorporated in the PREVAIL study analyses heavily influenced the study results for the first and second primary endpoints. As shown in Table 2, the January 2013 PREVAIL dataset discussed at the December 2013 panel meeting included 396.2 patient-years, whereas the discounted prior data borrowed from PROTECT AF included 618.8 patient-years. In contrast, in the June 2014 dataset, the mean follow-up duration for PREVAIL subjects was 25.9 ± 9.7 months, and all randomized subjects have reached or passed the window for their 18-month follow-up visit. As shown in Table 2, the June 2014 PREVAIL dataset follow-up duration increased to 860.3 patient-years, such that the PREVAIL data is no longer dominated by the prior data in the Bayesian analysis.

Table 2: Total patient-years for prior data borrowed from PROTECT AF with 50% discount and for PREVAIL (FDA analysis)

Date of PREVAIL Dataset	Prior Information in pt-yrs			PREVAIL data in pt-yrs		
	Device	Control	Total	Device N=269	Control N=138	Total N=407
January 2013	395.3	223.5	618.8	256.2	140.0	396.2
June 2014	395.3	223.5	618.8	562.6	297.7	860.3

[12] The third primary endpoint was intended to evaluate procedure-related adverse events in the WATCHMAN group only. The result of this endpoint (2.2%, 6/269 subjects) has not changed since the December 2013 panel meeting, and still meets the pre-specified performance goal of 2.67%.

PREVAIL first primary endpoint

The primary analysis of the first primary endpoint was the comparison of the composite 18-month rate of stroke, cardiovascular or unexplained death, and systemic embolism between the device and control groups in the ITT population based on a rate ratio criterion. The 18-month rate represents a model-based rate of an event occurring within 18 months.

As of June 2014, the 18-month rate was 0.065 for the WATCHMAN group and 0.057 for the Control group, and the 18-month rate ratio was 1.21 with a 95% credible interval of 0.69 to 2.05 (Table 3). For comparison, the endpoint results from the January 2013 dataset are also provided in Table 3. Of note, the 18-month rate of the WATCHMAN group remained essentially unchanged between the January 2013 and June 2014 datasets (0.064 in January 2013 to 0.065 in June 2014), while the Control rate decreased from 0.063 in January 2013 to 0.057 in June 2014. The upper bound of the 95% credible interval for the 18-month rate ratio (2.05) is not lower than the non-inferiority margin of 1.75. Thus, the pre-specified non-inferiority criterion *was not met* for the first primary endpoint.

Table 3: PREVAIL First Primary Endpoint

Date of Dataset	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CrI)	Posterior Prob. of non-inferiority (FDA analysis)	Rate Ratio Non-Inferiority Criteria*	Criteria Met? (Yes/No)
January 2013	0.064	0.063	1.07 (0.57, 1.89)	95.69%	95% CrI <1.75 (Post.Prob. ≥97.5%)	No
June 2014	0.065	0.057	1.21 (0.69,2.05)	92.60%	95% CrI <1.75 (Post.Prob. ≥97.5%)	No

*The non-inferiority criterion is that the upper bound of the equitailed 2-sided 95% CrI for the rate ratio is <1.75. This is equivalent to a posterior probability of non-inferiority (that rate ratio < 1.75) is at least 97.5%.

FDA Comment: Based on the January 2013 dataset (presented at the December 2013 panel meeting), the WATCHMAN device also did not meet non-inferiority vs. Control for the first primary endpoint. The new analysis of the June 2014 dataset, which includes a greater amount of follow-up data from PREVAIL subjects than were available for the January 2013 dataset, shows an *increased* difference in the 18 month rate ratio (increasing from 1.07 to 1.21 favoring the Control group), and the posterior probability of non-inferiority is more distant from the success criterion of 97.5% (from 95.69% to 92.60%).

PREVAIL second primary endpoint

The primary analysis of the second primary endpoint was the comparison of either the rate ratio or the rate difference of the composite 18-month rate of stroke and systemic embolism (excluding events occurring in the first 7 days) between the WATCHMAN and Control groups. Like the first primary endpoint, the 18-month rate represents a model-based rate of an event occurring within 18 months.

As shown in Table 4, the WATCHMAN device met the second primary endpoint for the 18 month rate difference based on the January 16, 2013 dataset (presented at the December 2013 Panel meeting). However, in the June 2014 dataset, the 18-month rate was 0.0294 for the WATCHMAN group and 0.0131 for the Control group (Table 4). Of note, the 18-month rate of the WATCHMAN group increased from 0.0253 to 0.0294 between the January 2013 and June 2014 datasets; in contrast, the Control rate decreased from 0.0200 to 0.0131. The rate ratio was 2.8 with a 95% CrI of 0.9 to 7.3. The upper bound (7.3) of the 95% credible interval for the 18-month rate ratio is not lower than the non-inferiority margin of 2.0, and therefore non-inferiority was not met for the rate ratio. The rate difference is 0.0163 with a 95% credible interval of -0.0023 to 0.0342. The rate difference upper bound of 0.0342 is not lower than the non-inferiority margin of 0.0275. Therefore, the WATCHMAN device *is no longer non-inferior* to the Control group for the second primary endpoint.

Table 4: PREVAIL Second Primary Endpoint

Date of Dataset	Device 18 Month Rate	Control 18 Month Rate	18 Month Rate Ratio (95% CI) *	Post. Prob. of Non-Inferiority* (FDA analysis)	18 Month Rate Difference (95% CrI)**	Post. Prob. of Non-Inferiority** (FDA analysis)	Non-Inferiority Criteria Met? (Yes/No)
January 2013	0.0253	0.0200	1.6 (0.5, 4.2)	77.2%	0.0053 (-0.0190, 0.0273)	97.6%	Yes
June 2014	0.0294	0.0131	2.8 (0.9, 7.3)	37.3%	0.0163 (-0.0023, 0.0342)	89.5%	No

*The rate ratio non-inferiority criterion is that the upper bound of the equitailed 2-sided 95% CrI for rate ratio is less than 2.0. This is equivalent to posterior probability of non-inferiority (that rate ratio < 2.0) is at least 97.5%.
**The rate difference non-inferiority criterion is that the upper bound of the equitailed 2-sided 95% CrI for rate difference is less than 0.0275. This is equivalent to posterior probability of non-inferiority (that rate difference < 0.0275) is at least 97.5%.

FDA Comment: The second primary endpoint is intended to measure device effectiveness (the ability of the device to prevent ischemic strokes and systemic embolism) without considering procedure-related events. There was one ischemic stroke in the PREVAIL WATCHMAN group that occurred within 7 days of the procedure and therefore contributed to the first primary endpoint but not the second primary endpoint. The new analysis of the June 2014 dataset, which includes a greater amount of follow-up data from PREVAIL subjects than were available for the January 2013 dataset, shows that the WATCHMAN device no longer meets the second primary endpoint. Further, compared to the January 2013 dataset, the June 2014 dataset shows that the risk ratio and the risk difference for WATCHMAN vs. Control *increased* significantly in favor of the Control group, and the posterior probabilities of non-inferiority became significantly more distant from the success criterion of 97.5%. This change in the second primary endpoint outcome was driven by new ischemic strokes occurring in the WATCHMAN group and not the Control group, resulting in an increased 18-month event rate difference.

6 BAYESIAN ANALYSIS: MODEL CHECKING AND SENSITIVITY ANALYSES

Constant hazard rate assessment

The piecewise exponential model used for the first and second primary endpoint analyses assumed a constant hazard rate for each treatment group at particular follow-up intervals (i.e., constant primary endpoint event rate over a particular follow-up interval). Both the sponsor and FDA conducted an evaluation of the pre-specified assumption of constant hazard rates for this model based on updated PREVAIL data and concluded that the constant hazard rate assumption was reasonable.

Comparison to the Kaplan-Meier non-parametric approach

The 18 month rates reported in the PREVAIL primary endpoint analyses represent the model-based rate of an event occurring within 18 months. Additional analyses based on Kaplan-Meier estimates are provided for appropriate representation of the data from the PREVAIL study only. All of the PREVAIL patients have now reached or passed the window for their 18-month follow-up visit.

When based on PREVAIL data only, the model-based 18 month event rates for the first primary endpoint are 0.067 for the WATCHMAN group and 0.041 for the Control group. Based on the Kaplan-Meier estimates, the observed 18 month rates are 0.076 for the WATCHMAN group and 0.047 for the Control group (Table 5).

Table 5: Model-Based and Kaplan-Meier Rates (PREVAIL First Primary Endpoint)

	Device 18 Month Rate (95% CI)	**Control 18 Month Rate (95% CI)**
Model-based rate: PREVAIL data only (June 2014) + non-informative prior	0.067 (0.043, 0.097)	0.041 (0.019, 0.072)
Kaplan-Meier estimates: PREVAIL data only (June 2014)	0.076 (0.049, 0.117)	0.047 (0.021, 0.101)

When based on PREVAIL data only, the model-based 18 month event rates for the second primary endpoint are 0.0327 for the WATCHMAN group and 0.0043 for the Control group. Based on the Kaplan-Meier estimates, the 18 month rates are 0.038 for the device group and 0.008 for the control group (Table 6).

Table 6: Model-Based and Kaplan-Meier Event Rates (PREVAIL Second Primary Endpoint)

	Device 18 Month Rate (95% CI)	Control 18 Month Rate (95% CI)
Model-based rate: PREVAIL data only (June 2014) + non-informative prior	0.0327 (0.0173, 0.0531)	0.0043 (0.0001, 0.0159)
Kaplan-Meier estimates: PREVAIL data only (June 2014)	0.038 (0.020, 0.073)	0.008 (0.001, 0.055)

FDA Comment: The model-based 18-month event rates based on the PREVAIL data only are similar to the Kaplan-Meier rates. There are no apparent concerns about the impact of the piecewise exponential model on the PREVAIL primary analyses.

The divergence between PREVAIL and PROTECT AF trials and the impact of the informative prior on the PREVAIL analyses

In the PREVAIL study, historical data from the previous PROTECT AF trial were incorporated as prior information in the analysis of the primary endpoints such that the PREVAIL analyses borrow "strength" from the prior PROTECT AF data. This prior data included only subjects with the same $CHADS_2$ inclusion criterion as the new PREVAIL subjects to ensure that a similar population was used.

At the December 2013 panel meeting, FDA noted that in addition to the results of the PREVAIL Bayesian analysis being dominated by the borrowed data from PROTECT AF, the PREVAIL data alone were divergent from PROTECT AF. The additional data submitted in the June 2014 dataset provides a substantial amount of new PREVAIL subject follow-up, such that the prior data from PROTECT AF no longer dominate over the PREVAIL data. As a result, an increased divergence of the PREVAIL outcomes compared to the results of PROTECT AF is evident (see Tables 7 and 8 and Figures 2 and 3).

In particular, the WATCHMAN 18-month event rates for both the first and second primary endpoints are slightly higher in PREVAIL when compared to the prior data. As shown in Table 7, for the first primary endpoint, the PROTECT AF prior WATCHMAN 18-month event rate is 0.062, and the PREVAIL WATCHMAN 18-month event rate decreased from 0.070 (January 2013 dataset) to 0.067 (June 2014 dataset).

As shown in Table 8, for the second primary endpoint, the PROTECT AF prior WATCHMAN 18-month event rate is 0.025, and the PREVAIL WATCHMAN 18-month event rate increased from 0.030 (January 2013 dataset) to 0.033 (June 2014 dataset). Moreover, the 18-month event rates in the Control group are much lower in PREVAIL compared to the 18-month event rates in the prior data. As shown in Table 7, for the first primary endpoint, the PROTECT AF prior control event rate is 0.077. In contrast, the PREVAIL control event rate was 0.047 based on the

January 2013 dataset and 0.041 based on the June 2014 dataset. As shown in Table 8, for the second primary endpoint, the PROTECT AF prior control event rate is 0.025. In comparison, the PREVAIL Control event rate decreased from 0.013 based on the January 2013 dataset to 0.004 based on the June 2014 dataset.

Consequently, compared to the rate ratio prior estimates, the rate ratio estimates for the first primary endpoint increased significantly in the PREVAIL study without incorporating the informative prior from PROTECT AF.
Figure 2 shows that the rate ratio PROTECT AF prior distribution (after 50% discount) is centered at a value lower than 1, in favor of non-inferiority (prior probability of non-inferiority is 97.1%, see Table 7); however, the PREVAIL data distribution for the rate ratio is relatively distant from 1, and the probability of non-inferiority based on the PREVAIL data only from the June 2014 dataset is only 54.4% (Table 7).

The Kolmogorov Smirnov test comparing the rate ratio PROTECT AF prior distribution to the rate ratio distribution based on PREVAIL data only yield very small p-values (<0.0001) meaning that these are two significantly different distributions.

Similarly, the 18-month rate difference estimates for the second primary endpoint increased significantly in the PREVAIL study only when compared to the prior estimates. In Figure 3, the rate difference prior distribution (after 50% discount) is centered at 0, in favor of non-inferiority (prior probability of non-inferiority is 95.7%, see Table 8); however, the PREVAIL data distribution for the rate difference is relatively distant from 0, and the probability of non-inferiority based on the PREVAIL data only from June 2014 is 48.8% (Table 8).

The Kolmogorov Smirnov test comparing the rate difference prior distribution to the rate difference distribution based on PREVAIL data only showed that these are also two significantly separate distributions (p-value < 0.0001).

Table 7: First Primary Endpoint – Results based on prior only and PREVAIL data only (FDA analysis)

Bayesian Approach	Device 18 Month Rate (95% CrI)	Control 18 Month Rate (95% CrI)	18 Month Rate Ratio (95% CrI)	Prior/Posterior Prob. of Non-inferiority	Dist. Test* p-value
The prior without 50% discount	0.062 (0.041, 0.087)	0.077 (0.049, 0.111)	0.843 (0.469, 1.404)	99.7%	
The prior after 50% discount	0.062 (0.034, 0.099)	0.077 (0.040, 0.126)	0.884 (0.374, 1.800)	97.1%	
PREVAIL data only Jan. 2013	0.070 (0.038, 0.112)	0.047 (0.013, 0.102)	2.00 (0.561, 5.830)	56.3%	< 0.0001
PREVAIL data only June 2014	0.067 (0.043, 0.097)	0.041 (0.019, 0.072)	1.84 (0.803, 3.851)	54.4%	< 0.0001

*Two-sample Kolmogorov-Smirnov test for the null hypothesis that the rate ratio sample based on the PREVAIL data only and the sample based on the prior come from the same distribution

Table 8: Second Primary Endpoint – Results based on prior only and PREVAIL data only (FDA analysis)

	Device 18 Month Rate (95% CrI)	Control 18 Month Rate (95% CrI)	18 Month Rate Diff. (95% CrI)	Prior/Posterior Prob. of Non-inferiority	Dist. Test* p-value
The prior before 50% discount	0.025 (0.013, 0.042)	0.025 (0.011, 0.045)	0.0003 (-0.0236,0.0226)	99.1%	
The prior after 50% discount	0.025 (0.009, 0.050)	0.025 (0.007 0.055)	0.0003 (-0.0341,0.0318)	95.7%	
PREVAIL data only Jan. 2013	0.030 (0.010, 0.062)	0.013 (0.000, 0.049)	0.0167 (-0.0243,0.0538)	73.6%	< 0.0001
PREVAIL data only June 2014	0.033 (0.017, 0.053)	0.004 (0.000, 0.016)	0.0284 (0.0097, 0.0499)	48.8%	< 0.0001

*Two-sample Kolmogorov-Smirnov test for the null hypothesis that the rate difference sample based on the PREVAIL data only and the sample based on the prior come from the same distribution

Figure 2: The first primary endpoint rate ratio distribution (the prior distribution based on data borrowed from PROTECT AF with 50% discount, the distribution based on PREVAIL data only and non-informative prior, and the posterior distribution combining the PROTECT AF prior after 50% discount and the PREVAIL data). (FDA analysis)

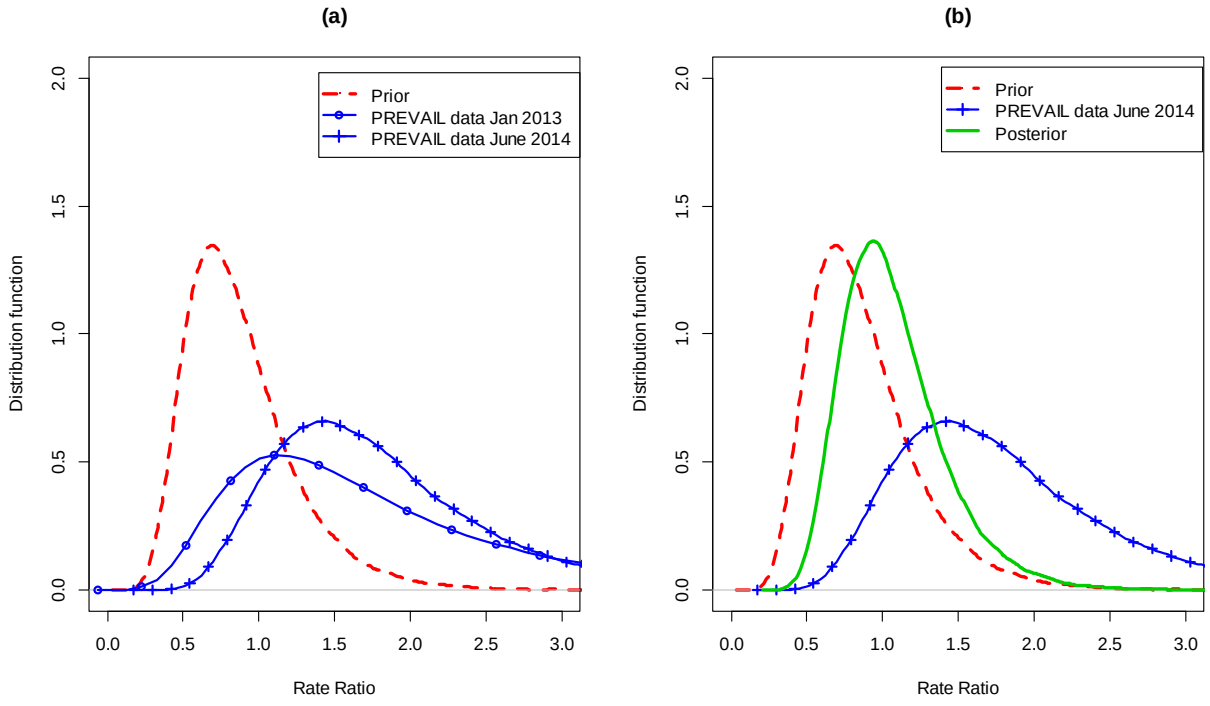
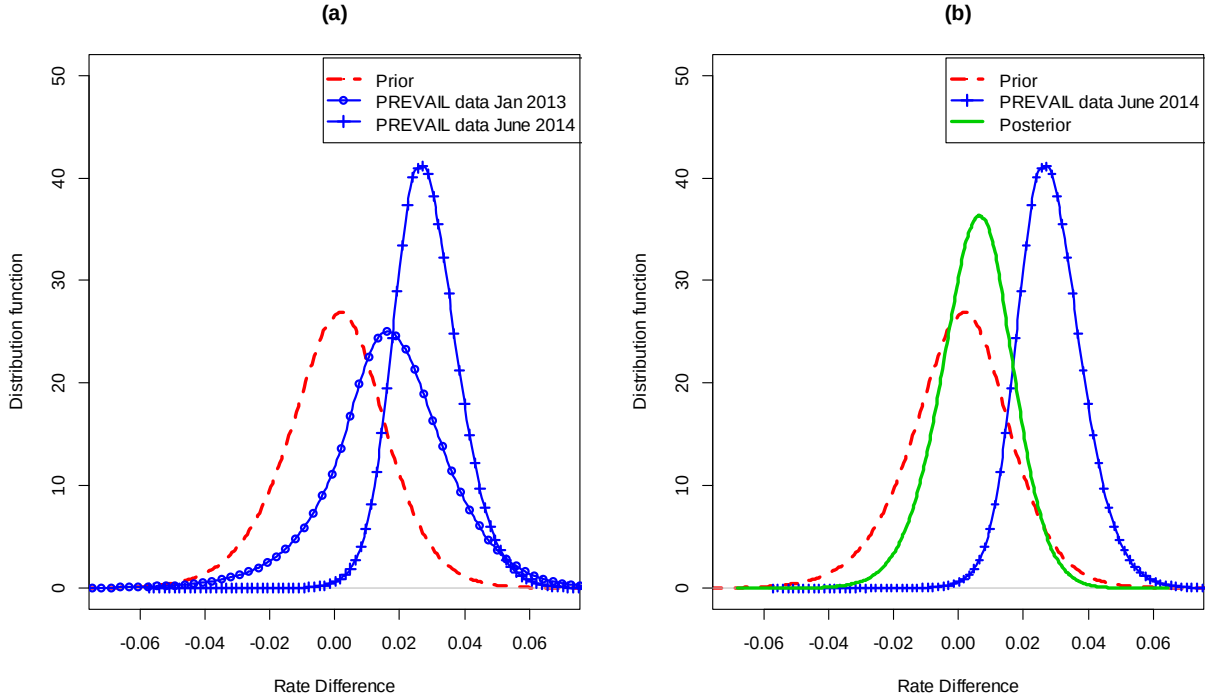


Figure 3: The second primary endpoint rate difference distribution (the prior distribution based on data borrowed from PROTECT AF with 50% discount, the distribution based on PREVAIL data only and non-informative prior, and the posterior distribution combining the PROTECT AF prior after 50% discount and the PREVAIL data) (FDA analysis)



In addition to comparing the 18-month rate ratio and rate difference distributions for the prior and the PREVAIL datasets, the Kaplan-Meier curves for the first primary and second primary endpoints (as shown in Figures 4 and 5, respectively) also reveal divergence between PROTECT AF and PREVAIL in both the WATCHMAN and Control groups. Note that the data presented in Figures 4 and 5 compare "PREVAIL-like" PROTECT AF subjects (PROTECT AF subjects who would have been eligible for PREVAIL based on $CHADS_2$ score) to PREVAIL subjects.

Figure 4. PREVAIL first primary endpoint K-M curves comparing PREVAIL-like PROTECT AF subjects to PREVAIL subjects.

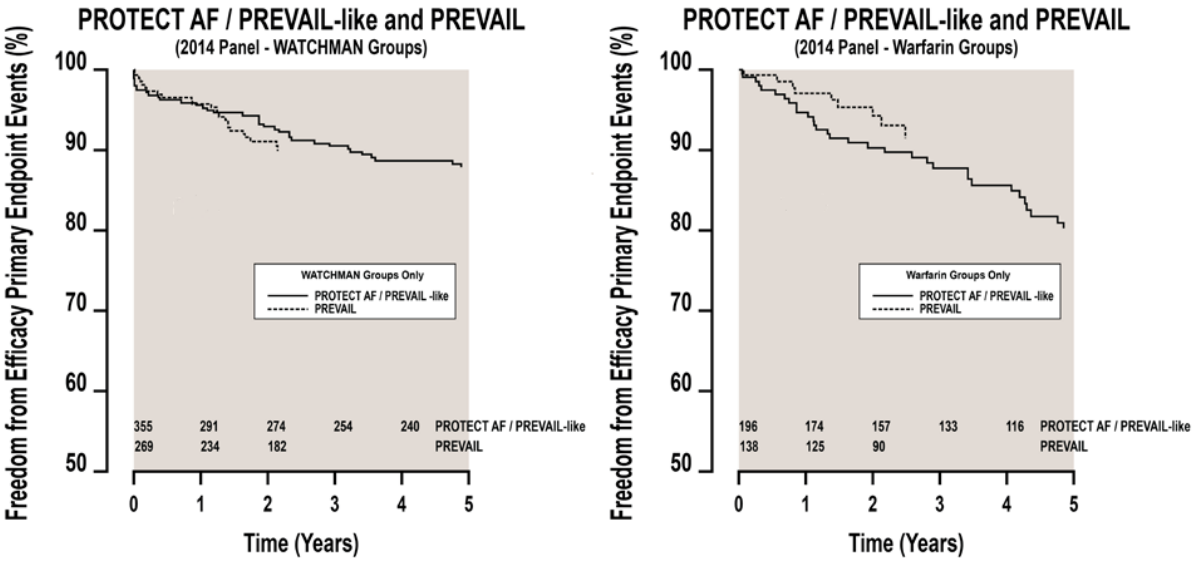
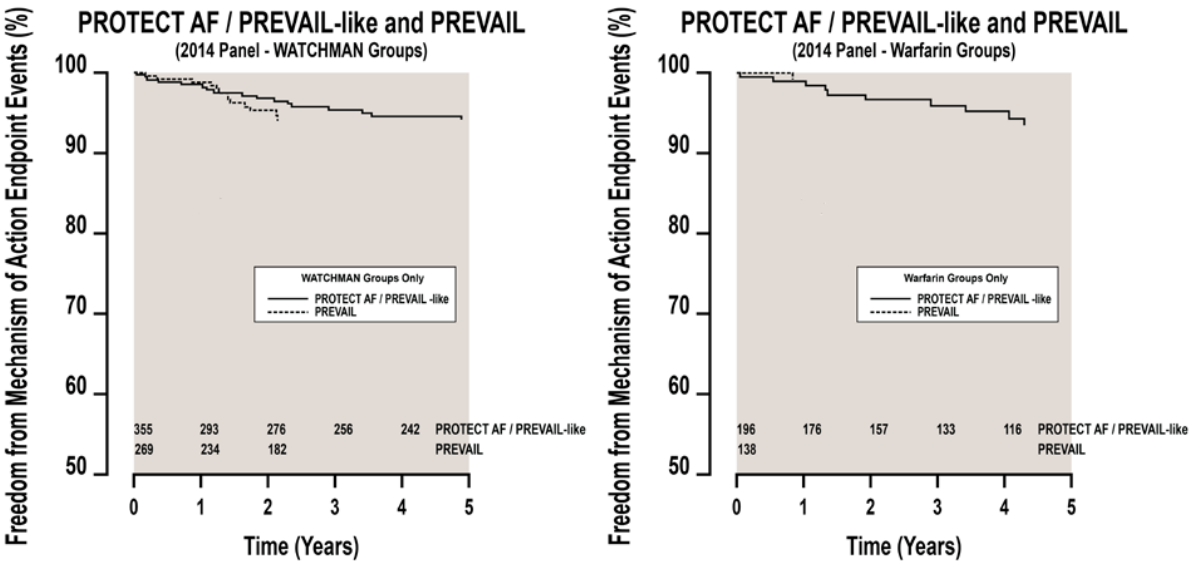


Figure 5. PREVAIL second primary endpoint K-M curves comparing PREVAIL-like PROTECT AF subjects to PREVAIL subjects.



The reasons for the divergent clinical outcomes in PROTECT AF vs. PREVAIL are not clearly evident, but differences in trial conduct and execution may be contributory. The specific issues of hemorrhagic stroke and ischemic stroke are discussed in Section 7.

Of note, in PROTECT AF:

- Subjects had INR measurements in the therapeutic range (between 2.0 and 3.0) approximately one-half of the time during protocol-required warfarin administration (46.3% of the time in the device group and 54.2% of the time in the control group).

- A substantial number of subjects in both treatment groups did not receive their intended treatment with respect to warfarin therapy. In the WATCHMAN group, 26.4% (117/442) of subjects remained on warfarin beyond the intended short-term duration of 45 days after device implantation. In the Control group, 27.3% (65/238) of subjects discontinued or interrupted warfarin therapy during follow-up.
- Subjects in both treatment groups were allowed to be on chronic clopidogrel therapy at the discretion of the treating physician. The percentage of follow-up duration that subjects were on clopidogrel was higher in the device group compared to the control group (51% versus 16%), raising the possibility that some of the outcome differences between the WATCHMAN and Control groups in PROTECT AF could be explained by the use of antiplatelet drugs.

In contrast, in PREVAIL:

- Warfarin monitoring and compliance were improved. Compliance with INR monitoring (defined as an INR measurement taken at least every 28 days) was approximately 85%.
- Subjects indicated for clopidogrel therapy were excluded.

FDA Comment: In the PREVAIL study Bayesian analysis (data as of June 2014), the prior information borrowed from PROTECT AF (discounted 50%) no longer dominate the new PREVAIL data. Importantly, PREVAIL outcomes diverge from the previous results in favor of the Control group, a divergence that becomes increasingly apparent with the inclusion of additional PREVAIL data during longer follow-up.

7 BENEFIT-RISK CONSIDERATIONS

In determining whether the WATCHMAN device is a reasonable alternative to warfarin and evaluating whether the totality of the data support a reasonable assurance of safety and effectiveness, there are four questions that are critical to the benefit-risk assessment of the device:

1. Is implantation of the WATCHMAN device associated with an acceptable rate of procedure-related complications?
2. Does the WATCHMAN device provide adequate protection from ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation?
3. Is the avoidance of long-term warfarin use following successful implantation of the WATCHMAN device associated with a reduced risk of hemorrhagic stroke?
4. Is there a signal of overall reduced bleeding complications due the avoidance of long-term use of anticoagulation therapy in patients treated with the WATCHMAN device?

Considering the four questions above in relation to the new information available on the WATCHMAN device, the data available regarding WATCHMAN procedural risks have not changed since the December 2013 panel meeting. However, the new data raises questions as to whether WATCHMAN adequately protects against ischemic stroke and systemic embolism. Additional data and discussion help address the issue of whether the WATCHMAN device is associated with a beneficial reduction in hemorrhagic stroke and overall bleeding risks vs. warfarin.

Table 9 shows the enrollment and available follow-up from the following WATCHMAN studies: PROTECT AF, PREVAIL, CAP and CAP2.

Table 9: Enrollment and Follow-up in WATCHMAN studies

Dataset	Subjects	Mean follow-up time	Total patient-years
Final PROTECT AF	707 randomized 463 WATCHMAN 244 Control (Warfarin)	47.6 ± 21.3 months	2717
June 2014 PREVAIL	407 randomized 269 WATCHMAN 138 Control (Warfarin)	25.9 ± 9.7 months	860.3
June 2014 CAP	566	43.9 ± 16.9 months	2022
June 2014 CAP2	579	6.9 ± 4.6 months	335

FDA Comment: Compared to PROTECT AF, PREVAIL, and CAP, the follow-up available from CAP2 is relatively limited.

Ischemic Stroke and Systemic Embolism

Since the postulated mechanism of device benefit is to prevent thromboembolism from the LAA, the rate of ischemic stroke plus systemic embolism is an essential element in assessing the benefit-risk profile of the WATCHMAN device.

PREVAIL Ischemic Stroke and Systemic Embolism

There were 13 ischemic strokes and one systemic embolism in the WATCHMAN group, and one ischemic stroke in the Control group (Table 10). The observed rates of ischemic stroke were 2.3/100 pt-yrs in the WATCHMAN group and 0.34/100 pt-yrs in the Control group. The observed rates of systemic embolism were 0.17/100 pt-yrs in the WATCHMAN group and 0/100 pt-yrs in the Control group (Table 10). Assuming Poisson distribution for the linearized rates and constant hazard rate for the entire follow-up period, the ischemic stroke rate ratio for Control vs. WATCHMAN is 0.15 (p-value = 0.044 in favor of the Control – FDA analysis). Also, the ischemic stroke or systemic embolism rate ratio for the Control vs. the WATCHMAN group is 0.14 (p-value = 0.027 in favor of the control – FDA analysis).

Table 10: PREVAIL-only Ischemic Stroke and Systemic Embolism Events (FDA analysis)

	WATCHMAN		Control	
	N Events/ Total pt-yrs	Rate* (95% CI**)	N Events/ Total Pt-yrs	Rate* (95% CI**)
Stroke - Ischemic	13/564.9	2.30 (1.23, 3.94)	1/298.1	0.34 (0.01,1.87)
Systemic Embolism	1/576.9	0.17 (0.004, 0.97)	0/300.2	0.00 (0.00,1.23)
Ischemic Stroke + Systemic Embolism	14/566	2.47 (1.35, 4.15)	1/298	0.34 (0.008, 1.87)

*Rate = Event rate per 100 patient-years
**The 95% CI calculations are performed assuming Poisson distribution.

FDA also applied the piecewise exponential model approach to estimate the 18-month rates for ischemic stroke and systemic embolism. The 95% CrI for the rate difference between the Control vs. WATCHMAN groups is less than 0 for both ischemic stroke and the composite of ischemic stroke and systemic embolism (Table 11), indicating a significant difference in favor of the control group.

Table 11: PREVAIL-only Ischemic Stroke and Systemic Embolism 18-month Event Rates (Bayesian modeling approach with non-informative prior - FDA analysis)

	Device 18 Month Rate (95% CrI)	Control 18 Month Rate (95% CrI)	18 Month Rate Difference Control vs. device (95% CrI)
Stroke - Ischemic	0.034 (0.018, 0.056)	0.004 (0.000, 0.016)	-0.0298 (-0.0523, -0.0106)
Ischemic Stroke + Systemic Embolism	0.036 (0.020, 0.058)	0.004 (0.000, 0.016)	-0.0320 (-0.0549, -0.0125)

The Kaplan-Meier curve and estimates for freedom from ischemic stroke and systemic embolism are included in Figure 6 and Table 12, respectively. The log-rank test for the Control vs. WATCHMAN groups yield a p-value of 0.024 in favor of the control group (FDA analysis).

Figure 6: PREVAIL-only Freedom from Ischemic Stroke or Systemic Embolism

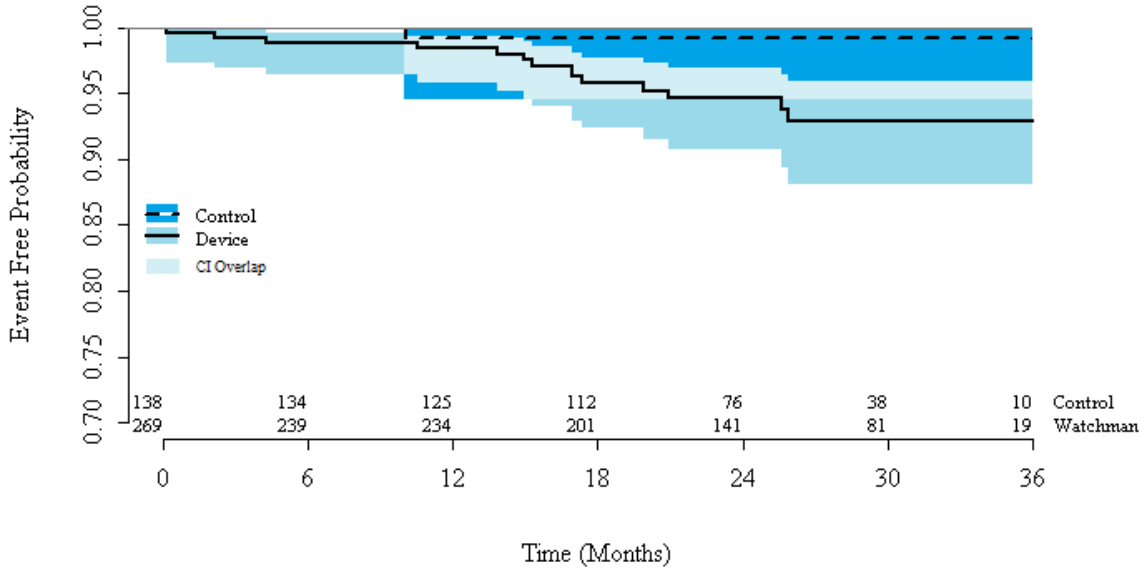


Table 12: PREVAIL-only Freedom from Ischemic Stroke or Systemic Embolism

	Device			Control		
Time Point	**N Events**	**N Cumulative Events***	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events***	**Event Free Rate (%) (95% CI)**
Baseline	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
7-days	1	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
45-days	0	1	99.6 (97.4, 99.9)	0	0	100.0 (100.0, 100.0)
6-months	2	3	98.8 (96.4, 99.6)	0	0	100.0 (100.0, 100.0)
1-year	1	4	98.4 (95.8, 99.4)	1	1	99.2 (94.5, 99.9)
18-months	6	10	95.8 (92.3, 97.7)	0	1	99.2 (94.5, 99.9)
2-year	2	12	94.6 (90.7, 96.9)	0	1	99.2 (94.5, 99.9)
3-year	2	14	92.9 (88.1, 95.9)	0	1	99.2 (94.5, 99.9)

* 2:1 Randomization Device to Control

FDA Comment: Even accounting for the 2:1 randomization, the observation of 14 events in the WATCHMAN group compared to one event in the Control group calls into question the effectiveness of the WATCHMAN device relative to warfarin. In addition, 10 of the 13 ischemic stroke events occurred more than one year after WATCHMAN implantation. The performance of the PREVAIL Control group in the context of contemporary trials is discussed later in this executive summary. The Panel will be asked to comment on the clinical significance of the PREVAIL device group ischemic stroke rate.

PROTECT AF Ischemic Stroke and Systemic Embolism

In PROTECT AF, there were 24 ischemic strokes and 2 systemic embolism events in the WATCHMAN group and 10 ischemic strokes in the Control group (Table 13). Of the 24 ischemic strokes in the WATCHMAN group, 6 were peri-procedural. The overall rates of ischemic stroke and systemic embolism were 1.5% in the WATCHMAN group and 1.1% in the Control group.

Table 13: PROTECT AF Ischemic Stroke and Systemic Embolism Events

	WATCHMAN		Control	
	N Events/ Total Pt-yrs	**Rate* (95% CI**)**	**N Events/ Total Pt-yrs**	**Rate* (95% CI**)**
Stroke - Ischemic	24/1788.2	1.3 (0.86, 2.00)	10/932.8	1.1 (0.51, 1.97)
Systemic Embolism	2/1843.7	0.1 (0.01, 0.39)	0/949.0	0.0 (0.00, 0.39)
Ischemic Stroke + System Embolism	26/1787.7	1.5 (0.95, 2.13)	10/933	1.1 (0.51, 1.97)

*Rate = Event rate per 100 patient-years
*The 95% CI calculations are performed assuming Poisson distribution.

The Kaplan-Meier curve and estimates for freedom from ischemic stroke and systemic embolism are included in Figure 7 and Table 14, respectively.

Figure 7: PROTECT AF Freedom from Ischemic Stroke/Systemic Embolism

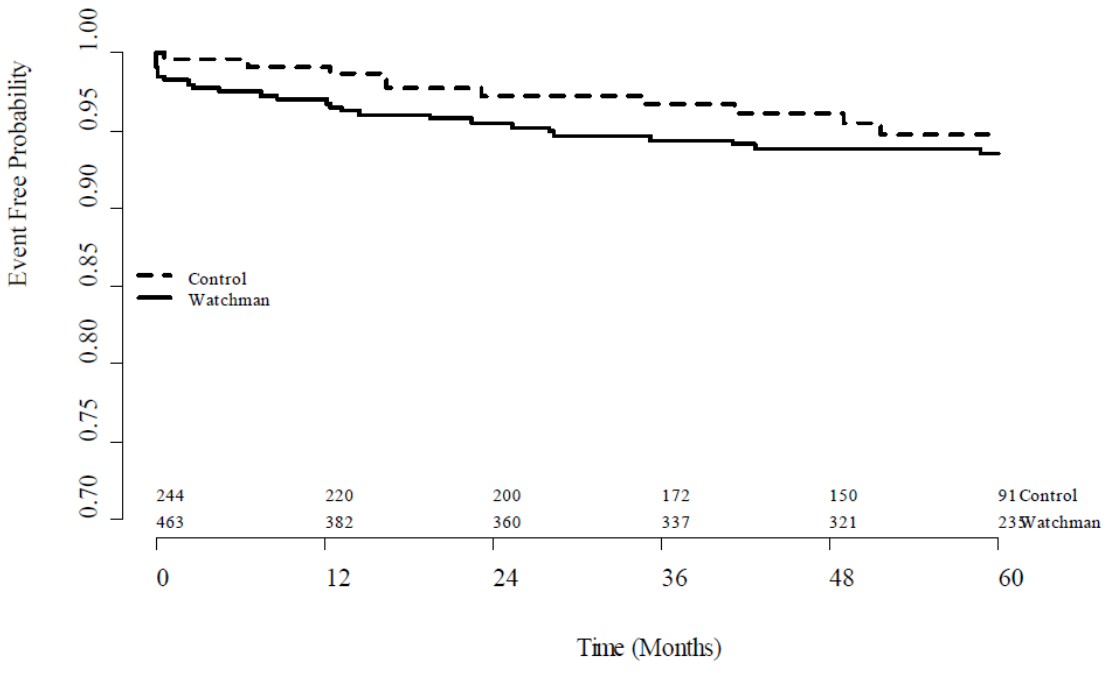


Table 14: PROTECT AF Freedom from Ischemic Stroke/Systemic Embolism

	Device			Control		
Time Point	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**	**N Events**	**N Cumulative Events**	**Event Free Rate (%) (95% CI)**
7-days	7	7	98.5 (96.8, 99.3)	0	0	100.0 (100.0, 100.0)
45-days	1	8	98.3 (96.5, 99.1)	1	1	99.6 (97.1, 99.9)
6-months	3	11	97.5 (95.6, 98.6)	0	1	99.6 (97.1, 99.9)
1-year	2	13	97.0 (95.0, 98.3)	1	2	99.2 (96.7, 99.8)
1.5-year	4	17	96.0 (93.7, 97.5)	3	5	97.8 (94.7, 99.1)
2-year	2	19	95.5 (93.0, 97.1)	1	6	97.3 (94.1, 98.8)
3-year	4	23	94.4 (91.7, 96.3)	1	7	96.7 (93.3, 98.4)
4-year	2	25	93.8 (91.0, 95.8)	1	8	96.1 (92.4, 98.1)
5-year	1	26	93.5 (90.6, 95.6)	2	10	94.8 (90.5, 97.2)

FDA Comment: The ischemic stroke plus systemic embolism rate numerically favored the Control group.

Continued Access to PROTECT AF (CAP) Registry Ischemic Stroke and Systemic Embolism

In the Continued Access to PROTECT AF (CAP) registry, there were 24 ischemic strokes and 1 systemic embolism in 566 subjects, representing an event rate of 1.2 events/100 pt-yrs (Table 15).

Table 15: CAP Ischemic Stroke and Systemic Embolism Events

	N Events/ Total Pt-yrs	**Rate* (95% CI**)**
Stroke - Ischemic	24/2026	1.2 (0.76, 1.76)
Systemic Embolism	1/2068	0.05 (0.001, 0.27)
Ischemic Stroke + Systemic Embolism	25/2028	1.2 (0.80, 1.82)

*Rate = Event rate per 100 patient-years
**The 95% CI calculations are performed assuming Poisson distribution.

FDA Comment: The ischemic stroke plus systemic embolism rate in the CAP registry is generally similar to the rate seen in the PROTECT AF trial.

Continued Access to PREVAIL (CAP2) Registry Ischemic Stroke and Systemic Embolism

There have been 9 ischemic strokes and 2 systemic embolism events in CAP2 (Table 16). Two subjects had ischemic strokes within 7 days post-procedure. Of the remaining 7 ischemic stroke

events, 2 occurred within 45 days of the procedure, and 5 occurred between 45 days and 6 months post-procedure. Both systemic embolism events and 3 of the ischemic strokes were associated with imaging findings of thrombus on the atrial face of the device.

Table 16: CAP2 Ischemic Stroke and Systemic Embolism Events

Endpoint Event Type	N Events/ Total pt-yrs	Rate* (95% CI**)
Stroke - Ischemic	9/329.9	2.7 (1.25, 5.18)
Systemic Embolism	2/332.4	0.6 (0.07, 2.17)
Total Ischemic Stroke+ System Embolism	11/330	3.3 (1.66, 5.96)

*Rate = Event rate per 100 patient-years
**The 95% CI calculations are performed assuming Poisson distribution.

FDA Comment: The ischemic stroke plus systemic embolism rate in the CAP2 registry is generally similar to the rate seen in the PREVAIL trial.

Ischemic Stroke and Systemic Embolism Summary

A summary of ischemic stroke and systemic embolism event rates across the four WATCHMAN studies is shown in Table 17. The rate of ischemic stroke in the WATCHMAN group ranged from 1.2 to 2.7 events per 100 patient-years. There were few systemic embolism events with one or two in the WATCHMAN group in each study, and none in the control groups.

Table 17: Ischemic Stroke and Systemic Embolism Across WATCHMAN Studies

Study	WATCHMAN Events (rate per 100 pt-yrs)			Control Events (rate per 100 pt-yrs)		
	Ischemic Stroke	Systemic Embolism	IS + SE	Ischemic Stroke	Systemic Embolism	IS + SE
PREVAIL-only	13 (2.30)	1 (0.17)	14 (2.47)	1 (0.34)	0 (0.00)	1 (0.34)
PROTECT AF	24 (1.3)	2 (0.2)	26 (1.5)	10 (1.1)	0 (0.00)	10 (1.1)
CAP	24 (1.2)	1 (0.05)	25 (1.2)	-	-	-
CAP2	9 (2.7)	2 (0.6)	11 (3.3)	-	-	-
Total across all studies	70 (1.5)	6 (.12)	76 (1.6)	11 (0.9)	0 (0.0)	11 (0.9)

IS = ischemic stroke. SE = systemic embolism

In summary, in both PROTECT AF and PREVAIL, the ischemic stroke plus systemic embolism rate favors the Control group with a significant difference in rates observed in PREVAIL.

Hemorrhagic Stroke

In PREVAIL, there were 2 hemorrhagic strokes each in the WATCHMAN and Control groups. In PROTECT AF, there were 3 hemorrhagic strokes in the WATCHMAN group and 10 in the Control group. There were also 2 hemorrhagic strokes in CAP. No hemorrhagic strokes have been reported in CAP2 (Table 18).

Table 18: Hemorrhagic Stroke Across WATCHMAN studies

	WATCHMAN N events (rate per 100 pt-yrs)	**Control N events (rate per 100 pt-yrs)**
PREVAIL-only	2 (0.35) (0.04, 1.25)	2 (0.67) (0.08, 2.41)
PROTECT AF	3 (0.2) (0.03, 0.48)	10 (1.1) (0.52, 2.00)
CAP	2 (0.10)	-
CAP2	0 (0.0)	-

*2:1 device:control randomization
**The 95% CI calculations are performed assuming Poisson distribution.

FDA Evaluation of the Hemorrhagic Stroke Signal

The results of the PROTECT AF study suggest that the WATCHMAN device offers an important benefit compared with warfarin therapy by lowering the risk of hemorrhagic stroke. This potential benefit is particularly important as hemorrhagic stroke is often associated with significant disability or death, and an assessment of hemorrhagic stroke risk is a key component of the assessment of the benefit-risk profile of the WATCHMAN device compared with warfarin therapy.

Table 19 shows the hemorrhagic stroke rate from the PROTECT AF final study report.

Table 19: Hemorrhagic Stroke in the PROTECT AF Study (2717 Pt-Yrs, ITT)

WATCHMAN			**Control**		
N Events	**% of 463 Randomized Subjects**	**Rate per 100 pt-yrs**	**N Events**	**% of 244 Randomized Subjects**	**Rate per 100 pt-yrs**
3	0.6%	0.2	10	4.1%	1.1

2:1 WATCHMAN:Control randomization

In assessing the robustness of the benefit of the WATCHMAN device in substantially lowering the risk of hemorrhagic stroke compared to warfarin as observed in the PROTECT AF study, the following points should be considered:

1. Historical perspective on the PROTECT AF Control group hemorrhagic stroke rate

As shown in Table 20, the hemorrhagic stroke rate in the Control group of PROTECT AF was at least 2-fold higher than reported in other contemporary oral anticoagulation trials in subjects with non-valvular AF. Drawing definitive conclusions from comparisons of event rates among similar trials should be done with caution, but the general consistency of hemorrhagic stroke rates across the contemporary oral anticoagulation trials is noteworthy.

Table 20: **Hemorrhagic Stroke Rates in Warfarin Control groups in contemporary anticoagulation trials (FDA analysis)**

ACTIVE W	BAFTA	RELY	ROCKET AF	ARISTOTLE	ENGAGE AF	PROTECT AF
Event Rate per 100 pt-yrs, (events/total pt-ys), (95% CI*)						
0.36	0.5	0.38	0.4	0.47	0.47	1.1
(15/4166.7)	(6/1200)	(45/11842)		(78/16595.7)	(90/19148.9)	(10/945.6)
(0.20, 0.59)	(0.18, 1.09)	(0.28,0.51)	-	(0.37, 0.59)	(0.38, 0.58)	(0.51, 1.94)

*The 95% CI calculations are performed assuming Poisson distribution.

Further, in a patient level meta-analysis of 6 randomized trials of oral anticoagulation (coumarin derivatives) vs. aspirin in patients with non-valvular AF, the hemorrhagic stroke rate in anticoagulant-treated subjects was 0.5 per 100 pt-yrs.[13] Thus, the historical data are internally consistent and suggest that the hemorrhagic stroke rate observed in the PROTECT AF Control group was considerably higher than expected.

2. Scrutiny of the 10 hemorrhagic stroke cases in the PROTECT AF Control group.

Review of the clinical narratives revealed the following:

1. Although appropriately included in the ITT analysis, one subject had been off warfarin for over 38 months at the time of the hemorrhagic stroke event (taking aspirin alone).

2. The PROTECT AF study protocol hemorrhagic stroke definition required imaging confirmation (see below). However, one subject had no imaging confirmation of a hemorrhagic stroke. The clinical narrative reported the following:

   > The patient was admitted to the hospital for an acute stroke with right-sided hemiplegia, loss of consciousness, left-sided mydriasis and hypertension (210/100). Diuresis and anti-hypertension therapy were initiated to no effect, and the patient went into a coma. While no CT scan was performed, the reporting physician noted: "Given the chronic anti-coagulation therapy and her clinical history, it was highly likely that there was severe hemorrhaging into the CNS."

   From the information provided, it is not possible to rule in or rule out a hemorrhagic stroke.

[13] van Walraven, et al. JAMA 2002; 288: 2441-8

3. Use of concomitant antiplatelet therapy. Four subjects were taking aspirin at the time of the hemorrhagic stroke, and no antiplatelet use information was available for another subject.

   Although there clearly are situations (such as a recent coronary stent implant or a recent acute coronary syndrome) in which antiplatelet therapy should be added to anticoagulants in AF patients with stroke risk factors, for individuals with stable vascular disease, multiple studies have shown that the addition of aspirin to anticoagulation offers no greater protection against stroke but is associated with a significantly higher bleeding risk. The 2006 American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines for the Management of Patients With Atrial Fibrillation state that combining aspirin with an oral anticoagulant at higher intensities may accentuate intracranial hemorrhage, particularly in elderly AF patients, and that for most patients with AF who have stable CAD, warfarin anticoagulation alone (target INR 2.0 to 3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events. The 2010 European Society of Cardiology (ESC) 2010 Guidelines for the Management of Atrial Fibrillation notes that the addition of aspirin to vitamin K antagonists does not reduce the risk of stroke or vascular events (including myocardial infarction), but substantially increases bleeding events. The ESC recommendation is that concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event (Class IIb, level of evidence C).

   It is reasonable to postulate that more appropriate and judicious use of antiplatelet agents in patients with stable vascular disease would be associated with a reduced risk of hemorrhagic stroke in patients taking warfarin.

4. Hemorrhagic strokes vs. cranial bleeding events. The definition of a hemorrhagic stroke in the PROTECT AF trial was as follows:

   > Sudden onset of a focal neurological deficit with CT or MRI evidence of tissue loss with evidence of blood vessel hemorrhage.

   However, a contemporary definition of hemorrhagic stroke reflecting the consensus opinion of Healthcare Professionals From the American Heart Association/American Stroke Association (Stroke 2013; 44) is as follows:

   > Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

   Subarachnoid hemorrhage can be considered a type of hemorrhagic stroke, but subdural hematomas are usually considered intracranial hemorrhage events and not strokes.

   Of the 10 events adjudicated as hemorrhagic strokes in the PROTECT AF Control group, 5 events occurred following falls; four were associated with subdural hematomas (one of which also had intracerebral bleeding in a subject on aspirin alone), and a subarachnoid hemorrhage was present in one subject. The narratives from two of these events indicate that the subject hit their head, one subject fell down steps, and information is lacking on the other two subjects. It is clearly possible that the use of warfarin (plus concomitant

use of antiplatelet agents in at least 2 of the 4 subjects taking warfarin) contributed to the seriousness of the events. Further, falls resulting in subdural hematoma were not unique to the Control group in PROTECT AF. Three WATCHMAN subjects, two on aspirin alone and one on aspirin plus warfarin, fell and suffered subdural hematomas; these cases were not adjudicated as hemorrhagic strokes. In total, there were 5 reported non-hemorrhagic stroke intracranial bleeding events in the WATCHMAN group vs. one in the Control group in PROTECT AF. Combining the reported hemorrhagic strokes with non-hemorrhagic stroke intracranial bleeds, there were 7 events in the WATCHMAN group and 11 events in the Control group.

In summary, the PROTECT AF trial demonstrates a signal that the WATCHMAN device reduces the risk of hemorrhagic stroke compared with warfarin therapy. However, the robustness of this signal is diminished by several factors including non-use of warfarin in one subject, absence of imaging confirmation in one subject, concomitant use of antiplatelet agents in several subjects, and events associated with trauma in several subjects. Further, the hemorrhagic stroke rate in the Control group in PROTECT AF was at least 2-fold higher than reported in other contemporary oral anticoagulation trials. A signal of a reduced risk of hemorrhagic stroke in WATCHMAN subjects compared with subjects taking warfarin was not observed in the PREVAIL trial, and the hemorrhagic stroke rate in in the PREVAIL Control group (0.67 per 100 pt-yrs) was in the range observed in the warfarin groups of contemporary anticoagulation trials.

Bleeding

A potential benefit of the WATCHMAN device compared to warfarin is a reduction in long-term bleeding complications associated with the use of chronic anticoagulation therapy. However, the risk of bleeding associated with the WATCHMAN device implantation procedure must also be considered. Although the WATCHMAN studies did not include a pre-specified hypothesis to compare major bleeding rates, a descriptive analysis of bleeding complications observed in the WATCHMAN and Control groups is informative when assessing the benefit-risk profile of the device.

Major bleeding was defined as bleeding complications that were adjudicated as serious adverse events.[14] Tables 21, 22, and 23 show the bleeding rates in PREVAIL, PROTECT AF, and CAP, respectively. Among WATCHMAN treated patients, there were 12 subjects (4.5%) in PREVAIL, 28 (6.0%) in PROTECT AF, and 18 (3.2%) in CAP who experienced procedure-related major bleeding complications. Within 45 days post-procedure (while the WATCHMAN group subjects were still on warfarin therapy), there were 4 major bleeds in WATCHMAN patients and 0 in Control patients (within 45 days of randomization) in PREVAIL (Table 21). In the same time period (within 45 days) in PROTECT AF, there were 5 (1.1%) major bleeds in the

[14] As defined in the PREVAIL protocol, an adverse event is considered serious if it results in one of the following:

- Death
- Life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Permanent impairment of a body function or permanent damage to a body structure

WATCHMAN group and 2 (0.8%) in the Control group (Table 22). In CAP there were 14 (2.5%) major bleeds during this time period (Table 22).

Beyond 6 months post-implant (terminal therapy) in PREVAIL, there were 5 (1.9%) major bleeds in WATCHMAN patients versus 11 (8.0%) major bleeds in Control patients (Table 21). In the same time period (>6 months) in PROTECT AF, there were 15 (3.8%) major bleeds in WATCHMAN patients versus 23 (10.1%) major bleeds in Control patients (Table 22). In CAP, there were 33 (5.8%) major bleeds in the >6 month time period (Table 22).

Table 21: PREVAIL-only First Major Bleeding Events

	WATCHMAN		Control	
Event	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs) (95% CI**)**	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs) (95% CI**)**
Major bleeding*	29/269 (10.8%)	5.5 (29/531.1) (3.8,7.9)	14/138 (10.1%)	5.0 (14/282.1) (2.9,8.4)
Procedure related major bleeding	12/269 (4.5%)	-	-	-
Non-procedure related major bleeding	20/269 (7.4%)	3.6 (20/550.1) (2.3,5.6)	14/138 (10.1%)	5.0 (14/282.1) (2.9,8.4)
0-45 days	8/269 (3.0%)	25.0 (8/31.9) (12.5,50.1)	0/138 (0.0%)	0.0 (0/16.9) (0.0,0.0)
45 days - 6 months	7/269 (2.6%)	7.9 (7/88.6) (3.8,16.6)	3/138 (2.2%)	6.0 (3/50.4) (1.9,18.5)
Beyond 6 months	5/269 (1.9%)	1.2 (5/429.6) (0.5,2.8)	11/138 (8.0%)	5.1 (11/214.8) (2.8,9.2)

*2:1 Randomization Device to Control

**The 95% CI calculations are performed assuming Poisson distribution

Table 22: PROTECT AF First Major Bleeding Events

	WATCHMAN		Control	
Event	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs) (95% CI**)**	**N Events/ Subjects (%)**	**Rate (N Events/ Total Pt-Yrs) (95% CI**)**
Major bleeding*	50/463 (10.8%)	2.9 (50/1743.4) (2.2,3.8)	29/244 (11.9%)	3.2 (29/904.9) (2.2,4.6)
Procedure related major bleeding	28/463 (6.0%)	-	-	-
Non-procedure related major bleeding	24/463 (5.2%)	1.3 (24/1803.7) (0.9,2.0)	29/244 (11.9%)	3.2 (29/904.9) (2.2,4.6)
0-45 days	5/463 (1.1%)	9.2 (5/54.6) (3.8,22.0)	2/244 (0.8%)	6.7 (2/29.7) (1.7, 27.0)
45 days - 6 months	4/431 (0.9%)	2.6 (4/153.6) (1.0, 6.9)	4/239 (1.7%)	4.6 (4/87.8) (1.7,12.1)
Beyond 6 months	15/397 (3.8%)	0.9 (15/1595.5) (0.6, 1.6)	23/228 (10.1%)	2.9 (23/787.5) (1.9, 4.4)

*2:1 Randomization Device to Control
**The 95% CI calculations are performed assuming Poisson distribution

Table 23: CAP First Major Bleeding Events

Event	**N Subjects with Events/Total Subjects (%)**	**Rate (N Events/Total Pt-Yrs) (95% CI*)**
Major Bleeding	74/566 (13.1%)	4.0 (74/1873.2) (3.1, 5.0)
Procedure Related Major Bleeding	18/566 (3.2%)	-
Non-Procedure Related Major Bleeding	61/566 (10.8%)	3.2 (61/1918.0) (2.5, 4.1)
0-45 days	14/566 (2.5%)	-
45 days – 6 months	14/566 (2.5%)	-
Beyond 6 months	33/566 (5.8%)	-

*The 95% CI calculations are performed assuming Poisson distribution

FDA Comment: Neither PROTECT AF nor PREVAIL had a pre-specified hypothesis to compare major bleeding rates between subjects treated with the WATCHMAN device or warfarin, and bleeding was not analyzed by scales used in other major clinical trials (e.g., GUSTO, TIMI). Although late (>6 months post-randomization) bleeding rates favored the WATCHMAN group, this was balanced by the up-front risk of procedure-related bleeding events, which resulted in no overall advantage of the WATCHMAN device vs. warfarin. The Panel will be asked to comment on the clinical significance of the major bleeding events.

Mortality

Cardiovascular and unexplained deaths comprised the third component of the first primary endpoint in PREVAIL and the primary effectiveness endpoint in PROTECT AF. In PREVAIL, there were 8 events in the WATCHMAN group and 7 in the Control group, corresponding to rates of 1.38 and 2.33 events per 100 patient-years in the WATCHMAN and Control groups, respectively. In PROTECT AF, there were 19 events in the WATCHMAN group and 22 in the Control group, corresponding to rates of 1.0 and 2.3 events per 100 patient-years in the WATCHMAN and Control groups, respectively. There were 27 events in CAP for a rate of 1.3 events per 100 patient-years (Table 24). There have been no cardiovascular or unexplained deaths in CAP2.

Table 24: Cardiovascular/Unexplained Deaths Across WATCHMAN Studies

	WATCHMAN **N events/total pt-yrs** **rate per 100 pt-yrs (CI**)**	**Control** **N events/total pt-yrs** **rate per 100 pt-yrs (CI**)**
PREVAIL-only	8/578.1 1.38 (0.60, 2.73)	7/300.2 2.33 (0.94, 4.80)
PROTECT AF	19/1843.2 1.0 (0.6, 1.6)	22/948.9 2.3 (1.4, 3.3)
CAP	27/2070.3 1.3 (0.9, 1.9)	-
CAP2	0/335 0.0 (0.0, 1.10)	-

*2:1 Randomization Device to Control
**The 95% CI calculations are performed assuming Poisson distribution.

FDA Comment: In PROTECT AF, the difference in cardiovascular/unexplained death rates between the control and device groups is largely due to deaths related to hemorrhagic stroke. Of the 22 cardiovascular or unexplained deaths in the PROTECT AF control group, 8 occurred in subjects adjudicated as having hemorrhagic stroke. In PREVAIL, the rate of cardiovascular/unexplained death numerically favored the device group, but none of the deaths was causally linked to the WATCHMAN device, implantation procedure, or anticoagulant therapy.

All-cause mortality

In PREVAIL, there were 22 deaths in the WATCHMAN group and 13 deaths in the Control Group. In PROTECT AF, there were 60 deaths in the WATCHMAN group and 44 deaths in the control group. In CAP and CAP2, there were 83 and 8 deaths, respectively (Table 25).

Table 25: All-Cause Mortality Across WATCHMAN Studies

	Device N events/total pt-yrs rate per 100 pt-yrs (CI**)	Control N events/total pt-yrs rate per 100 pt-yrs (CI**)
PREVAIL-only	22/578 3.8 (2.39, 5.76)	13/300 4.3 (2.31, 7.41)
PROTECT AF	60/1884.4 3.3 (2.5, 4.2)	44/949.0 4.6 (3.2, 5.8)
CAP	83/2066.7 4.0 (3.2, 4.9)	-
CAP2	8/335.4 2.4 (1.2, 4.3)	-

**2:1 Randomization Device to Control
*The 95% CI calculations are performed assuming Poisson distribution.

FDA Comment: Inferences based on the mortality rate differences in PREVAIL are significantly limited by the underlying co-morbidities in the study subjects, and the modes of death in most subjects, which bore little if any relationship to the WATCHMAN device or anticoagulation.

8 WARFARIN CONTROL GROUP OUTCOMES

There were relatively low rates of ischemic and hemorrhagic stroke in the PREVAIL Control group and a higher than expected rate of hemorrhagic stroke in the PROTECT AF control group (which is discussed in detail in Section 7 above). FDA evaluated the performance of these control groups compared to the warfarin treatment in anticoagulation drug trials. As shown in Table 26, the hemorrhagic stroke rate in the Control group of PROTECT AF was at least 2-fold higher than in other anticoagulation trials. In contrast, the ischemic stroke rate in the Control group of PREVAIL was at least 2-fold lower than other anticoagulation trials. For comparison, the outcomes for the WATCHMAN group in PROTECT AF, PREVAIL, CAP, and CAP2 are shown in Table 27.

Table 26: Event Rates in Warfarin Control groups across anticoagulation trials (FDA analysis)

Event Rate per 100 pt-yrs, (Events/total pt-ys), (95% CI*)					
	All Stroke	**Ischemic Stroke**	**Hemorrhagic Stroke**	**Systemic Embolism**	**Cardiovascular Death**
ACTIVE W	1.40 (59/4214.3) (1.07, 1.81)	1.00 (42/4200) (0.72, 1.35)	0.36 (15/4166.7) (0.20, 0.59)	0.10 (4/4000) (0.03, 0.25)	2.52 (106/4206.3) (2.06, 3.05)
BAFTA	1.6 (21/1312.5) (0.99, 2.45)	0.8 (10/1250) (0.38, 1.47)	0.5 (6/1200) (0.18, 1.09)	0.1 (1/1000) (0.003, 0.56)	3.1 (41/1322.6) (2.22, 4.21)
RELY	1.57 (187/11910.83) (1.35, 1.81)	1.20 (142/11833) (1.01, 1.41)	0.38 (45/11842) (0.28,0.51)	-	2.69 (317/11784) (2.40, 3.00)
ROCKET AF	2.2 (241/10954.6) (1.93, 2.50)	1.6 -	0.4 -	0.2 -	 -
ARISTOTLE	1.51 (250/16556.3) (1.33, 1.71)	1.05 (175/16666.7) (0.90, 1.22)	0.47 (78/16595.7) (0.37, 0.59)	0.10 (17/17000) (0.06, 0.16)	2.02 -
ENGAGE AF	1.69 (317/18757.4) (1.51, 1.89)	1.25 (235/18800) (1.10, 1.42)	0.47 (90/19148.9) (0.38, 0.58)	0.12 (23/19166.7) (0.08, 0.18)	3.17 (611/19274.5) (2.92, 3.43)
PROTECT AF	2.2 (20/929.4) (1.31, 3.32)	1.1 (10/932.8) (0.51, 1.97)	1.1 (10/945.6) (0.51, 1.94)	0.0	2.3 (22/948.9) (1.45, 3.51)
PREVAIL-only	1.00 (3/299) (0.208,2.941)	0.34 (1/298.1) (0.008, 1.869)	0.67 (2/300.1) (0.081, 2.407)	0.0	2.33 (7/300.2) (0.937,4.804)

*The 95% CI calculations are performed assuming Poisson distribution.

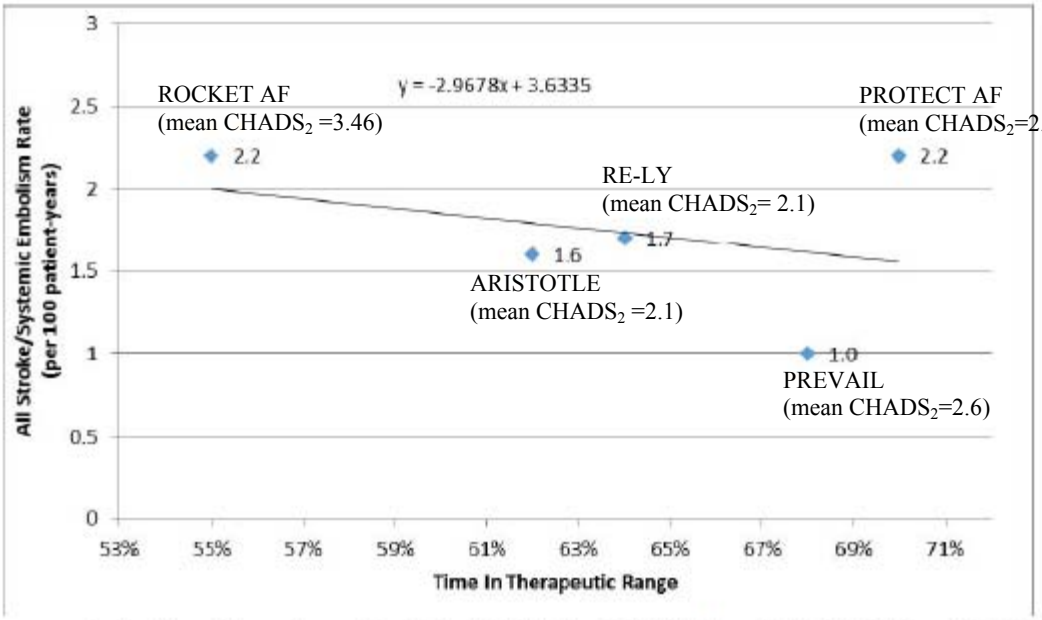
Table 27: Comparison table for the WATCHMAN subjects in PROTECT, PREVAIL, CAP, and CAP2

Event Rate per 100 pt-yrs, (Events/total pt-ys), (95% CI*)					
	All Stroke	**Ischemic Stroke**	**Hemorrhagic Stroke**	**Systemic Embolism**	**Cardiovascular Death**
PROTECT AF	1.5 (26/1788.2) (1.0, 2.2)	1.3 (24/1788.2) (0.86, 2.00)	0.2 (3/1844.3) (0.03, 0.48)	0.1 (2/1843.7) (0.01, 0.39)	1.0 (19/1843.2) (0.6, 1.6)
PREVAIL-only	2.65 (15/567) (1.48, 4.36)	2.3 (13/564.9) (1.23, 3.94)	0.35 (2/577.3) (0.04, 1.25)	0.17 (1/576.9) (0.004, 0.97)	1.38 (8/578.1) (0.60, 2.73)
CAP	1.3 (26/2024.8) (0.9, 1.9)	1.2 (24/2026) (0.76, 1.76)	0.10 (2/2069.1) (0.01, 0.35)	0.05 (1/2068) (0.001, 0.27)	1.3 (27/2070.3) (0.9, 1.9)
CAP2	2.7 (9/329.9) (1.25, 5.18)	2.7 (9/329.9) (1.25, 5.18)	0.0 (0/335) (0.00, 1.10)	0.6 (2/332.4) (0.07, 2.17)	0.0 (0/335) (0.0, 1.10)

*The 95% CI calculations are performed assuming Poisson distribution.

To explore the PREVAIL Control group outcomes compared with results from other randomized trials, additional analyses were performed by the sponsor and FDA. The time-in-therapeutic range (TTR) is the standard for reporting quality of INR control and warfarin dosing. It has been established that the more time warfarin therapy is maintained in the INR target therapeutic range, the better the subject outcome. Figure 8 below displays the reported TTR for contemporary randomized studies that used warfarin as their control group, graphed against the reported all stroke/systemic embolism event rate. The straight line is the linear regression trend line fit to these data points. This figure is consistent with expectations of therapy management for warfarin; studies with a higher TTR tend to have a lower rate of events. The TTR reported in the PREVAIL trial is near the upper end of the TTR reported among these contemporary randomized studies consistent with an expected lower event rate. Even though the actual event rate is below the trend line indicating an event rate lower than expected, it is still within the bounds of random variation (as seen in Table 26). Conversely, PROTECT AF reported the highest TTR among these studies, so the Control group event rate in PROTECT AF appears to be higher than expected.

Figure 8: All stroke and systemic embolism vs. time in therapeutic range (TTR) in Warfarin Control groups across studies



Randomized warfarin control groups: Rate of 2.2 and 55% TTR from ROCKET AF; Rate of 1.6 and 62% TTR from ARISTOTLE; Rate of 1.7 and 64% TTR from RE-LY; Rate of 2.2. and 70% TTR from PROTECT AF all stroke/systemic embolism ; Rate of 1.0 and 68% TTR from PREVAIL.

FDA Comment: Drawing conclusions from comparisons of event rates among different trials should be done cautiously as there may be differences in measured and unmeasured baseline covariates and trial design elements. The divergent results seen in the WATCHMAN randomized trials present challenges to assessing the benefit-risk profile of the device.

- The favorable outcome of the WATCHMAN group observed in PROTECT AF that supports device non-inferiority was driven by a significantly higher than expected hemorrhagic stroke rate in the warfarin group. In addition, there are approved NOACS,

which, in randomized trials, had a reduced rate of hemorrhagic stroke vs. warfarin, such that physicians can now consider alternatives to warfarin that effectively lower the risk of ischemic stroke but are associated with a lower risk of the most feared complication of anticoagulation.

- The disproportionate number of ischemic strokes observed in the WATCHMAN group in the updated PREVAIL dataset raises questions about device effectiveness, but the lower than expected ischemic stroke rate in the Control group is notable, even though it is within the bounds of random variation.

9 FDA CONSIDERATIONS AND CONCLUSIONS

Fundamentally, the PREVAIL and PROTECT AF trials were both designed to compare two treatment strategies:

1. WATCHMAN device implantation, 45 days of warfarin plus 81mg aspirin through 45 days post-implantation, followed by 325 mg aspirin plus 75 mg clopidogrel through 6 months post-implantation, followed by indefinite use of 325 mg aspirin; vs.

2. Chronic warfarin therapy.

The fundamental clinical question intended to be addressed in the WATCHMAN device studies is whether the data support stopping warfarin after successful implantation of the device. That is, does implantation of the WATCHMAN device provide comparable protection against thromboembolic events vs. warfarin in subjects with non-valvular atrial fibrillation, and does the device offer an advantage compared to warfarin with respect to major bleeding complications (particularly hemorrhagic stroke)?

When evaluating whether the totality of the data (including PREVAIL, PROTECT AF, and the CAP and CAP2 registries) provide a reasonable assurance of safety and effectiveness of the WATCHMAN device for the proposed indications, the following points should be considered:

1. Based on the updated June 2014 PREVAIL dataset, the WATCHMAN device no longer meets the second primary endpoint and still does not meet the first primary endpoint of the PREVAIL Bayesian analysis.

2. The new ischemic strokes in the updated PREVAIL dataset occurred more than 1 year post-WATCHMAN implantation, raising questions about long-term device effectiveness.

3. The results of PROTECT AF and PREVAIL appear to be diverging, which introduces challenges in the interpretation of results of the pre-specified Bayesian analysis.

4. PROTECT AF demonstrated a benefit of the WATCHMAN device driven by a reduction in hemorrhagic stroke rate; however, the Control group hemorrhagic stroke rate was substantially higher than observed in contemporary anticoagulation trials, and there are questions regarding the robustness of this potential benefit.

5. A reduction in long-term bleeding complications due to discontinuation of warfarin is a potential benefit of the WATCHMAN device. However, when accounting for bleeding associated with the WATCHMAN implantation procedure, there was no overall difference in the bleeding rates.

6. An imputed placebo analysis suggests that WATCHMAN is better than no treatment or ineffective therapy; however, this analysis is based on comparison of results from different patient populations in different studies, and randomized trials to support this hypothesis are lacking.

The data presented in this executive summary and the PMA characterize the safety and effectiveness of the WATCHMAN LAAC Therapy when used to treat patients with non-valvular atrial fibrillation who are eligible for warfarin therapy. The Advisory Panel will be asked to assess: (1) whether the totality of the data demonstrate a reasonable assurance of WATCHMAN device safety and effectiveness; and (2) the benefit-risk profile of the device.

Appendix A – Imputed Placebo Analysis

The sponsor and FDA performed analyses to compare the ischemic stroke rates in the PREVAIL, PROTECT AF, and CAP WATCHMAN groups to an imputed placebo group. Based on the average $CHADS_2$ score of patients in PROTECT AF, PREVAIL, and CAP, the sponsor estimated an expected control event rate assuming a linear relationship between event rates and $CHADS_2$ score data from two studies[15,16] that established and validated the $CHADS_2$ risk classification scheme. They also compared this imputed event rate to the observed event rate in each study using relative risk reduction (Table 28). The two-sided 95% confidence bounds for the observed WATCHMAN ischemic stroke rate are calculated based on the Poisson distribution. The relative risk reduction calculated based on this analysis ranged from 62% to 83%, with wide confidence intervals.

Table 28: Imputed Placebo versus Observed WATCHMAN Ischemic Stroke Rate

Study (Date of Dataset Lock)	**Average $CHADS_2$ Score WATCHMAN Patients**	**Imputed Untreated Control Event Rate**	**Observed WATCHMAN Ischemic Stroke Rate (95% CI)**	**Relative Risk Reduction**
PROTECT AF (3/3/2014)	2.2	5.6 to 5.7	1.3 (0.9, 2.0)	77% (64%, 84%)
CAP (3/7/2014)	2.5	6.4	1.1 (0.8, 1.7)	83% (73%, 88%)
PREVAIL only (4/18/2014)	2.6	6.6 to 6.7	2.5 (1.5, 4.3)	62% (35%, 77%)

Table 29 provides the results from published trials, including the 95% confidence interval (CI) for the event rates when available. The paper by Gage published in 2001[16] reported an overall ischemic stroke rate of 4.4/100pt-yrs and a 95% CI of 3.6-5.4 based on a dataset of untreated/aspirin patients with a mean $CHADS_2$ score of 2.2. In comparison, as shown in Table 29, the PROTECT AF WATCHMAN group ischemic stroke rate was 1.3/100 pt-yrs (95% CI: 0.8-2.0) and the PREVAIL WATCHMAN group ischemic stroke rate was 2.3/100 pt-yrs (95% CI: 1.2-4.0).

[15] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285(22):2864-70.

[16] Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BSP, Petersen P. Selecting Patients With Atrial Fibrillation for Anticoagulation: Stroke Risk Stratification in Patients Taking Aspirin. Circulation. 2004; 110: 2287-2292

Table 29. Rates of ischemic stroke from different published studies (FDA analyses)

Article	Short study description	Ischemic Stroke Rate (95% CI)
Gage 2001 (National Registry of AF – Medicare claims data)	- 1733 pts with chronic or recurrent non-rheumatic AF - 31% of all pts had aspirin - no warfarin prescribed - mean $CHADS_2$ 2.2	94/2121 = 4.4/100pt-yrs (3.6-5.4)
Gage 2004 (6 prospective rand. trials)	- 2580 pts with nonvalvular AF - all on aspirin 75-325 mg - mean $CHADS_2$ 1.7	207/4887 = 4.2/100pt-yrs (3.7-4.9)
Van Walraven, JAMA 2002 (6 rand. trials – pooled data meta-analysis)	- 2113 pts with nonvalvular AF - on aspirin 75-325mg	4.3/100pt-yrs
PROTECT AF Watchman group	- 463 pts with nonvalvular AF - mean $CHADS_2$ 2.2	24/1788.25= 1.3/100pt-yrs (0.8-2.0)
PREVAIL June 2014 data Watchman group	-269 pts. with nonvalvular AF Mean (SD) $CHADS_2$ 2.6 (1.0)	13/562.6= 2.3/100pt-yrs (1.2-4.0)

FDA Comment: The benefit of anticoagulation compared to placebo or antiplatelet therapy to reduce the incidence of stroke and systemic embolism in appropriate patients with non-valvular atrial fibrillation is well-established. The WATCHMAN randomized trials were designed to evaluate the safety and effectiveness of the WATCHMAN device in a warfarin-eligible population. In clinical use, it may be anticipated that the WATCHMAN device would be considered as an option for patients and physicians who seek an alternative to long-term warfarin. The disproportionate number of ischemic strokes observed in the WATCHMAN group in the updated PREVAIL dataset raises the question whether the WATCHMAN device offers a clinical benefit compared to no treatment or ineffective treatment (i.e., antiplatelet therapy) in patients with risk factors for stroke. The imputed placebo analysis is favorable for the WATCHMAN device, but it must be noted that there are no randomized studies comparing WATCHMAN to no therapy or antiplatelet therapy. Furthermore, conclusions drawn from statistical comparison of results across different trials are limited by known and unknown differences in patient populations and trial conduct.