Statistical Analysis Plan

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT

WATCHMAN FLX™ Pro CT

S2517

CLINICAL INVESTIGATION PLAN

National Clinical Trial (NCT) Identifier Number: NCT05567172

Revision History

Revision Number	Protocol Version	Date
A	92929614 Rev/Ver C	27-Mar-2023

2. Protocol Synopsis

A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography: WATCHMAN FLX™ Pro CT	
Study Objective(s)	The primary objective of this study is to measure device tissue coverage post-implantation of the WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device (WATCHMAN FLX Pro) using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE) and assess its relationship, if any, to clinical events.
Planned Indication(s) for Use	As per the clinical Instructions for Use (IFU), WATCHMAN FLX Pro is intended to prevent thrombus embolization from the left atrial appendage and reduce the risk of life-threatening bleeding events in patients with non-valvular atrial fibrillation who are eligible for anticoagulation therapy or who have a contraindication to anticoagulation therapy.
Investigational Devices and Sizes	Investigational devices include the WATCHMAN FLX™ Pro Left Atrial Appendage Closure Device sizes 20mm, 24mm, 27mm, 31mm, 35mm and 40mm **Note 1:** The WATCHMAN FLX Pro LAAC Device comes preloaded on the WATCHMAN FLX Pro Delivery Catheter. The preloaded delivery system is used in conjunction with any commercially available WATCHMAN® Access System (access sheath and dilator).
Study Design	WATCHMAN FLX™ Pro CT is a prospective, single-arm, single-center, premarket investigation to assess device tissue coverage in subjects with non-valvular atrial fibrillation (AF) who receive the WATCHMAN FLX Pro device to reduce the risk of stroke. Serial advanced imaging modalities such as CT and TEE will be used. A core laboratory will independently assess select results. A subject is considered enrolled in the study when the subject or the subject's legally authorized representative signs an Informed Consent Form (ICF) approved by the Independent Ethics Committee (IEC). Up to 25 subjects in whom placement of a WATCHMAN FLX Pro device is attempted will be enrolled. A baseline assessment including TEE and/or CT imaging with optional cardiac magnetic resonance imaging (MRI) will be done within 14 days prior to the implant procedure following core

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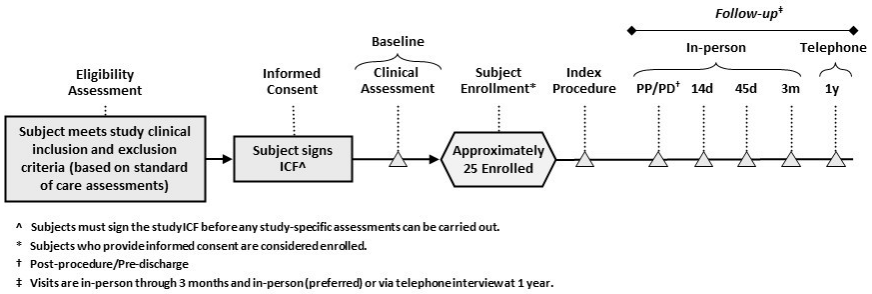
	laboratory guidelines. Follow-up clinical assessment and imaging will occur at 14 days, 45 days, and 3 months post implant procedure; only clinical assessment will be required at 12 months (unless an in-person assessment is required based on other data). Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro LAAC device will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. The study design is summarized below.  **WATCHMAN FLX Pro CT Study Design Overview** Eligibility is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria must be done after the ICF is signed. Abbreviation: ICF=Informed Consent Form
Planned Number of Subjects	Up to 25 subjects in whom placement of a WATCHMAN FLX Pro device is attempted will be enrolled.
Planned Number of Centers / Countries	There will be 1 investigational center in western Europe.
Primary Endpoint	Device surface morphology (inclusive of tissue coverage) post implant procedure as assessed over time using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE) with data evaluated by an independent core laboratory.

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Additional Endpoints	Additional measurements will be collected peri- and post-procedure, predischarge, and at 14 days, 45 days, 3 months, and 12 months (if needed) after the implant procedure, unless otherwise specified below. • Safety endpoints (adjudicated by an independent Clinical Events Committee [CEC]): o All-cause mortality (cardiovascular/unknown and non-cardiovascular) o Stroke (disabling and non-disabling; ischemic and hemorrhagic; see **Note 2**) o Systemic embolism o Bleeding: International Society on Thrombosis and Haemostasis (ISTH) major and non-major clinically significant[a] ▪ Procedural bleeding (≤7 days post-procedure) ▪ Non-procedural bleeding (>7 days post-procedure) o Pericardial effusion/tamponade requiring pericardiocentesis or surgery **Note 2:** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack [TIA]), Modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) should be performed after the event. It is recommended that the subject be contacted regarding mRS assessment at 90±14 days following any suspected stroke; the simplified mRS questionnaire[b] may be used for this follow-up assessment. It is also recommended that imaging be performed after the event to screen for device related thrombus. If performed, imaging results should be sent to the core laboratory. • Device Success: defined as implantation of a WATCHMAN FLX Pro device without in-hospital mortality • Assessments by serial imaging modalities (CT and TEE; cardiac MRI optional) at 14 days, 45 days, and 3 months; data will be evaluated by an independent core lab o Device seal post implant procedure (see **Note 3** and **Note 4**) o Device-related thrombus (including hypoattenuated thickening [HAT] per CT analysis)

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	Note 3: Results are classified as no leak, leak >0 and ≤5mm, or leak >5mm. **Note 4:** TEE is required at 12 months if the 3-month TEE assessment suggests a leak > 5mm or the 3-month CT assessment suggests a leak > 3mm; results must be sent to the core laboratory. • 4D cardiac MRI flow analysis (if available) of the left atrium (LA) and LAA before and serially after device implant at 14 days, 45 days, and 3 months; data will be evaluated by an independent core lab • Changes compared to baseline in measures of biochemical markers including coagulation, platelet and endothelial activation and inflammation at 14 days, 45 days, and 3 months post implant procedure; correlations with morphological findings from imaging assessment of the device surface will be examined a: Schulman S and Kearon C. *J Thromb Haemost* 2005;3:692-694 Kaatz S, et al. *J Thromb Haemost* 2015;13:2119-26 b: Bruno A, et al. *Stroke* 2011;42:2276-2279
Follow-up Schedule	Follow-up for all subjects will occur post-implant on the procedure day, at predischarge, and at 14 days, 45 days, 3 months, and 12 months post implant procedure. Follow-up will include clinical assessments at all time points and imaging assessments at 14 days, 45 days, and 3 months. Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device in the correct position will be followed for safety through 12 months after the initial attempted implant procedure by telephone or review of clinical files but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. The study will be considered complete after all available subjects have finished the 12-month follow-up visit.
Study Duration	Subjects will be followed for 12 months after the implant procedure. Enrollment is expected to take minimally 5 months; therefore, the total study duration from first subject enrolled to last subject follow-up is estimated to be at least 17 months.

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Inclusion Criteria	Inclusion criteria are listed below. IC1. Subject is of legal age to participate in the study per the laws of their respective geography. IC2. Subject has documented non-valvular atrial fibrillation (i.e., atrial fibrillation in the absence of moderate or greater mitral stenosis or a mechanical heart valve) and who has a relative or absolute contraindication to anticoagulation. IC3. Subject is deemed suitable for the protocol-defined pharmacologic regimen. IC4. Subject or legal representative is able to understand and willing to provide written informed consent to participate in the study. IC5. Subject is able and willing to return for required follow-up visits and examinations.
Exclusion Criteria	Exclusion criteria are listed below. EC1. Subject is currently enrolled in another investigational study, except if the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatment. EC2. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). EC3. Subject is contraindicated for TEE. EC4. Subject requires long-term anticoagulation therapy for reasons other than AF-related stroke risk reduction (e.g., due to an underlying hypercoagulable state). EC5. Subject had or is planning to have any cardiac or non-cardiac intervention or surgical procedure within 30 days prior to or 60 days after implant (including, but not limited to, cardioversion, percutaneous coronary intervention, cardiac ablation, cataract surgery, etc.). EC6. Subject had a prior stroke (of any cause, whether ischemic or hemorrhagic) or TIA within the 30 days prior to enrollment. EC7. Subject had a prior major bleeding event per ISTH definitions within the 30 days prior to enrollment. Lack of resolution of related clinical sequelae or planned and pending interventions to resolve bleeding/bleeding source are a further exclusion regardless of timing of the bleeding event.

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	EC8. Subject has an active bleed. EC9. Subject has a reversible cause for AF or has transient AF. EC10. Subject has no LAA or the LAA is surgically ligated. EC11. Subject has had a myocardial infarction (MI) documented in the clinical record as either a non-ST elevation MI (NSTEMI) or as an ST-elevation MI (STEMI), with or without intervention, within 30 days prior to enrollment. EC12. Subject has a history of atrial septal repair or has an atrial septal defect/patent foramen ovale (ASD/PFO) device. EC13. Subject has a known contraindication to percutaneous catheterization procedure. EC14. Subject has a cardiac tumor. EC15. Subject has signs/symptoms of acute or chronic pericarditis. EC16. Subject has an active infection. EC17. There is evidence of tamponade physiology. EC18. Subject has New York Heart Association Class IV congestive heart failure at the time of enrollment. EC19. Subject is of childbearing potential and is, or plans to become, pregnant during the time of the study (method of assessment per study physician's discretion). EC20. Subject has a documented life expectancy of less than 6 months.
Adjunctive Pharmacologic Therapy	Subjects must be treated with single antiplatelet therapy (SAPT; aspirin or $P2Y_{12}$ inhibitor) for at least 3 months following WATCHMAN FLX Pro implantation.
Multiple Interventions During Index Procedure	No concomitant procedures are to be performed at the time of the WATCHMAN FLX Pro implant procedure with the exception of implantable loop recorder implants/explants. This includes, but is not limited to, cardiac ablation procedures, transcutaneous valve procedures, cardioversions, coronary stent implantation, pacemaker or implantable cardioverter defibrillator generator change, etc.
Statistical Methods	
Analysis Sets	Analysis sets are listed below.

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	- Intention-To-Treat (ITT): This population includes all subjects who sign an ICF and are enrolled in the study, regardless of whether the study device is implanted. - Implanted: This population includes all subjects who sign an ICF, are enrolled in the study, and are successfully implanted with the study device in the correct position.
Statistical Hypothesis	There is no formal statistical hypothesis for this observational, single-arm study. No statistical inference will be made in the study.
Methods	Outcomes in the overall treatment cohort will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample).

3. Table of Contents

3.1. *Table of Figures*

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4. Introduction

This statistical analysis plan (SAP) addresses the planned analyses for the clinical study entitled "A Pilot Study to Assess WATCHMAN FLX™ Pro Implants by Cardiac Computed Tomography, Magnetic Resonance Imaging and Transesophageal Echocardiography" (WATCHMAN FLX™ Pro CT). Approximately 25 consented subjects will be enrolled. Data for subjects receiving the WATCHMAN FLX Pro device will be collected over 12 months.

There is no formal statistical hypothesis for this observational, single-arm study.

5. Study Objectives and Endpoints

5.1. *Study Objectives*

The primary objective of this study is to measure device tissue coverage post-implantation of the WATCHMAN FLX™ Pro Left Atrial Appendage Closure (LAAC) Device (WATCHMAN FLX Pro) using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE) and assess its relationship, if any, to clinical events.

5.2. *Study Endpoints*

Outcomes in WATCHMAN FLX Pro CT will be assessed on an intention-to-treat (ITT) basis and an implanted basis. The ITT analysis set includes all subjects who sign an Informed Consent Form approved by the Independent Ethics Committee (IEC) and are enrolled in the study, whether or not the WATCHMAN FLX Pro device is implanted. The implanted analysis set includes ITT subjects who are successfully implanted with the study device in the correct position.

Endpoints are listed below. Measurements will be collected peri- and post-procedure, predischarge, and at 14 days, 45 days, 3 months and 12 months after the implant procedure, unless specified otherwise.

The primary endpoint is device surface morphology (inclusive of tissue coverage) post implant procedure as assessed over time using the serial advanced imaging modalities of cardiac computed tomography (CT) and transesophageal echocardiography (TEE).

Additional endpoints will include the following:

- Endpoints adjudicated by an Independent Clinical Events Committee (CEC):
  - All-cause mortality (cardiovascular/unknown and non-cardiovascular)
  - Stroke (disabling and non-disabling; ischemic and hemorrhagic)
    - **Note 1:** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack [TIA]), mRS and NIHSS should be performed after the event. It is recommended that the subject be contacted regarding mRS assessment at 90±14

days following any suspected stroke; the simplified mRS questionnaire may be used for this follow-up assessment. It is recommended that imaging be performed after the event to screen for device related thrombus (DRT). If performed, imaging results should be sent to the core laboratory.

  - Systemic embolism
  - Bleeding: International Society on Thrombosis and Haemostasis (ISTH) major and non-major clinically significant
    - Procedural bleeding (≤7 days post-procedure)
    - Non-procedural bleeding (>7 days post-procedure)
  - Pericardial effusion/tamponade requiring pericardiocentesis or surgery
- Endpoints not adjudicated by an Independent Clinical Events Committee (CEC):
- Device success: defined as implantation of a WATCHMAN FLX Pro device without in-hospital mortality
- Assessments by serial imaging modalities (CT and TEE, optional cardiac magnetic resonance imaging [MRI]) at 14 days, 45 days, and 3 months (TEE optional at 3 months if there is no leak at 45 days). Data will be evaluated by an independent core lab.
  - Device seal at 45 days post index implant procedure (see **Note 2**)
  - Device-related thrombus (including hypoattenuated thickening [HAT] per CT analysis)
  - Device surface morphology (inclusive of tissue coverage) post implant procedure as assessed over time

  Note 2: Results are classified as no leak, leak >0 and ≤5mm, or leak >5mm

  Note 3: TEE should be performed at 12 months if the 3-month TEE assessment suggests a leak > 5mm or the 3-month CT assessment suggests a leak > 3mm; results must be sent to the core laboratory.
- 4D MRI flow analysis (if available) of the left atrium (LA) and LAA before (7 days prior to the index procedure) and serially after device implant (at 14 days, 45 days, and 3 months); data will be evaluated by an independent core lab
- Changes compared to baseline in measures of biochemical markers including coagulation, platelet and endothelial activation and inflammation over time post implant procedure (at 14 days, 45 days, and 3 months); correlations with morphological findings from imaging assessment of the device surface will be examined

5.3. *Overview of Objectives and Endpoints*

Table 5.3-1 provides an overview of the aforementioned study objectives and endpoints and a rationale for the specific endpoints.

Table 5.3-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Evaluate safety of the implant and the procedure	Safety measures peri- and post-procedure and at 14 days, 45 days, 3 months, and 12 months post index procedure	Safety assessments per society guidelines.
Evaluate effectiveness of the implant	Implant performance and other effectiveness measures peri- and post-procedure and at 14 days, 45 days, 3 months, and 12 months (if needed) post index procedure, including core laboratory review of serial imaging post implant	Effectiveness assessments per society guidelines[39,40].

a: Includes computed tomography and transesophageal echocardiography and optional cardiac magnetic resonance imaging

6. Study Design

WATCHMAN FLX™ Pro CT is a prospective, single-arm, single-center, post-market investigation to assess device tissue coverage in subjects with non-valvular atrial fibrillation (AF) who receive the WATCHMAN FLX Pro device to reduce the risk of stroke. Serial advanced imaging modalities such as CT and TEE will be used. A core laboratory will independently assess select results.

6.1. *Scale and Duration*

Up to 25 subjects in whom placement of a WATCHMAN device is attempted will be enrolled in WATCHMAN FLX Pro CT in 1 investigational center in western Europe. Eligibility for the study is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria (see Section10 below) must be done after the ICF is signed.

All subjects will be assessed at baseline and post-implant on the procedure day, at predischarge, and at 14 days, 45 days, 3 months, and 12 months post index procedure. Follow-up will include in-person clinical assessments at all time points except 12 months (in person [preferred] or by telephone). Follow-up imaging assessments will occur at 14 days, 45 days, and 3 months. Additional imaging may be done at 12 months if required based on imaging data obtained at earlier time points.

Subjects who are enrolled but not implanted with a WATCHMAN FLX Pro device will be followed for safety through 12 months after the initial attempted index procedure but will not undergo imaging assessments or evaluation of biochemical markers including measures of coagulation, platelet and endothelial activation and inflammation. **Figure 6.1-1** provides an overview of the study design.

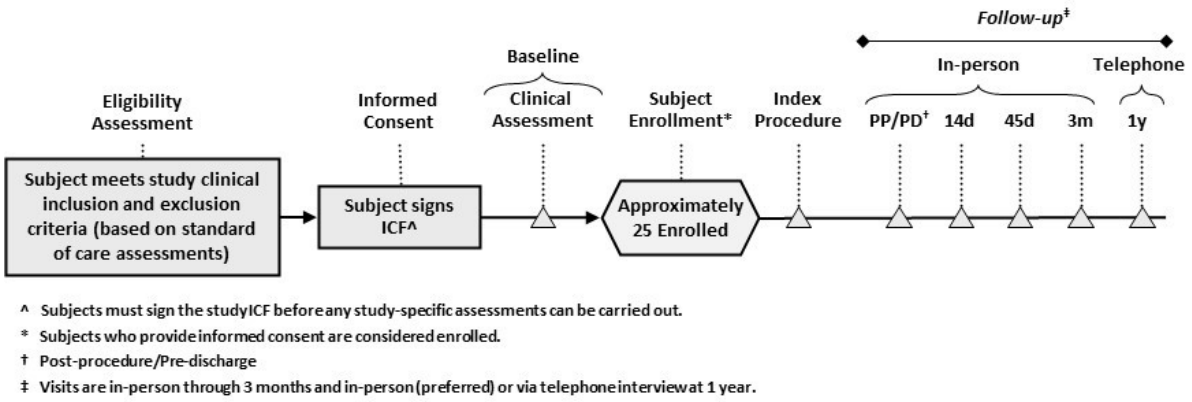

Figure 6.1-1: WATCHMAN FLX Pro CT Study Design Overview

Eligibility for the study is determined per standard of care. Any additional study specific testing to verify inclusion/exclusion criteria must be done after the ICF is signed.
Abbreviations: CT=computed tomography; ICF=Informed Consent Form

Enrollment is expected to take minimally 5 months; therefore, the total study duration from first subject enrolled to last subject follow-up is estimated to be at least 17 months. The study duration for each subject is expected to be approximately 12 months.

7. Statistical Considerations

7.1. *Endpoints*

Procedural and post-procedure information will be collected as detailed in the clinical study schedule and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. The Kaplan-Meier product-limit method will be used to estimate rates for time-to-event endpoints. Adverse event and SAE rates will be reported.

7.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific statistical analysis plan.

Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes).

7.2.1. Analysis Sets

Endpoints will be analyzed on an intention-to-treat (ITT) basis and an implanted basis. For ITT analyses, all subjects who sign the IEC-approved study ICF and are enrolled in the study

will be included in the analysis, whether or not a study device was implanted. For implanted analyses, ITT subjects who had the study device implanted in the correct position during the index procedure will be included in the analysis.

7.2.2. Control of Systematic Error/Bias

To control for inter-observer variability, data from an independent core laboratory will be used for analysis at pre-specified time points. An independent CEC will adjudicate study endpoint related clinical events.

7.2.3. Number of Subjects per Investigative Center

A single center may enroll up to 25 subjects.

7.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). Study endpoints are listed in Section **5.2**.

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

8. Validation

The Global Clinical WI (BSC: 90702587): Clinical Data Reporting Validation will apply to all clinical data reports being generated per this document.

9. Programming Considerations

9.1. *Format of Output*

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

9.2. *Methods for Handling Missing Data*

All subjects who are enrolled will be eligible for evaluation, regardless of the treatment that ensues. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Adjustments for missing outcomes data will be performed if deemed necessary to eliminate or minimize bias and will be described completely. Statistical models that account for censored data will be employed in appropriate circumstances, e.g.,

for time-to-event outcomes. Outlier values will be evaluated, and values determined to be invalid will be queried. All data will be included in the analysis unless judged to be invalid.

When calculating rates of adverse events, missing and partial dates will be handled as shown in the table below.

Partial Date	Action Taken
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

9.3. *Rules and Definitions*

Binary event rates (proportions) will be calculated on a per subject basis.

The number of subjects included in the outcome rates will be based on subjects who have adequate follow-up (see Section 9.4) and/or have experienced any events.

For baseline categorical variables, “unknown” responses and missing values will not be counted in rate denominators.

The date of last follow-up will be the latest of the following dates for each subject: date of a major event with CEC adjudication, index procedure date, discharge date, and scheduled follow-up visit date.

Days to (event or last known status) = (event or status) date minus procedure date.

Length of hospital stay = discharge date minus procedure date.

In-hospital event rates are calculated as the proportion of subjects who experience the specified event from index procedure through day of discharge out of all subjects enrolled.

Out-of-hospital event rates are calculated as the proportion of subjects who experience the specified event from the day after discharge through the number of days as specified out of all subjects who were discharged following index procedure and have adequate follow-up or have experienced the event as specified.

9.4. *Summarization of Site-Reported Serious and Non-Serious Adverse Events*

Site-reported subject-based event rates will be calculated at various time points based on all events reported by the site.

The calculation method will follow the table below and extend to other endpoints and time points (e.g., 1 year death) with the appropriate modifications to the numbers of days. For example, for 90 days, the event must have occurred within 90 days of procedure and the valid data point must be 60 days (early portion of window for the 90-day visit).

The following are the maximum days to event and number of days post-procedure that are adequate follow-up:

Follow-up Visit	Maximum Days to Event*	Days for Adequate Follow-up**
14 Days	14	11
45 Days	45	30
3 Months	90	60
1 Year	365	335

* - this is the target date for the follow-up visit except for the 1-year visit where this is the end of the visit window
** - this is the start of the visit window

All event rates will be calculated relative to the date of procedure (i.e., post-procedure).

10. Bibliography

1. WATCHMAN FLX Pro CT Protocol, 92929614 Rev/Ver C.