Statistical Analysis Plan

Hong Kong WATCHMAN FLX™ Observation HK FLX Study S2461

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Revision History

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1 STUDY SUMMARY

Title	Hong Kong WATCHMAN FLX™ Observation HK FLX
Protocol #	S2461
Phase	Observational study
Design	This study is a prospective, non-randomized, multi-center observational study.
Study Device	The WATCHMAN FLX Left Atrial Appendage Closure Device with Delivery System (consisting of the Delivery Catheter with a pre-loaded Closure Device)
Device Sizes	WATCHMAN FLX is available in 20, 24, 27, 31, and 35mm models to fit left atrial appendage ostia widths ranging from 14.0 – 31.5mm.
Indication(s) for Use	WATCHMAN FLX 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.
Population	Patients with non-valvular atrial fibrillation in Hong Kong area.
Enrolment	Up to 50 patients at up to 5 investigational centres in Hong Kong will be enrolled in the study.
Study Duration	Enrollment is expected to be completed in approximately 12 months and each subject is expected to be followed for approximately 12 months with primary endpoints collected at First Follow-up (30-100 days); therefore, the total study duration is estimated to be approximately 24 months. The study duration for each subject is expected to be approximately 12 months.
Patient follow-up	Each subject will be followed for a period of one year after implantation according to the device labelling. Study procedures and follow-up visits will occur as follows: - Enrolment Visit - WATCHMAN FLX implant - First Follow Up (FU) (30 to 100 days) - 12-month FU (365 ±30 days)

Objectives	The primary objective of this study is to observe the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation to reduce the risk of stroke in Hong Kong area.
Endpoints	**Primary Effectiveness Endpoint:** The occurrence of non-effective LAA closure defined as any peri-device flow > 5mm demonstrated by TEE/CT/MRI at First Follow-up. **Primary Safety Endpoint:** The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: 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. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint. **Secondary Endpoint:** The occurrence of ischemic stroke or systemic embolism at 12 months from the time of implant. **Additional Analysis:** The occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular death (cardiovascular and/or unexplained cause) and systemic embolism.
Inclusion Criteria	1. Patients who are eligible for a WATCHMAN FLX device according to current international and local guidelines (and future revisions) and per physician discretion. 2. Patients who are willing and capable of providing informed consent, participating in all testing associated with this clinical investigation at an approved clinical investigational center. 3. Patients whose age is 18 years or above, or of legal age to give informed consent specific to state and national law.

<table>
<tr><td>Exclusion Criteria</td><td>1. Patients who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the patient is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance should be brought to the attention of the sponsor to determine eligibility.

2. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion);

3. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study.</td></tr>
<tr><td>Multiple Interventions During Treatment/Implant</td><td>Multiple interventions are allowed in the study.</td></tr>
<tr><td>Statistical Methods</td><td></td></tr>
<tr><td>Primary Statistical Hypothesis</td><td>There is no hypotheses testing will be conducted for this small sample size observational study.</td></tr>
<tr><td>Statistical Test Method</td><td>Descriptive statistics will be used for baseline, procedure, and follow-up data collected through the study.

For the Primary Effectiveness Endpoint, it might be considered reasonable if up to 3 primary effectiveness endpoint events should occur in this small sample size study.

For the Primary Safety Endpoint, it might be considered reasonable if up to 3 primary safety endpoint events should occur in this small sample size study.</td></tr>
<tr><td>Sample Size Parameters</td><td>No formal sample size calculation is performed because there is no formal hypothesis testing in the study. The following table provides a 95% confidence interval (exact methods) for a sample size of 50 if there are 0 ~ 5 events.

<table>
<tr><td>Events</td><td>Rates (n=50)</td><td>Lower 95%CI</td><td>Upper 95%CI</td></tr>
<tr><td>0</td><td>0%</td><td>0.0%</td><td>7.1%</td></tr>
<tr><td>1</td><td>2%</td><td>0.1%</td><td>10.6%</td></tr>
<tr><td>2</td><td>4%</td><td>0.5%</td><td>13.7%</td></tr>
<tr><td>3</td><td>6%</td><td>1.3%</td><td>16.5%</td></tr>
<tr><td>4</td><td>8%</td><td>2.2%</td><td>19.2%</td></tr>
<tr><td>5</td><td>10%</td><td>3.3%</td><td>21.8%</td></tr>
</table>
</td></tr>
</table>

2 INTRODUCTION

The purpose of this prospective, non-randomized, multi-center observational study is to observe the safety and effectiveness of the WATCHMAN FLX™ Left Atrial Appendage Closure (LAAC) Device for subjects with non-valvular atrial fibrillation to reduce the risk of stroke in Hong Kong area. The data collected in this study may also be used for product registration in other areas to show that ethnic difference might not play an important role in the performance of WATCHMAN FLX™.

This statistical analysis plan addresses the planned analyses for the Hong Kong WATCHMAN FLX Clinical trial based on the protocol version Dated July 19, 2021.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

The Primary effective endpoint is the occurrence of non-effective LAA closure defined as any peri-device flow > 5mm demonstrated by TEE/CT/MRI at First Follow-up.
The Primary safety endpoint is the occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: 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. Percutaneous catheter drainage of pericardial effusions, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint.

No formal hypothesis will be tested for the primary endpoint. So, no formal sample size calculation is performed based on the primary endpoint. The following table provides a 95% confidence interval (exact methods) for a sample size of 50 if there are 0 ~ 5 events.

Events	Rates (n=50)	Lower 95%CI	Upper 95%CI
0	0%	0.0%	7.1%
1	2%	0.1%	10.6%
2	4%	0.5%	13.7%
3	6%	1.3%	16.5%
4	8%	2.2%	19.2%
5	10%	3.3%	21.8%

3.2 Secondary Endpoints

The secondary endpoint is the occurrence of ischemic stroke or systemic embolism at 12 months from the time of implant.

3.3 Additional Analysis

The occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular death (cardiovascular and/or unexplained cause) and systemic embolism.

3.4 Statistical Methods

No formal hypothesis will be tested for this small observational study. Data and outcome variables collected at baseline, procedure and post procedure follow up will be summarized using descriptive statistics.

For continuous variables, the mean, standard deviation, median, interquartile range (IQR), range, and 95% confidence intervals will be reported. Confidence intervals (95%) for the difference between means will be used to compare groups. For proportions, percentage, count/sample, and 95% confidence intervals will be reported. For time-to-event analyses, all patients not having an event or who are lost to follow-up will be censored at the time of the last documented follow-up visit.

3.5 Endpoints Analysis Included in the Clinical Study Report

For the primary endpoint report (30-100 days post procedure), below endpoint assessments will be included:

- Primary effectiveness endpoint, which refers to the occurrence of non-effective LAA closure at first 30-100 days follow-up.
- Primary safety endpoint, which refers to the occurrence of the primary safety endpoint events between the time of implant and within 7 days following the procedure or by hospital discharge (whichever is later).
- Additional endpoints and other major clinical events, including the occurrence of below events at 30-100 days follow-up:
  - stroke, including ischemic and/or hemorrhagic
  - TIA
  - cardiovascular death, including cardiovascular and/or unexplained cause
  - systemic embolism
  - device embolization
  - device thrombus
  - serious pericardial effusion
  - major bleeding

For the 12-month report, below endpoint assessments will be included:

- Primary effectiveness endpoint, which refers to the occurrence of non-effective LAA closure at 30-100 days follow-up.
- Primary safety endpoint, which refers to the occurrence of the primary safety endpoint events between the time of implant and within 7 days following the procedure or by hospital discharge (whichever is later).
- Secondary endpoint, which refers to the occurrence of ischemic stroke or systemic embolism at 12-month follow-up.
- Additional endpoints and other major clinical events, including the occurrence of below events at 12-month follow-up:

- stroke, including ischemic and/or hemorrhagic
- TIA
- cardiovascular death, including cardiovascular and/or unexplained cause
- systemic embolism
- device embolization
- device thrombus
- serious pericardial effusion
- major bleeding

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

Roll-in subjects are excluded from all primary and secondary endpoints analyses and will be treated separately.

The primary analysis set for the primary effectiveness analysis will be the "per-protocol" analysis set, including implanted subjects with a completed first follow-up visit. The primary analysis set for the primary safety analysis will be the "intent-to-treat" analysis set, including implanted or attempted subjects. It is estimated that both primary effectiveness analysis and primary safety analysis dataset will include at least 40 subjects. For secondary endpoint and additional analysis, different datasets could be used exploratively.

The definitions on the different subject status and classification are provided as below:

Consent Ineligible: A subject who has signed informed consent but is found to not meet eligibility criteria will be classified as "**Consent Ineligible**". There are no FU or adverse event reporting requirements for consent ineligible subjects. Subjects determined to be Consent Ineligible do not count towards the enrollment ceiling and will not be used for analysis of the endpoints.

Intent: A subject who signs informed consent, meets eligibility criteria, but then does not undergo an implant of a WATCHMAN FLX device will be classified as "**Intent**". There are no FU or adverse event reporting or primary endpoint analysis requirements for Intent subjects. Intent subjects do not count towards the enrollment ceiling and will not be used for analysis of the endpoints.

Attempt: A subject who signs informed consent, meets eligibility criteria and has had the WATCHMAN FLX Access Sheath inserted to implant the device, but eventually does not receive a WATCHMAN FLX device will be classified as "**Attempt**". There are no FU requirements for Attempt subjects; however, adverse events will be collected up to the point of subject withdrawal. Attempt subjects count towards the enrollment ceiling and will be used for analyses of the endpoints.

Implant: A subject who is successfully implanted with the WATCHMAN FLX device will be classified as "**Implant**". These subjects are followed in accordance with the FU schedule and included in all study analyses.

Roll-in and non-roll-in: Each site might have up to 2 roll-in subjects if the site has never implanted a WATCHMAN FLX before. Roll-in subjects should be decided before the implant procedure and might be classified as Attempt or Implant after the procedure. Roll-in subjects are enrolled and counted to the ceiling of the sample size. Other enrolled subjects are defined as non-roll-in.

4.2 Statistical Methods

Data and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, median, IQR, number of observations, minimum, maximum and 95% confidence intervals) and discrete variables (percentage, count/sample and 95% confidence intervals). Confidence intervals (95%) for the difference between means will be used to compare groups. For proportions, 95% confidence intervals will be reported. For time-to-event analyses, all subjects not having an event or lost to follow-up will be censored at the time of the last documented follow-up visit.

Explorative analyses may include but will not be limited to the study endpoints. A variety of methods may be utilized to assess associations between the likelihood of each of the study endpoints and the patient and procedural characteristics.

Methods to model multivariate associations may include but are not limited to the following:

1. Univariate analysis of individual predictors, and subsequent construction of multivariate logistic regression models incorporating all significant univariate predictors.
2. Parsimonious multivariate logistic regression models constructed through stepwise selection algorithm.
3. Classification and regression tree models.

4.3 Control of Systematic Error/Bias

Selection of subjects will be made from the Investigator's usual subject load. Non-valvular AF patients who require treatment for potential thrombus formation and meet the inclusion/exclusion criteria will undergo an echocardiographic examination (via TTE and TEE) to further evaluate other Echocardiographic Exclusion Criteria to minimize the selection bias.

If the baseline TTE and TEE confirms the subject does not meet any of the Echocardiographic Exclusion Criteria, the subject is eligible for study enrollment. If the baseline TEE confirms the presence of any intracardiac thrombus, the subject may be treated with anticoagulation therapy. After an appropriate period of time, these subjects will return for another baseline TEE to assess evidence of intracardiac thrombus and other baseline criteria. Only when the thrombus has completely resolved is the subject eligible for study enrollment.

In addition, screen failures who experience an AE associated with diagnostic testing or medication changes in preparation for device implantation will also be followed for 45 days from AE onset or until the AE is resolved.

4.4 Number of Subjects per Investigative Site

No limitations on the maximum number of enrolled subjects for each investigative site will be set.

5 ADDITIONAL DATA ANALYSES

The analyses described in this section will be performed after the corresponding primary or secondary endpoint analysis has been completed. No adjustments for multiple comparisons will be made. Additional analyses will be performed as appropriate.

5.1 Justification of Pooling

Poolability across investigational center will be assessed for all primary and secondary endpoints. Poolability of the primary effectiveness and safety endpoints across investigational center will be assessed by adding center into a logistic regression model as a random effect. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to be significantly different from zero using a significance level of 0.15. Regardless of the results of the poolability analyses, results by investigational center will be provided for each primary and secondary endpoint.

5.2 Interim Analyses

No Interim analysis is planned for the study.

5.3 Subgroup Analyses

No subgroup analysis is planned for the study.

5.4 Multivariable Analyses

Multivariate analyses may be utilized in order to assess associations between the likelihood of outcomes and the pre-specified patient and procedural characteristics outlines in **Error! Reference source not found.**1.

Table 5-1: Covariates of Interest

Age (< 80 years vs. ≥ 80 years)
Sex (Female vs. Male)
Type of AF (paroxysmal; persistent; permanent)
Previous Stroke/TIA
Previous major bleeding event (intracranial/extracranial)
Bleeding risk (HAS-BLED < 3 vs ≥3)
Stroke risk ($CHADS_2$ < 3 vs ≥ 3)
Stroke risk (CHA_2DS_2-VASc < 5 vs ≥5)
Type of anticoagulation therapy (Warfarin; NOACs; antiplatelet)
Multiple concomitant procedures vs watchman implant only

Methods to model multivariate associations may include but are not limited to the following:

(1) Univariate analysis of individual predictors, and subsequent construction of multivariate logistic regression models incorporating all significant univariate predictors.
(2) Parsimonious multivariate logistic regression models constructed through stepwise selection algorithm.
(3) Classification and regression tree models.

5.5 Other Analyses

Baseline and procedural characteristics, patient and device dispositions, antiplatelet and anticoagulants medication usage, additional echocardiographic measurements, device deficiency, site-reported adverse events, protocol deviations will be reported. Data and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, median, IQR, number of observations, minimum, maximum and 95% confidence intervals as applicable) and discrete variables (percentage, count/sample and 95% confidence intervals).

5.6 Changes to Planned Analyses

Any changes to the planned statistical will be documented in a Statistical Analysis Plan. Changes from the planned statistical methods will be documented in the clinical study report along with a reason for the deviation.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

7 PROGRAMMING CONSIDERATIONS

7.1 Statistical Analysis Software

All statistical analyses will be performed using the SAS System software, version 9.4 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.

7.2 Subject Days (last follow-up days)

Each subject will be followed for 12 months after the implant. In case of premature termination of the study, data collection will stop accordingly. As this is an observational study, subjects will be managed according to standard of care as per centers practice following termination/completion of the study.

1. The date on End of Study form (subject exits the study due to death, withdrawal, lost to follow up, or completed study).
2. If subject didn't exit the study and has a corresponding follow-up visit (eg: procedure date, discharge date, adverse event date, site-reported echo date, follow-up visit date, hospitalization date), then visit date is used.

3. The procedure date is considered as the starting point of a patient for any of the analysis specified in this statistical analysis plan.

7.3 Clinical Event Rates

1. Rates at Procedure: the proportion of subjects who experience an event on the same day as the index procedure out of all subjects.
2. Rates through Discharge/7 days Post-procedure: the proportion of subjects who experience an event through discharge or 7 days post-procedure (whichever comes later) out of all subjects.
3. Rates at 30-100 Days Post procedure: the proportion of subjects who experience an event through 30-100 days post-procedure out of the subjects who have either had an event within 30-100 days post-procedure or who were event-free with last follow-up at least 30 days post-procedure.
4. Rates through 1-Year Post procedure: the proportion of subjects who experience an event through 365 days post-procedure out of the subjects who have either had an event within 395 days post-procedure or who were event-free with last follow-up at least 335 days post-procedure.

7.4 Calculation of age

The age will be calculated between the date of birth and the date of screening following this formula Age (in years) = (date of screening – date of birth) / 365. In case the day in the date of birth is reported as unknown (e.g. UN/05/1955), the value will be modified to 01 (e.g. 01/05/1955).

7.5 Missing data

Missing data will not be dealt with systematically in this small sample size study. For the primary safety endpoint, all attempted subjects will be eligible for evaluation, regardless of implant success. Statistical models that account for censored data will be employed for time-to-event outcomes.

When calculating rates of adverse events, missing and partial dates will be handled as shown below:

Partial Date Description	**Action Taken**
Entire 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.

Missing data for primary end point analysis will follow imputation techniques

Missing data due to dropped out or withdrawn subjects will be considered as missing at random and multiple imputation will be done based on the same assumption, while missing of the follow up data will be considered as missing not at random and imputation will follow the same techniques.

A tipping-point analysis might be conducted for the Primary Effectiveness Endpoint to assess the impact of different assumptions about the missing data on interpretation of the results.