

## **Appendix E: Entrance Criteria**

### ***PROTECT AF Study Inclusion Criteria***

A patient was enrolled in the study if all of the following inclusion criteria were met:

- The patient is 18 years of age or older
- The patient has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease)
- The patient is eligible for long-term warfarin therapy
- The patient is eligible to come off warfarin therapy if the LAA is sealed (i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice)
- The patient has a calculated CHADS<sub>2</sub> score of 1 or greater
- The patient or legal representative is able to understand and willing to provide written informed consent to participate in the trial
- The patient is able and willing to return for required follow-up visits and examinations

### ***PROTECT AF Exclusion Criteria***

A patient was excluded from the study if any of the following clinical exclusion criteria were met:

- The patient suffers from New York Heart Association Class IV Congestive Heart Failure
- The patient has had a recent MI (within 3 months)
- The patient has an atrial septal defect (ASD) and/or atrial septal repair or closure device
- The patient had a single occurrence of AF
- The patient has an ablation procedure planned within 30 days of potential WATCHMAN Device implant
- The patient has a planned cardioversion 30 days post implant of the WATCHMAN Device
- The patient has a resting heart rate > 110 bpm
- The patient had a transient case of AF (i.e., secondary to recent coronary artery bypass graft (CABG) (within 3 months), etc.)
- The patient has an implanted mechanical valve prosthesis
- The patient's left atrial appendage is obliterated
- The patient has undergone heart transplantation

- The patient has symptomatic carotid disease (i.e., carotid stenosis  $\geq 50\%$  associated with ipsilateral transient or visual transient ischemic attack (TIA) evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)
- The patient had a prior embolic stroke or TIA within the last 30 days
- The patient requires long-term warfarin therapy (refer to protocol for additional details)
- The patient is contraindicated for warfarin therapy
- The patient has thrombocytopenia ( $< 100,000$  platelets/mm<sup>3</sup>) or anemia with hemoglobin concentration of  $< 10$  g/dl
- The patient is contraindicated for aspirin
- The patient is actively enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug (post-market study participation is acceptable)
- The patient is pregnant or pregnancy is planned during the course of the investigation if patient is of child bearing potential
- The patient has an active infection of any kind
- The patient has a terminal illness with life expectancy less than two years
- The patient has a life expectancy of less than two years

### ***PROTECT AF Echo Exclusion Criteria***

A patient was excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via transthoracic (TTE) and TEE) were met:

- The patient has LVEF  $< 30\%$
- The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE within 2 days prior to implant
- The patient has a high risk patent foramen ovale (PFO) (refer to protocol for additional details):
- The patient has significant mitral valve stenosis (i.e., MV  $< 1.5$  cm<sup>2</sup>)
- The patient has an existing pericardial effusion of  $> 2 \pm 1$  mm
- The patient has complex atheroma with mobile plaque of the descending aorta and/or aortic arch
- The patient has a cardiac tumor

### ***PREVAIL Inclusion Criteria***

Patients were required to meet all of the following inclusion criteria:

1. The patient is 18 years of age or older
2. The patient has documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the patient has not been diagnosed with rheumatic mitral valvular heart disease)
3. The patient is eligible for long-term warfarin therapy
4. The patient is eligible to come off warfarin therapy if the LAA is sealed (i.e., the patient has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice)
5. The patient has a calculated CHADS<sub>2</sub> score of 2 or greater; Patients with a CHADS<sub>2</sub> score of 1 may be included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation patients requiring warfarin therapy) :
  - The patient is a female age 75 or older
  - The patient has a baseline LVEF  $\geq 30$  and  $< 35\%$
  - The patient is age 65-74 and has diabetes or coronary artery disease
  - The patient is age 65 or greater and has documented congestive heart failure
6. The patient or legal representative is able to understand and willing to provide written informed consent to participate in the study
7. The patient is able and willing to return for required follow-up visits and examinations

### ***PREVAIL Exclusion Criteria***

Patients were excluded from the study if they meet any of the following exclusion criteria:

1. The patient requires long-term warfarin therapy (i.e., even if the device is implanted, the patients would not be eligible to discontinue warfarin due to other medical conditions requiring chronic warfarin therapy). Additionally, a patient with any of the following is excluded:
  - Thrombosis occurring at a young age (<40 years old)
  - Idiopathic or recurrent venous thromboembolism
  - Thrombosis at an unusual site (i.e., cerebral veins, hepatic veins, renal veins, inferior vena cava, mesenteric veins)
  - Family history of venous thromboembolism or of inherited prothrombotic disorder
  - Recurrence or extension of thrombosis while adequately anticoagulated
2. The patient is contraindicated for warfarin therapy or cannot tolerate long-term warfarin therapy

3. The patient is contraindicated or allergic to aspirin
4. The patient is indicated for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment
5. The patient had or is planning to have any cardiac or non-cardiac interventional or surgical procedure within 30 days prior to or 60 days after the WATCHMAN device implant (e.g., cardioversion, ablation, cataract surgery)
6. The patient had a prior stroke or TIA within the 90 days prior to enrollment
7. The patient has had an MI within 90 days prior to enrollment
8. The patient has a history of atrial septal repair or has an ASD/PFO device
9. The patient has an implanted mechanical valve prosthesis
10. The patient suffers from New York Heart Association Class IV Congestive Heart Failure
11. The patient has symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if patient has a history of carotid stent or endarterectomy the patient is eligible if there is < 50% stenosis
12. The patient's AF is defined by a single occurrence of AF
13. The patient had a transient case of AF (i.e., secondary to CABG, interventional procedure, etc.)
14. The patient's left atrial appendage is obliterated
15. The patient has undergone heart transplantation
16. The patient has an active infection of any kind
17. The patient has a resting heart rate > 110 bpm
18. The patient has thrombocytopenia (defined as < 70,000 platelets/mm<sup>3</sup>) or anemia with hemoglobin concentration of < 10 g/dl (i.e., anemia as determined by the investigator which would require transfusion)
19. The patient is actively enrolled or plans to enroll in a concurrent clinical study in which the investigational drug or device is of cardiovascular/neurologic nature or may confound the results of the study (including studies for treatment of arrhythmias)
20. The patient participated in the PROTECT AF study or the CAP Registry
21. The patient is pregnant or pregnancy is planned during the course of the investigation
22. The patient has a life expectancy of less than two years
23. The patient is unable to complete follow-up visits for the duration of the study

### ***PREVAIL Echocardiographic Exclusion Criteria***

Patients were excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) were met:

1. The patient has LVEF < 30%
2. The patient has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
3. The patient has an existing pericardial effusion > 2mm
4. The patient has a high risk patent foramen ovale (PFO), defined as an atrial septal aneurysm (excursion > 15mm or length  $\geq$  15mm) or large shunt (early, within 3 beats and/or substantial passage of bubbles)
5. The patient has significant mitral valve stenosis (i.e., MV < 1.5 cm<sup>2</sup>)
6. The patient has complex atheroma with mobile plaque of the descending aorta and/or aortic arch
7. The patient has a cardiac tumor

### ***CAP Study Inclusion Criteria***

A subject was eligible to be enrolled in the study if all of the following inclusion criteria were met:

- The subject is 18 years of age or older
- The subject has paroxysmal (with appropriate documentation) persistent, or permanent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease)
- The subject is eligible for long-term warfarin therapy
- The subject is eligible to come off warfarin therapy if the LAA is sealed, i.e., the subject has no other conditions that would require long-term warfarin therapy suggested by current standard medical practice
- The subject has a calculated CHADS<sub>2</sub> score of 1 or greater
- The subject or legal representative is able to understand and willing to provide written informed consent to participate in the trial
- The subject is able and willing to return for required follow-up visits and examinations

### ***CAP Exclusion Criteria***

A subject was excluded from the study if any of the following clinical exclusion criteria were met:

- The subject suffers from New York Heart Association Class IV Congestive Heart Failure (defined as: a subject with severe physical limitations, experiencing symptoms even while at rest)
- The subject has had a recent myocardial infarction (MI) (within 3 months)
- The subject has an atrial septal defect (ASD) and/or atrial septal repair or closure device
- The subject had a single occurrence of AF
- The subject has an ablation procedure planned within 30 days of potential WATCHMAN device implant
- The subject has a planned cardioversion 30 days post implant of the WATCHMAN device.
- The subject has a resting heart rate >110 beats per minute
- The subject had a transient case of AF [i.e., secondary to recent coronary artery bypass graft (CABG) (within 3 months), etc.]
- The subject has an implanted mechanical valve prosthesis
- The subject's left atrial appendage is obliterated
- The subject has undergone heart transplantation
- The subject has symptomatic carotid disease (i.e., carotid stenosis  $\geq 50\%$  associated with ipsilateral transient or visual transient ischemic attack (TIA) evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)
- The subject had a prior embolic stroke or TIA within the last 30 days
- The subject requires long-term warfarin therapy:
  - Secondary to conditions such as prior arterial embolism or other indications such

- as pulmonary embolism or deep vein thrombosis within the previous 6 months
- The subject is in a hypercoagulable state; exclude the subject if per medical record documentation, the subject meets any of the following criteria:
  - Thrombosis occurring at a young age (i.e. less than 40 y/o)
  - Idiopathic or recurrent VTE (venous thromboembolism)
  - Thrombosis at an unusual site (cerebral veins, hepatic veins, renal veins, IVC, mesenteric veins)
  - Family history of VTE or of inherited prothrombotic disorder
  - Recurrence/extension of thrombosis while adequately anti-coagulated
- The subject is contraindicated for warfarin therapy due to at least one of the following:
  - Warfarin-induced skin necrosis
  - Bacterial endocarditis
  - Mycotic aneurysm
  - High risk of systemic hemorrhage or active, uncontrollable bleeding
  - Uncontrolled hypertension (Systolic Blood Pressure >180 mm Hg or Diastolic Pressure >100 mm Hg)
  - Cerebral amyloid angiopathy
  - Previous history of hemorrhagic, lacunar, or aneurysmal strokes; previous history of gastrointestinal, genitourinary bleeding or history of positive stool for occult blood such that long term warfarin therapy cannot be prescribed
  - Chronic alcoholism habituation
  - Dementia
  - Non-compliance with dosing or dose monitoring
  - Physician refused anticoagulation therapy
  - Predisposition to head trauma due to recurrent syncope, uncontrolled seizure disorder, repeated falls, unstable gait, occupational hazards
- The subject has thrombocytopenia (< 70,000 platelets/mm<sup>3</sup>) or anemia with hemoglobin concentration of < 10 g/dl
- The subject is contraindicated for aspirin
- The subject is actively enrolled in another IDE or IND investigation of a cardiovascular device or an investigational drug (post-market study participation is acceptable)
- The subject is pregnant or pregnancy is planned during the course of the investigation if subject is of child bearing potential
- The subject has an active infection of any kind
- The subject has a life expectancy less than two years

### ***CAP Echo Exclusion Criteria***

A subject was excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) were met:

- The subject has LVEF <30%
- The subject has intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echo cardiologist within 2 days prior to implant
- The subject has a high risk patent foramen ovale (PFO):

- o PFO with an atrial septal aneurysm (total excursion >15mm or length  $\geq$ 15 mm) or
  - o Large shunt (early, within 3 beats, substantial passage of bubbles)
- The subject has significant mitral valve stenosis (i.e., MV <1.5 cm<sup>2</sup>)
- The subject has an existing pericardial effusion of  $\geq$ 3 mm
- The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch
- The subject has a cardiac tumor

### ***CAP2 Study Inclusion Criteria***

A subject was enrolled in the study if all of the following inclusion criteria were met:

- The subject was 18 years of age or older
- The subject had documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease)
- The subject was eligible for long-term warfarin therapy
- The subject had a calculated CHADS<sub>2</sub> score of 2 or greater; Subjects with a CHADS<sub>2</sub> score of 1 were included if any of the following apply (according to the ACC/AHA/ESC 2006 Guidelines for the Management of Subjects with Atrial Fibrillation subjects requiring warfarin therapy) :
  - The subject was a female age 75 or older
  - The subject had a baseline Left Ventricular Ejection Fraction (LVEF)  $\geq$  30% and  $<$  35%
  - The subject was age 65-74 and has diabetes or coronary artery disease
  - The subject was age 65 or greater and has documented congestive heart failure
- The subject or legal representative was able to understand and willing to provide written informed consent to participate in the trial.
- The subject was able and willing to return for required follow-up visits and examinations

### ***CAP2 Exclusion Criteria***

Subjects were excluded from the study if they meet any of the following criteria:

1. The subject required long-term warfarin therapy (i.e., even if the device was implanted, the subjects would not be eligible to discontinue warfarin due to other medical conditions requiring chronic warfarin therapy). Additionally, a subject with any of the following was excluded:
  - Thrombosis occurred at a young age (<40 years old)
  - Idiopathic or recurrent venous thromboembolism
  - Thrombosis at an unusual site (i.e., cerebral veins, hepatic veins, renal veins, inferior vena cava, mesenteric veins)
  - Family history of venous thromboembolism or of inherited prothrombotic disorder
  - Recurrence or extension of thrombosis while adequately anticoagulated
2. The subject was contraindicated for warfarin therapy or could not tolerate long-term warfarin therapy
3. The subject was contraindicated or allergic to aspirin
4. The subject was indicated for antiplatelet therapy other than aspirin (for example, a subject indicated for clopidogrel, prasugrel, ticlopidine or ticagrelor due to DES was excluded from enrollment during the dosing regimen). A subject completing a course of antiplatelet therapy may have been enrolled after a 7 day washout period
5. The subject had any interventional or surgical procedure within 30 days prior to enrollment or was planning to have an interventional or surgical procedure in the time between the WATCHMAN device implant and 45-day TEE (e.g., cardioversion, ablation, cataract surgery, dental surgery)

6. The subject had a prior stroke or TIA within the 90 days prior to enrollment
7. The subject had an MI within 90 days prior to enrollment
8. The subject had a history of atrial septal repair or has an ASD/PFO device
9. The subject had an implanted mechanical valve prosthesis
10. The subject suffers from New York Heart Association Class IV Congestive Heart Failure at the time of enrollment
11. The subject had symptomatic carotid disease (defined as >50% stenosis with symptoms of ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke); if subject had a history of carotid stent or endarterectomy the subject was eligible if there is < 50% stenosis
12. The subject's AF was defined by a single occurrence of AF
13. The subject had a transient case of AF (i.e., secondary to CABG, interventional procedure, etc.)
14. The subject's left atrial appendage was obliterated
15. The subject had undergone heart transplantation
16. The subject was currently treated with antibiotics for an active infection
17. The subject had a resting heart rate > 110 bpm
18. The subject had thrombocytopenia (defined as < 70,000 platelets/mm<sup>3</sup>) or anemia with hemoglobin concentration of < 10 g/dl (i.e., anemia as determined by the investigator which would require transfusion)
19. The subject was actively enrolled in a concurrent clinical study of an investigational drug or investigational device (study specifics were reviewed with the sponsor prior to enrollment to confirm a concurrent study did not interfere with the outcomes of this study)
20. The subject participated in any of the following studies: PROTECT AF, CAP Registry, or PREVAIL. If the subject received a subject ID number for a prior WATCHMAN study, the subject could not be enrolled. PROTECT AF control subjects was considered for participation if they had completed 5 year follow up
21. The subject was pregnant or pregnancy is planned during the course of the investigation
22. The subject had a life expectancy of less than two years
23. The subject was unable to complete follow-up visits for the duration of the study

### ***CAP2 Echo Exclusion Criteria***

A subject was excluded from the study if any of the following echocardiographic exclusion criteria (as assessed via TTE and TEE) were met:

1. The subject had LVEF < 30%
2. The subject had intracardiac thrombus or dense spontaneous echo contrast as visualized by TEE and determined by the echocardiographer within 2 days prior to implant
3. The subject had an existing pericardial effusion > 2mm
4. The subject had a high risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length  $\geq$  15mm
5. The subject had a high risk PFO with a large shunt defined as early, within 3 beats or substantial passage of bubbles
6. The subject had significant mitral valve stenosis (i.e., MV < 1.5 cm<sup>2</sup>)

7. The subject had complex atheroma with mobile plaque of the descending aorta or aortic arch
8. The subject had a cardiac tumor