Statistical Analysis Plan (SAP)

WATCHMAN For Patients With Atrial Fibrillation Undergoing **T**ranscatheter **A**ortic **V**alve **R**eplacement

(WATCH-TAVR)

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Version 1.0

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LIST OF ABBREVIATIONS

AF/AFib	Atrial fibrillation
AS	Aortic stenosis
KCCQ-12	Kansas City Cardiomyopathy Questionnaire
INR	International normalized ratio
ITT	Intention-to-Treat
LAAC	Left Atrial Appendage Closure
LVEF	Left Ventricular Ejection Fraction
MMRM	Mixed model for repeated measures
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
OAC	Oral anticoagulation
QoL	Quality of life
TAVR	Transcatheter Aortic Valve Replacement
TIA	transient ischemic attack
SD	Standard deviation

1 INTRODUCTION

1.1Preface

Atrial fibrillation (AF) is a common baseline comorbidity and the commonest arrhythmia in patients with aortic stenosis (AS) undergoing Transcatheter Aortic Valve Replacement (TAVR). The TAVR population is at increased long-term bleeding risk, with cognitive impairment, high risk of falls, history of spontaneous bleeding, etc. Standard medical therapy for emboli prevention in AF, long term oral anticoagulation (OAC), carries risk of hemorrhagic stroke, as well as major bleeding complications [1]. The WATCHMAN Left Atrial Appendage Closure (LAAC) System is the only device that has been approved by the FDA for preventing thrombo-embolic events in patients with non-valvular atrial fibrillation (AF) [2]. The WATCHMAN device has shown improved safety compared to OAC, with reduced event rates for hemorrhagic stroke and major bleeding in patients receiving the implant [3, 4]. However given the previous WATCHMAN device trials excluding patients with valvular heart disease, data on safety and efficacy of the device in TAVR patients with AF is lacking [5].

1.2 Scope of the analyses

These analyses will investigate the safety and effectiveness of the left atrial appendage occlusion with WATCHMAN Device in prevention of stroke and bleeding in AF patients undergoing TAVR. We will evaluate this by the primary composite endpoint (all-cause mortality, stroke and life-threatening/major bleeding events) for both TAVR and WATCHMAN.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1Study Objectives

We aim to demonstrate the non-inferiority of TAVR plus WATCHMAN group in terms of the primary composite endpoint, compared to TAVR alone group.

2.2Endpoints

2.2.1 Primary endpoint

The primary endpoint is the first occurrence of all-cause mortality, stroke or major/life-threatening bleeding event following randomization.

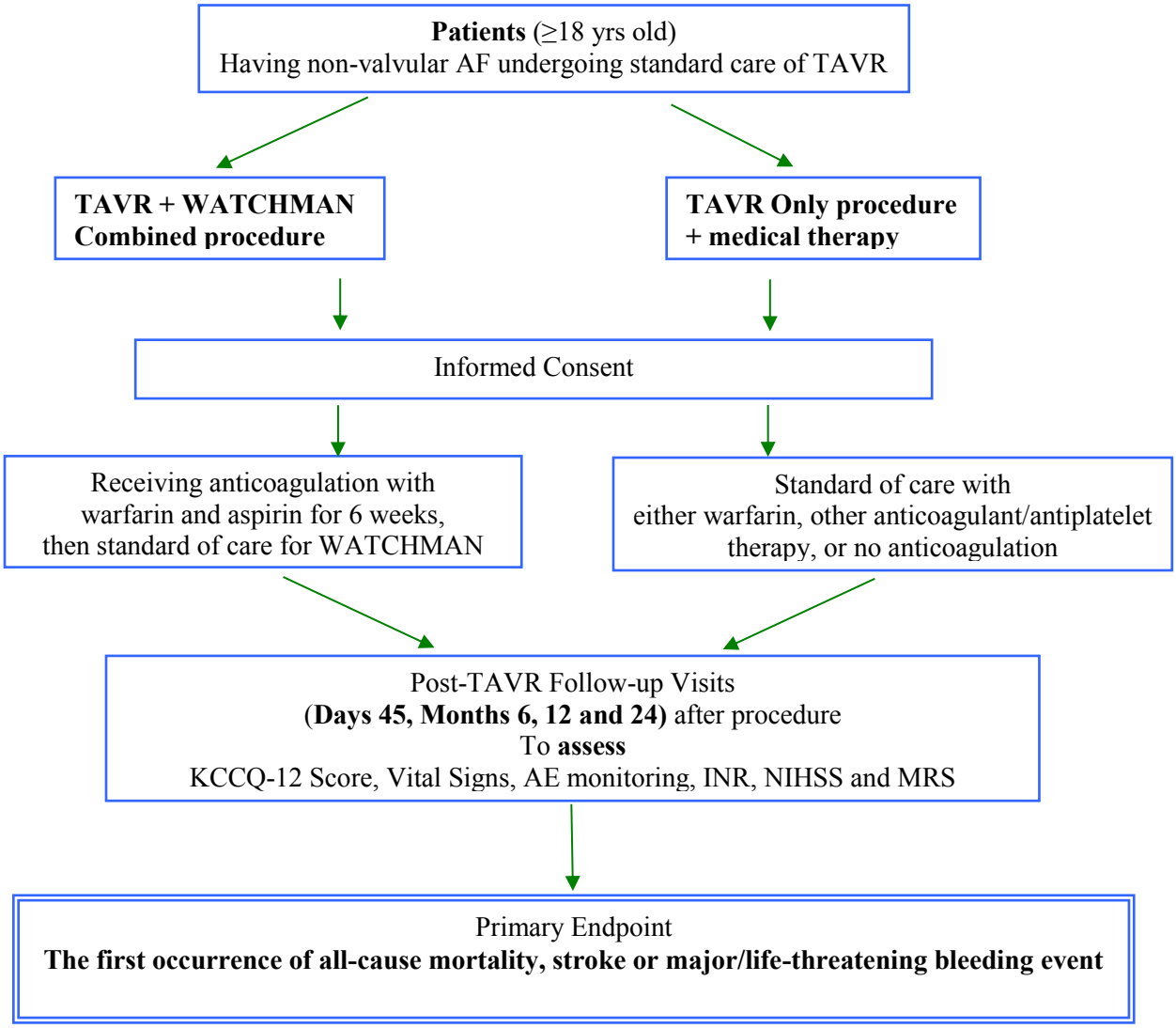
2.2.2 Secondary endpoints

1. Time from randomization to each component of the primary endpoint: all-cause mortality, any stroke and any occurrence of major or life-threatening bleeding (as per VARC2 definition of bleeding).
2. Time to death from cardiovascular causes
3. Time to ischemic stroke
4. Time to hemorrhagic stroke
5. Arterial or venous thrombosis or embolism
6. Rehospitalization related to WATCHMAN procedure or WATCHMAN device.

3 STUDY METHODS

3.1General Study Design and Plan

WATCH-TAVR is a prospective, multicenter, randomized event-driven controlled trial. Only centers with approval for commercial WATCHMAN implantation will be included in this trial. Subjects will be enrolled at approximately 33 centers in the United States. There will be approximately 350 subjects enrolled, with 175 patients being randomized to TAVR + medical therapy and 175 patients randomized to simultaneous TAVR+WATCHMAN to accumulate the 191 primary events needed. Patients with non-valvular AF undergoing standard of care TAVR will be enrolled in the trial. Patients randomized to receive the WATCHMAN device will receive anticoagulation with warfarin and aspirin for 6 weeks after the procedure. After 6 weeks, the plan of care will follow WATCHMAN labeling. Patients randomized to the TAVR + medical therapy arm will be treated in accordance with standard of care with either warfarin, other anticoagulant/antiplatelet therapy, or no anticoagulation at the discretion of the treating physician. All patients will continue to receive routine post-TAVR follow-up and care. Patients will be monitored for primary and secondary endpoints as outlined. Baseline information and laboratory data will be collected as described in the protocol.



3.2Inclusion-Exclusion Criteria and General Study Population

3.2.1 Inclusion Criteria

Patients who fulfill the following criteria will be included: Determination for participation in the study is based upon standard of care practice for assessment of TAVR & WATCHMAN eligibility [6].

1. Men and Women ≥ 18 years of age
2. The patient meets criteria for and is eligible to undergo TAVR procedure
3. The patient has documented paroxysmal, persistent, or permanent atrial fibrillation
4. The patient meets the WATCHMAN labeling guidelines and is eligible to undergo the WATCHMAN implantation procedure
5. The patient is eligible for short term warfarin therapy
6. The patient or legal representative is able to understand and willing to provide written informed consent to participate in the trial
7. The patient is able and willing to return for required follow-up visits and examinations

3.2.2 Exclusion Criteria

Any patient who fulfills any of these criteria shall be excluded [6]:

1. The patient had a stroke or TIA within the last 6 months prior to enrollment
2. Contraindication for short term anticoagulation
3. Moderate or severe MS with mean gradient across MV >10 mm Hg or MVA < 1.2cm^2.
4. The patient has symptomatic carotid disease (i.e., carotid stenosis ≥ 50% associated with ipsilateral transient or visual TIA evidenced by amaurosis fugax, ipsilateral hemispheric TIAs or ipsilateral stroke within 6 months)
5. Prior occlusion of LAA
6. The patient has an implanted mechanical mitral valve
7. The patient requires long-term warfarin therapy due to:
    a. Secondary to conditions such as prior arterial embolism or other indications such as pulmonary embolism or deep vein thrombosis within the previous 6 months.
    b. The patient is in a hypercoaguable state; exclude the patient if per medical record documentation, the patient meets any of the following criteria:
        - Thrombosis occurring at a young age (i.e. less than 40 y/o)
        - Idiopathic or recurrent VTE (venous thrombo-embolism)
        - 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 anticoagulated.
8. The patient is actively enrolled in another trial of a cardiovascular device or an investigational drug (post-market study participation and registries are acceptable)
9. The patient is pregnant or pregnancy is planned during the course of the investigation if patient is of child bearing potential.
10. Any clinically significant medical condition or presence of any laboratory abnormality prior to randomization that is considered by the investigator to be clinically important and could interfere with the conduct of the study or not meeting procedure guidelines for TAVR or Watchman.
11. The patient has a life expectancy of less than two years.

3.2.3 General Study Population

350 patients having non-valvular AF undergoing standard care of TAVR

3.3Study Assessments

All study assessments for both TAVR plus WATCHMAN combined arm and TAVR only arm are summarized in these two tables shown below.

Study Assessment		Visit after **TAVR plus WATCHMAN procedure**			
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**[1]
	Baseline	45 days (± 15 days)	6 Months (± 1 month)	12 Months (± 1 month)	24 Months (± 1 month)
Informed Consent	+				
Inclusion/Exclusion Criteria	+				
Randomization	+				
WATCHMAN Procedure	+				
TEE[2]	+ (during WATCHMAN procedure)	+			
KCCQ-12 Score	+	+	+	+	+
Vital Signs	+	+	+	+	+
AE Monitoring	+	+	+	+	+
INR	+	+	+[3]	+[3]	+[3]
Blood Work	+[4]				
NIH Stroke Scale (NIHSS)	+	+	+	+	+
Modified Rankin Scale (MRS)	+	+	+	+	+
Brain Image (CT or MRI)[5]	As Required				
Neuro Assessment[6]	As Required				

1. May be visit or phone follow up.
2. TEE during the WATCHMAN procedure and 45 days (+/-15 days) after the WATCHMAN Procedure. Patients randomized to WATCHMAN who have intracardiac thrombus visualized are contraindicated from receiving the device per labeling guidelines, but Will remain in the trial as intent to treat and should be followed for all study visits.
3. If patient continues to be on warfarin.
4. Tests include serum creatinine, platelet count and hemoglobin level. To be obtained within 7 days of randomization/WATCHMAN Procedure.
5. Required following a Stroke or TIA event including neurological assessment by a Neurologist.
6. Neurological assessment by neurologist if a patient experiences a stroke or TIA throughout the duration of the study.

Study Assessment		Visit after **TAVR ALONE procedure**			
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**[1]
	Baseline	45 days (± 15 days)	6 Months (± 1 month)	12 Months (± 1 month)	24 Months (± 1 month)
Informed Consent	+				
Inclusion/Exclusion Criteria	+				
Randomization	+				
KCCQ-12 Score	+	+	+	+	+
Vital Signs	+	+	+	+	+
AE Monitoring	+	+	+	+	+
INR	+	+	+	+	+[2]
Blood Work	+[3]				
NIH Stroke Scale (NIHSS)	+	+	+	+	+
Modified Rankin Scale (MRS)	+	+	+	+	+
Brain Image (CT or MRI)[4]	As Required				
Neuro Assessment[5]	As Required				

1. May be visit or phone follow up
2. If patient continues to be on warfarin
3. Tests include serum creatinine, platelet count and hemoglobin level. To be obtained within 7 days of randomization.
4. Required following a Stroke or TIA event including neurological assessment by a Neurologist.
5. Neurological assessment by neurologist if a patient experiences a stroke or TIA throughout the duration of the study.

4 SAMPLE SIZE

This randomized control trial will aim to prospectively enroll 350 patients having non-valvular AF undergoing standard care of TAVR. The control group consists of patients undergoing TAVR who are on standard medical practice, with oral anticoagulation at the discretion of the treating physician. The treatment group will have the WATCHMAN implantation procedure performed simultaneously with TAVR. The primary endpoint is a composite of all-cause mortality, stroke, life-threatening or major bleeding. The objective of the study is to demonstrate non-inferiority of the TAVR plus WATCHMAN device compared to the TAVR only group.

The following assumptions were used to determine the sample size needed to assess the non-inferiority hypothesis for the composite primary endpoint of all-cause mortality, stroke or major or life-threatening bleeding:

- One-sided α =0.025
- Primary event rate in the control population (TAVR only) of 35% at one year
- Non-inferiority margin of 1.5
- Underlying hazard ratio of active to control is 1.0
- Power at least 80%
- Lost to follow-up rate 10%

Assuming level of significance (α) to be 0.05 (or α =0.025 one-sided) and aiming for a study power (1-β) of 80%, we estimate 191 primary events will be needed to rule out an upper limit of the one-sided 97.5%

confidence interval of 1.5. Assuming an enrollment duration of 18 months, follow-up period of 24 months, and 10% drop out rate per annum, the minimum total sample size required is 350 (175per group).

5 GENERAL ANALYSIS CONSIDERATIONS

5.1Timing of Analyses

The final analysis will be performed when 191 primary events are observed for the primary analysis, or if the study is stopped for administrative reasons.

5.2 Analysis Populations

Intention-to-Treat Population (ITT):
The primary analysis will be based on the ITT population. All randomized subjects will be analyzed according to their original randomization assignment (WATCHMAN+TAVR or TAVR) regardless of treatment received. The ITT analysis will be censored at 2 years (730 days) after randomization.

Per-protocol population (PP):
The per-protocol population is defined as patients in the WATCHMAN groups who received both the WATCHMAN and the prosthetic valve. In the TAVR only group, it is defined as patients who had the prosthetic valve placed. The PP analysis will be censored at 2 years (730 days) after randomization.

5.3 Covariates

Treatment will be the only covariate in the Cox proportional-hazards regression model.

5.4 Data Handling

5.4.1 Missing Data

Missing data will not be imputed for analysis purposes.

5.4.2 Durations

- Time to Event (e.g. time to primary endpoint) will be calculated as (event date/time – randomization date/time). Patients not having an event, or lost to follow-up will be censored at the minimum of the time of their last documented follow-up date, death date, or 2 years (730 days).

- Other durations of time will be calculated similarly as (date/time of interest – reference date/time +1)

5.4.3 Change from Baseline

Change from baseline to post-baseline visits will be calculated as the absolute change: post-baseline value – baseline value.

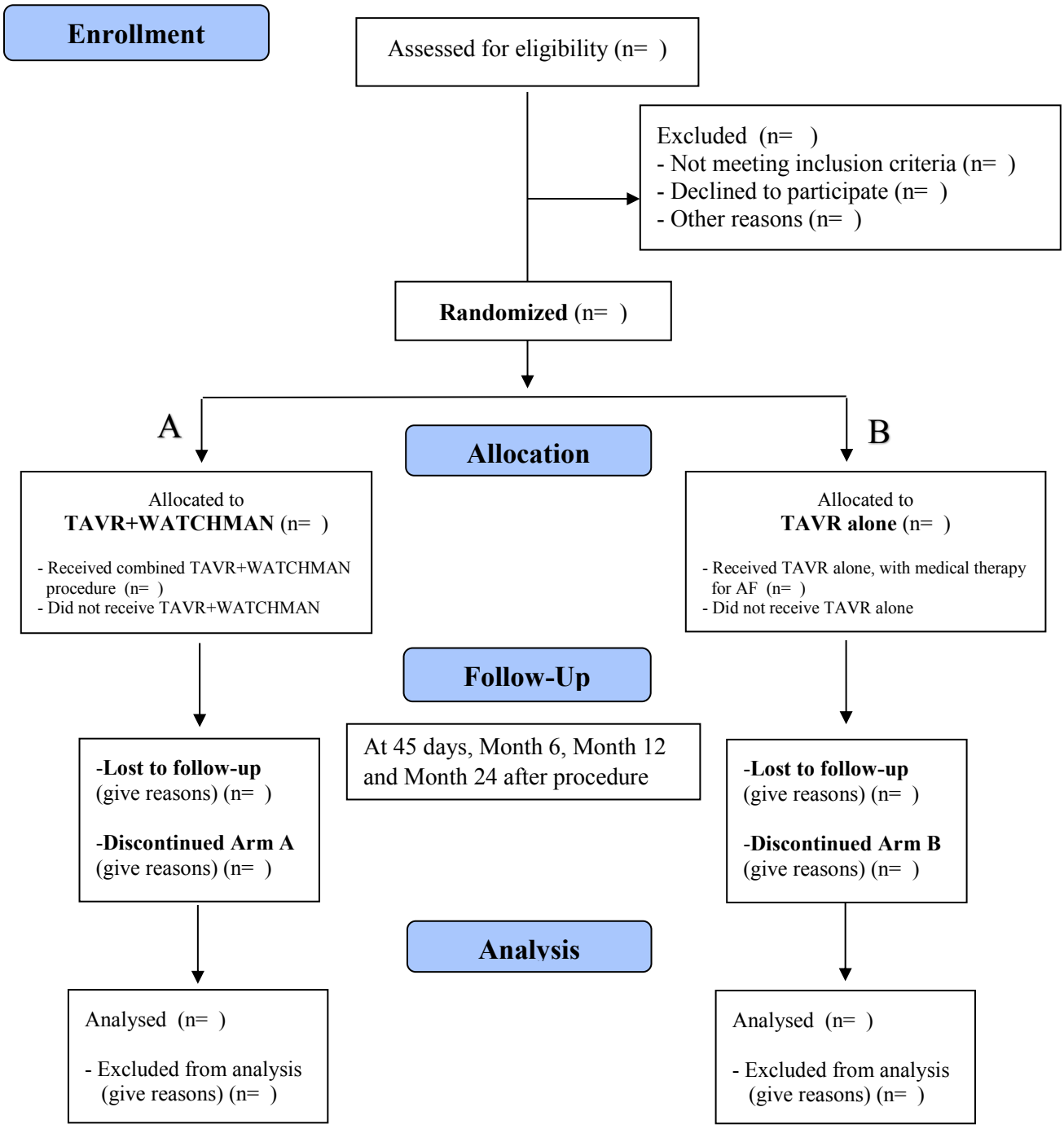
5.5 Interim Analyses

No interim statistical analysis will be performed.

6 SUMMARY OF STUDY DATA

6.1 Subject Disposition

A consort flow diagram will be provided as listed below. The summary statistics will be produced in accordance with section 5.



6.2 Demographic and Baseline Variables

Descriptive statistics will be generated for all baseline patient characteristics. Continuous variables will be summarized with reporting of mean, standard deviation (SD), median, interquartile range (Q1, Q3) and range (minimum and maximum). General linear models will be used to compare continuous variables across treatment groups. Categorical variables will be summarized using counts and percentage of subjects and compared using the standard Chi-square statistic or Fisher's exact test, as appropriate.

6.3 Concurrent Illnesses and Medical Conditions

The summary statistics will be produced in accordance with section 5.

7 ANALYSES

7.1 Primary Analysis

The ITT analysis will include all positively adjudicated post-randomization primary endpoints within the ITT analysis set through 24 months (730 days) after randomization.

The study is designed to demonstrate the non-inferiority of the WATCHMAN device compared to the control group, with regards to the primary endpoint (composite of all-cause mortality, stroke (ischemic and hemorrhagic), or bleeding (major and/or life-threatening)). Non-inferiority will be assessed using the 1-sided 97.5% confidence interval around the hazard ratio (WATCHMAN-TAVR: TAVR only). Non-inferiority will be demonstrated if the 1-sided 97.5% upper confidence limit for the difference in proportions is less than 1.5. If the non-inferiority objective is met, additional analyses to assess superiority of the WATCHMAN group to the control group will be performed. The composite primary endpoint will also be summarized as events per 100 patient-years of follow-up.

7.2 Secondary Analyses

The Secondary endpoints will include the following:

- Time from randomization to each component of the primary endpoint:
  - All-cause mortality
  - Any stroke (ischemic and hemorrhagic)
  - Any occurrence of major or life-threatening bleeding (as per VARC2 definition of bleeding)

- Time to death from cardiovascular causes
- Time to ischemic stroke
- Time to hemorrhagic stroke
- Arterial or venous thrombosis or embolism
- Rehospitalization related to WATCHMAN procedure or WATCHMAN device.

Analysis of time-to-event endpoints for the components will be analyzed similarly to that of the primary endpoint, except there will be no testing of the non-inferiority hypothesis. Point estimates and 95% confidence intervals will be derived from a Cox proportional model with treatment group as a factor. Descriptive frequencies of the endpoints and Kaplan-Meier curves will be presented. P-values may be

provided for descriptive purposes, but should not be considered informative. The frequency of procedure related complications, device/implant failure or systemic embolism will be summarized with descriptive statistics.

KCCQ-12 score quality of life (QoL) subdomains at baseline and follow-up visits will be summarized with descriptive statistics. Change from baseline in KCCQ-12 will be analyzed using the mixed model for repeated measures (MMRM). The model will include treatment group, baseline value, visit, visit and treatment interaction. Subject will be treated as the random effect, and variance covariance component will be compound symmetry.

7.3 Sub-group Analyses

The primary endpoint will be analyzed for each treatment comparison using time-to-event methodology as described above within the following pre-specified study subgroups:

1. Females
2. Males
3. Age <75 years
4. Age ≥75 years
5. Subjects without previously diagnosed diabetes at baseline.
6. Subjects with previously diagnosed diabetes at baseline.
7. Subjects without previously diagnosed TIA/Ischemic Stroke at baseline.
8. Subjects with previously diagnosed TIA/Ischemic Stroke at baseline.
9. Primary Diagnosis of Paroxysmal Atrial fibrillation (AFib) at baseline.
10. Primary Diagnosis of Persistent AFib at baseline.
11. Primary Diagnosis of Permanent AFib at baseline.
12. Primary Diagnosis of Unknown AFib at baseline.

7.4 Sensitivity Analyses

A sensitivity analysis for the primary endpoint in the per-protocol population will be performed.

8 REFERENCES

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