

The Panel will need to integrate information from multiple datasets (PREVAIL, PROTECT AF, and CAP) in order to determine whether the totality of the data demonstrate a reasonable assurance of device safety and effectiveness. The questions below are designed to guide the panel.

Question 1: WATCHMAN Device Acute Procedural Outcomes

The acute safety of the WATCHMAN device was a major concern in the PROTECT AF trial dataset discussed at the previous panel meeting. There were 5 procedural ischemic strokes (3 due to air embolism), a 5.3% (24/449) rate of procedure-related serious pericardial effusions and cardiac perforations in randomized Device subjects, a 9.1% (41/449) rate of failed implant attempts, and an impression that the operator learning curve can be significant for new operators and sites. The sponsor subsequently worked on addressing these issues in the CAP registry and the PREVAIL trial. Procedural success was improved vs. PROTECT AF in both the CAP registry and PREVAIL trial, with procedural success rates of 94.3% and 95.1%, respectively. The rates of acute stroke and pericardial effusion were also lower in the CAP registry and PREVAIL, as shown in Table 1.

Table 1: Summary of Procedure Related Results (PREVAIL and CAP Registry)

Procedural Complication	PREVAIL Device Group	CAP Registry
Implant Success N Successful/N Implant Attempts (%)	252/265 (95.1)	534/566 (94.3)
Procedure Related Ischemic Stroke N Events/ N Implant Attempts (%)	1/265 (0.4)	0/566 (0.0)
Procedure Related Pericardial Effusion or Cardiac Perforation N Events/ N Implant Attempts (%)	5/265 (1.9)	8/566 (1.4)

Please comment on whether the new data presented in the CAP registry and PREVAIL trial address these concerns regarding acute WATCHMAN implantation procedural outcomes.

Question 2: Evaluation of the PREVAIL First Primary Endpoint

The WATCHMAN device did not meet the non-inferiority criterion for the first primary endpoint (18-month rate of stroke, systemic embolism, and cardiovascular or unexplained death), as shown in Table 2.

Table 2: PREVAIL First Primary Endpoint Results (ITT)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion
0.064	0.063	1.07 (0.57, 1.89)	95% CrI Upper Bound < 1.75

The individual components of the first primary endpoint composite are shown in Table 3.

Table 3: PREVAIL First Primary Endpoint Events by Type

Endpoint Event Type	Device Group			Control Group		
	N Events	% of Subjects	% of Endpoints	N Events	% of Subjects	% of Endpoints
Stroke-Ischemic	5	1.9	35.7	1	0.7	25.0
Stroke-Hemorrhagic	1	0.4	7.1	0	0.0	0.0
Systemic Embolism	1	0.4	7.1	0	0.0	0.0
Death (Cardiovascular or Unexplained)	7	2.6	50.0	3	2.2	75.0

When interpreting the PREVAIL trial outcomes, the following issues should be considered:

- Deaths accounted for at least 50% of all events, which were likely unrelated to the procedure, the WATCHMAN device, or oral anticoagulation therapy.
- The stroke (ischemic and hemorrhagic) rate in control subjects was lower than expected, with only one ischemic stroke and no hemorrhagic strokes in the control arm (Table 2).
- The non-inferiority rate ratio criterion of <1.75 was set lower than the criterion used in PROTECT AF (<2.0), but is higher than that used in typical drug trials of anticoagulants used to prevent stroke and systemic embolism in subjects with non-valvular atrial fibrillation.

Please comment on the clinical significance of these results.

Question 3: Evaluation of the PREVAIL Second Primary Endpoint

The WATCHMAN device is a locally targeted intervention that is intended to reduce the risk of ischemic stroke by preventing the embolization of thrombi formed in the left atrial appendage. The second primary endpoint in PREVAIL (18-month rate of ischemic stroke and systemic embolism, excluding events occurring within 7 days following randomization) was designed to support this mechanism of action beyond the peri-procedural period, and non-inferiority of this endpoint was met by meeting the pre-specified risk difference (Table 4).

Table 4: PREVAIL Second Primary Endpoint Results (ITT)

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CrI)	Rate Ratio Non-Inferiority Criterion	18-Month Rate Difference (95% CrI)	Rate Difference Non-Inferiority Criterion
0.0253	0.0200	1.6 (0.5, 4.2)	95% CrI Upper Bound <2.0	0.0053 (-0.0190, 0.0273)	95% CrI Upper Bound <0.0275

However, the rate of all ischemic strokes in both PROTECT AF and PREVAIL numerically favored the control arm (Table 5).

Table 5: Ischemic Stroke Rates in PROTECT AF and PREVAIL (ITT)

Study	Device Group		Control Group	
	N Events	N Events/ Total Pt-Yrs (Rate)	N Events	N Events/ Total Pt-Yrs (Rate)
PROTECT AF	24	24/1720.7 (1.4)	10	10/901.2 (1.1)
PREVAIL	5	5/257.1 (1.94)	1	1/140.1 (0.71)

In considering only ischemic stroke, please comment on the clinical significance of these results. Please discuss the effectiveness of the device in comparison to warfarin in terms of reducing the risk of ischemic stroke.

Question 4: Evaluation of Major Bleeding Events

A proposed benefit of the WATCHMAN device compared to warfarin is a reduction in long-term bleeding complications associated with the use of chronic anticoagulation therapy. As expected with most invasive procedures, bleeding events in the WATCHMAN group in PREVAIL were clustered in the peri-procedural period. However, beyond the post-procedural period, there did not appear to be significant evidence of reduced bleeding rates in WATCHMAN subjects vs. warfarin subjects (Table 6).

Table 6: PREVAIL Rates of Major Bleeding

Time Point	Device Group			Control Group		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	14	14	94.8 (91.3, 96.9)	0	0	100.0 (100.0, 100.0)
45-days	4	18	93.3 (89.5, 95.7)	0	0	100.0 (100.0, 100.0)
6-months	6	24	90.8 (86.5, 93.7)	3	3	97.7 (93.0, 99.3)
1-year	0	24	90.8 (86.5, 93.7)	4	7	93.4 (86.5, 96.9)
2-year	0	24	90.8 (86.5, 93.7)	0	7	N/A

Randomization Allocation (2 Device: 1 Control)

Please comment on the clinical significance of the major bleeding events.

Question 5: Evaluation of Long-Term Safety and Effectiveness

The sponsor provided important long-term follow-up data from the PROTECT AF trial for the composite effectiveness endpoint (rate of stroke, systemic embolism, and cardiovascular or unexplained death – Table 7 and Figure 1) and rate of ischemic stroke for the ITT (Table 8 and Figure 2) and Post-Procedure populations (Table 9 and Figure 3).

Table 7: PROTECT AF Primary Effectiveness Endpoint Results (ITT)

Analysis Cohort	Device		Control		Relative Risk (95% CrI)		Posterior Probabilities	
	Rate (95% CrI)	Rate (95% CrI)	Rate (95% CrI)	Rate (95% CrI)			Non-inferiority	Superiority
1500 pt-yrs	3.0	(2.1,4.3)	4.3	(2.6, 5.9)	0.71	(0.44, 1.30)	>0.999	0.846
2621 pt-yrs	2.3	(1.7, 3.2)	3.8	(2.5, 4.9)	0.60	(0.41, 1.05)	>0.999	0.960

Pt-yrs = patient-years CrI = credible interval

Rate = event rate per 100 patient-years (calculated as $100 \times N \text{ events} / \text{Total patient-years}$) Rel. risk = relative risk or rate ratio, calculated as Device rate over Control rate

Figure 1: Kaplan-Meier Curve: Freedom from Primary Effectiveness Event – 2621 pt-yrs (ITT)

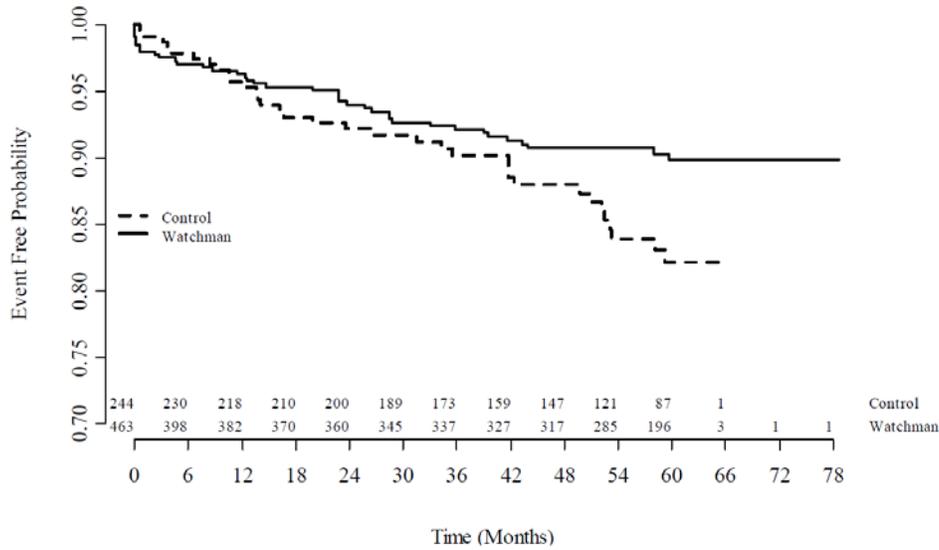


Figure 2: Kaplan-Meier Curve: Freedom from Ischemic Stroke – 2621 pt-yrs (ITT)

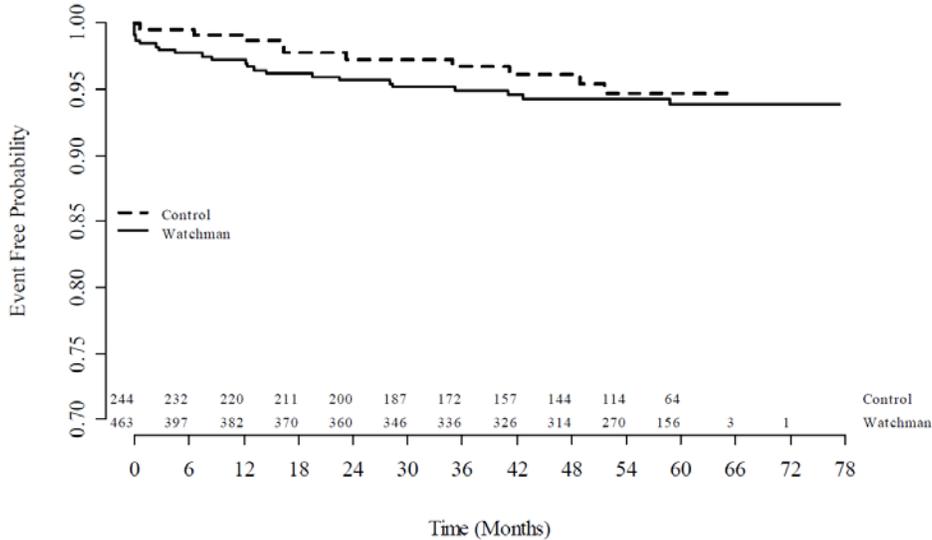
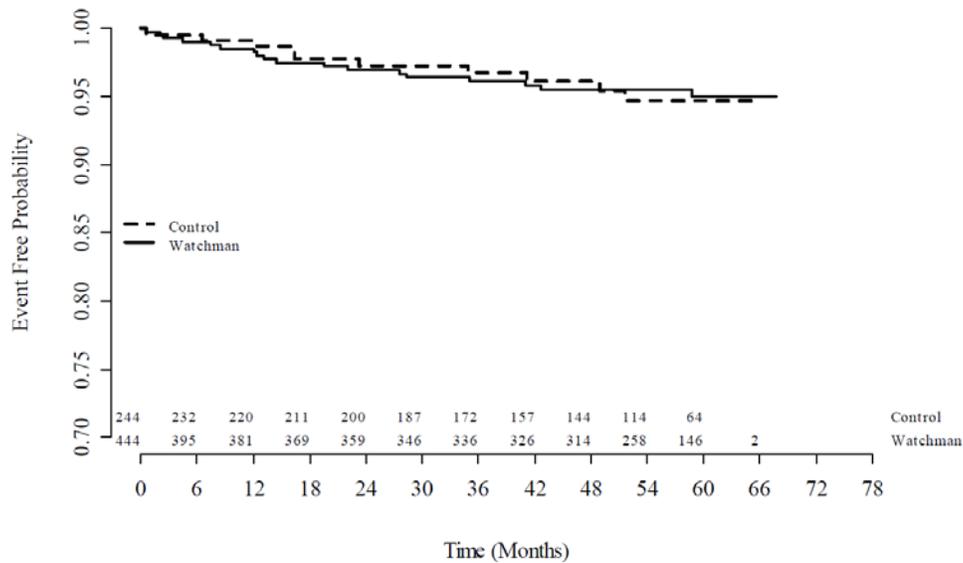


Table 8: Kaplan-Meier Estimates: Freedom from Ischemic Stroke – 2621 pt-yrs (ITT)

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	6	6	98.7 (97.1, 99.4)	0	0	100.0 (100.0, 100.0)
45-days	1	7	98.5 (96.8, 99.3)	1	1	99.6 (97.1, 99.9)
6-months	3	10	97.8 (95.9, 98.8)	0	1	99.6 (97.1, 99.9)
1-year	2	12	97.3 (95.2, 98.4)	1	2	99.2 (96.7, 99.8)
2-year	6	18	95.7 (93.3, 97.3)	4	6	97.3 (94.1, 98.8)
3-year	3	21	94.9 (92.3, 96.6)	1	7	96.7 (93.3, 98.4)
4-year	2	23	94.3 (91.5, 96.2)	1	8	96.1 (92.4, 98.1)
5-year	1	24	93.8 (90.9, 95.9)	2	10	94.7 (90.2, 97.2)

Figure 3: Kaplan-Meier Curve: Freedom from Ischemic Stroke 2621 pt-yrs (Post-Procedure)



**Table 9: Kaplan-Meier Estimates: Freedom from Ischemic Stroke
2621 pt-yrs (Post-Procedure)**

Time Point	Device			Control		
	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)	N Events	N Cumulative Events	Event Free Rate (%) (95% CI)
7-days	0	0	100.0 (100.0, 100.0)	0	0	100.0 (100.0, 100.0)
45-days	1	1	99.8 (98.4, 100.0)	1	1	99.6 (97.1, 99.9)
6-months	3	4	99.0 (97.5, 99.6)	0	1	99.6 (97.1, 99.9)
1-year	2	6	98.5 (96.8, 99.3)	1	2	99.2 (96.7, 99.8)
2-year	6	12	97.0 (94.7, 98.3)	4	6	97.3 (94.1, 98.8)
3-year	3	15	96.1 (93.6, 97.6)	1	7	96.7 (93.3, 98.4)
4-year	2	17	95.5 (92.9, 97.2)	1	8	96.1 (92.4, 98.1)
5-year	1	18	95.1 (92.2, 96.9)	2	10	94.7 (90.2, 97.2)

These data appear to show acceptable long-term effectiveness of the WATCHMAN device compared with the warfarin control group. Importantly, there does not seem to be a diminution of treatment effect over time. However, the following issues with the PROTECT AF trial raise questions about the interpretation and robustness of these long-term results:

- Inclusion of CHADS₂ score = 1 subjects who were eligible for aspirin therapy
- Inclusion of subjects taking clopidogrel
- A higher than expected hemorrhagic stroke rate in the control arm
- Problems with monitoring and maintenance of a therapeutic INR in control subjects
- A higher rate of dropout in the control group vs. the device group

Please comment on the clinical significance of these long-term safety and effectiveness results.

Question 6: Proposed Indications For Use

The sponsor has proposed the following indications for use:

“The WATCHMAN LAAC Therapy is intended to prevent embolism of thrombus from the left atrial appendage and thus reduce the risk of stroke, systemic embolism, and cardiovascular death in high risk patients with non-valvular atrial fibrillation who are eligible for warfarin therapy, but, for whom the risks posed by long term warfarin therapy outweigh the benefits.”

Please comment on this Indications For Use statement.

Question 7: Evaluation of the Totality of the Data from the WATCHMAN trials (Overall Benefit/Risk Assessment)

The sponsor has presented comprehensive data from two randomized controlled trials (PROTECT AF and PREVAIL) and an important continued access registry (CAP). What does the totality of the currently available data suggest about the benefit/risk profile of the WATCHMAN device? In answering this question, please comment on the following:

- a. Is the central role of thromboembolism from the left atrial appendage (LAA) in the pathogenesis of ischemic stroke in patients with nonvalvular atrial fibrillation, and effective the prevention of thromboembolism from the LAA by the WATCHMAN device supported by the WATCHMAN studies?
- b. Are acute procedural success and safety results acceptable?
- c. Do the long-term safety and effectiveness results from PROTECT AF and PREVAIL indicate that the WATCHMAN device is a clinically acceptable alternative to warfarin therapy?

Question 8: Labeling

The sponsor provided draft labeling in the panel pack.

Please discuss whether the proposed labeling is acceptable or whether modifications are recommended.

Question 9: Proposed Post Approval Study (PAS)

To address postmarket concerns, the sponsor has proposed to conduct a 5-year post-approval study (PAS) to evaluate the long-term safety and effectiveness of the WATCHMAN device intended for use in the prevention of thrombus embolization from the left atrial appendage in subjects with non-valvular atrial fibrillation who are eligible for warfarin therapy. Please discuss the following:

- a. The proposed PAS population will be comprised of actively enrolled subjects from the Continued Access to PROTECT AF (CAP) Registry, PREVAIL trial, Continued Access to PREVAIL (CAP2) Registry, and newly enrolled patients. It should be noted that the CAP registry permitted the enrollment of subjects with a CHADS₂ score =1 (without requiring other CHA₂DS₂ - VASc criteria that identify patient for whom anticoagulation is recommended). In CAP, there are 132 CHADS₂ score = 1 subjects (comprising 23.3% of the enrolled population), and inclusion of these low risk subjects could bias the PAS results in favor of the WATCHMAN device meeting its performance goals. Please discuss the appropriateness of including CHADS₂ score = 1 subjects from the CAP registry in the PAS.
- b. In the PROTECT AF and PREVAIL trials, clinical outcomes after implantation of the WATCHMAN device were compared warfarin therapy. There are also three novel anticoagulants that have been approved as alternatives to warfarin in patients with non-valvular AF. In the proposed PAS, the results for the primary endpoints will be

compared to performance goals derived from projected event rates observed in the PREVAIL trial Device group. Please discuss the appropriateness of the proposed single arm study design and performance goals.

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