STUDY TITLE

Left Atrial Appendage Occlusion with The Amplatzer™ Amulet™ Device: The Southeast Asia Observational Study

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This protocol is accompanied by/ incorporates the following amendment(s):

Amendment no.	Changes	Reason
Version 1.1	Section 12 Confidentiality Section 13.3 Database management and structure	To clarify that the data will not be shared with the funder or other third parties. Addition of new section, to clarify that the data will not be shared with the funder or other third parties.
Version 1.2	Section 3 Eligibility Section 13.2 Study documentation and record keeping	Clarification on the inclusion criteria Clarification on the duration of record keeping after study completion.

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List of abbreviations

AF	Atrial Fibrillation
CT	Computed Tomography
ECG	Electrocardiogram
ICE	Intracardiac echocardiogram
IRB	Institutional Review Board
LAAO	Left Atrial Appendage Occlusion
mRS	Modified Rankin Scale
MRI	Magnetic Resonance Imaging
NICL	Non-invasive Cardiac Laboratory
OAC	Oral anti-coagulants
REB	Research Ethics Board
SHC	Sarawak Heart Centre
TIA	Transient Ischemic Attack
TOE	Transesophageal Echocardiogram
TTE	Transthoracic Echocardiogram

Protocol Summary

Full Title	Left Atrial Appendage Occlusion with The Amplatzer™ Amulet™ Device: The Southeast Asia Prospective Observational Study	
Short Title	SEA Amulet™ Study	
Principal Investigator	Dr. Koh Keng Tat	
Sponsor	Sarawak Heart Centre	
Funder	St. Jude Abbott Medical	
Primary Objective	To explore on the short-term and long-term (1 year) safety and efficacy of LAA occlusion with the Amplatzer™ Amulet™ Device in the Southeast Asia population on a real-world basis.	
Secondary Objectives	To compare the practice of LAA occlusion with Amplatzer™ Amulet™ Device in Southeast Asia population with the European registries.	
Exploratory Objectives	Cost effectiveness of LAA occlusion with the Amplatzer™ Amulet™ Device in the Southeast Asia.	
Study Population	All-comer study for patients indicated for LAA occlusion with Amplatzer™ Amulet™ Device according to the international guidelines	
Study Design	Multicenter, observational study	
Sample Size	100 patients	
Accrual Period	12 months recruitment + 1-year follow-up.	
Study Duration	Start Date: 1 October 2022	End Date: 1 October 2024
Inclusion Criteria	1. 18 year of age or older 2. Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation 3. At high risk of stroke or systemic embolism defined as CHA2DS2-VASc score of more than or equal to 3. 4. Deemed suitable for LAA occlusion by the treating physician, who might or might not be the investigator. 5. Able to comply with the required medication regimen post-device implant 6. Able and willing to return for required follow-up visits and examinations	
Exclusion Criteria	1. With active endocarditis or other infections producing bacteremia 2. Where placement of the device would interfere with any intracardiac or intravascular structures 3. Reversible cause of AF (i.e. secondary to thyroid disorders, acute alcohol intoxication, trauma, recent major surgical procedures) 4. Hypersensitivity to any portion of the device material or individual components of the Amulet LAA closure device 5. Actively enrolled or plans to enroll in a concurrent clinical study in which the active treatment arm may confound the results of this trial 6. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the patient's ability to participate in the clinical trial or to	

	comply with follow up requirements, or impact the scientific soundness of the clinical trial results.
Outcomes	Safety: i. All-cause and cardiovascular mortality ii. Bleeding events iii. Pericardial effusion iv. Device dislocation and device related thrombus v. Access site complication Efficacy: i. All cause and cardiovascular mortality ii. Ischemic stroke or transient ischemic attack iii. Systemic embolization iv. Occurrence of leak at the device supporting incomplete occlusion of the LAA. Secondary outcomes To compare the following with the European registries: i. Indication for LAA occlusion ii. Rate of technical and procedural success iii. Practice of antiplatelet and anticoagulation therapy
Study Intervention Device	Amplatzer™ Amulet™ Left Atrial Appendage Occlusion Device
Assessments	Subjects will be followed through 1 year post implant. **Required Testing** • Baseline evaluation: Informed consent, history and physical, 12-lead electrocardiogram (ECG), CHA2DS2-VASc score, HAS-BLED score, Modified Rankin Scale (mRS), medication assessment. Pre-procedural Imaging planning with TOE or CT scan • Procedure: TOE or ICE only when combined with baseline/pre-procedural imaging, and adverse event assessment • Post procedure/Pre-discharge: TTE, medication assessment, adverse event assessment • 1M to 3M: TOE or CT scan, medication assessment, adverse event assessment • 6M (+/- 2 weeks): TOE or CT scan, medication and AE assessment • 12 (+/- 6 weeks): Medication and adverse event assessment • Interim/unscheduled visits: per physician discretion

Baseline visit
- Informed consent
- Demographics and concomitant medications
- Indication for LAA occlusion
- Medical history (mRS, CHA2DS2-VASc score, HAS-BLED score)
- 12-lead ECG and echocardiogram
- Pre-procedural imaging with CT scan or TOE

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Amplatzer™ Amulet™ LAAO implant
- Procedural setting and time
- ICE or TOE guided
- Transeptal puncture/sheath/vascular ultrasound
- Number of attempt/changing of device size
- Immediate success and adverse events

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Pre-discharge
- Duration of hospital stay
- Adverse events
- Medications (antiplatelet and OAC)

↓

1-month to 3-month
- TOE or CT Scan
- Medication assessment
- Efficacy and safety endpoints assessment

↓

6-month (+/- 2 weeks)
- TOE or CT Scan
- Medication assessment
- Efficacy and safety endpoints assessment

↓

12-month (+/- 6 weeks)
- Medication assessment
- Efficacy and safety endpoints assessment

*interim/unscheduled visit per physician discretion

1. BACKGROUND

The safety and efficacy of left atrial appendage occlusion (LAAO) with the Amplatzer™ Amulet™ occluder device has been well studied in the European population. This include the LAARGE registry (n=641) and the prospective global observational study from the Amulet Observational Study Investigators (n=1088).(1, 2) In the LAARGE registry, bleeding events was the main indication for LAAO implantation (79.4%). There were 163 (25.7%) of the LAAO implanted with Amplatzer™ Amulet™. Overall, the LAARGE registry demonstrated a favorable outcome at 1-year follow-up in terms of stroke/TIA (1.3%) and major bleeding (1.6%). On the other hand, the Amulet Observational Study was able to demonstrate a reduction of 67% of ischemic stroke rate compared to the predicted risk. Closure was complete in 98.4% and device related thrombus was only seen in 1.6%.

While the registry studies from the European countries showed a favorable efficacy and safety outcomes, there is no data on LAAO with Amplatzer™ Amulet™ from the Asia population. The WASP registry, which was comparing LAAO implantation with WATCHMAN device in Asian population found that the efficacy of LAAO with WATCHMAN was more pronounced in Asian population.(3) Asian population also has a larger LAA ostium diameter and hence required a larger LAAO device. The interaction and the influence of the demographic, genetic, health economy, and clinical practice in Asia population on the efficacy and safety of Amplatzer™ Amulet™ device is unknown. Knowing that Asia population is equivalent to 59.76% of the total world population, it is therefore imperative to have a regional study on the safety and efficacy of LAAO with Amplatzer™ Amulet™ in the Southeast Asia region.

2. STUDY OBJECTIVES

The primary objectives of this study:

To explore on the short-term and long-term (1 year) safety and efficacy of LAA occlusion with the Amplatzer™ Amulet™ Device in Southeast Asia population on a real-world basis

The secondary objectives are:

To compare the practice of LAA occlusion with Amplatzer™ Amulet™ Device in Southeast Asia population with the European registries.

The exploratory objective:

> To explore the cost effectiveness of LAA occlusion with the Amplatzer™ Amulet™ Device in the Southeast Asia.

3. ELIGIBILITY CRITERIA

This is an all-comer observational study and therefore all patients indicated for LAAO with the Amplatzer™ Amulet™ are eligible for the study. Subjects who meet criteria for eligibility will be asked to participate. Since this observational study is both retrospective and prospective, subjects who had their occluder implanted, been recently implanted or intended to undergo the procedure may be considered to participate in the study. Informed consent will be obtained for data collection purposes.

3.1 Inclusion Criteria

- 18 year of age or older
- Documented paroxysmal, persistent, or permanent non-valvular atrial fibrillation
- At high risk of stroke or systemic embolism defined as CHA2DS2-VASc score of more than or equal to 3.
- Deemed suitable for LAA occlusion by the treating physician, who might or might not be the investigator.
- Able to comply with the required medication regimen post-device implant
- Able and willing to return for required follow-up visits and examinations

3.2 Exclusion Criteria

- With active endocarditis or other infections producing bacteremia
- Where placement of the device would interfere with any intracardiac or intravascular structures
- Reversible cause of AF (i.e. secondary to thyroid disorders, acute alcohol intoxication, trauma, recent major surgical procedures)
- Hypersensitivity to any portion of the device material or individual components of the Amulet LAA closure device
- Actively enrolled or plans to enroll in a concurrent clinical study in which the active treatment arm may confound the results of this trial
- Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the patient's ability to participate in the clinical trial or to comply with follow up requirements, or impact the scientific soundness of the clinical trial results.

4. STUDY DESIGN

4.1 Study Description

This is a both prospective and retrospective, multicenter observational study for all patient indicated for LAAO with the Amplatzer™ Amulet™ device.

4.2 Study Outcomes

Primary outcome:

Safety:

i. All-cause and cardiovascular mortality
ii. Bleeding events
iii. Pericardial effusion
iv. Device dislocation and device related thrombus
v. Access site complication

Efficacy:

i. All cause and cardiovascular mortality
ii. Ischemic stroke or transient ischemic attack
iii. Systemic embolization
iv. Occurrence of leak at the device supporting incomplete occlusion of the LAA.

Secondary outcomes

To compare the following with the European registries:

i. Indication for LAA occlusion
ii. Rate of technical and procedural success
iii. Practice of antiplatelet and anticoagulation therapy

Exploratory outcome:

To explore on the cost effectiveness of LAAO with Amplatzer™ Amulet™ in the region.

5. STUDY DURATION

The study duration is 12 months of recruitment plus 1 year follow-up for outcomes. Each study subject's participation will last approximately 1 year, including the follow-up for outcomes and adverse events.

5.1 Early Termination

Participation of this study is entirely voluntary. Not participating in this study will not change current standards of care, which are consistent with National Guidelines and international

standards. Patients have full autonomy to withdraw from the study if they are unwilling to continue the study for whatsoever reasons throughout the study period.

Before a subject is declared lost to follow-up, all efforts should have been made to contact the patient for a final assessment.

5.2 Criteria for Suspending or Terminating Study

Not applicable. This is an observational study and not an interventional study, the study aims to collect data of patients who had undergone the treatment, undergoing the treatment or will undergo the treatment. All the patients are managed under standard of care.

6. STUDY INTERVENTIONS

6.1 Amplatzer™ Amulet™ LAAO Device

The Amplatzer™ Amulet™ LAAO is a transcatheter, self-expanding device intended for use in preventing thrombus embolization from the left atrial appendage. The device is constructed from a nitinol mesh and consists of a lobe and a disc connected by a central waist. Polyester patches are sewn into both the lobe and disc to facilitate occlusion. The lobe has stabilizing wires to improve device placement and retention. The device has threaded screw attachments at each end for connection to the delivery and loading cables. The device has radiopaque markers at each end and at the stabilizing wires that permit Visibility during fluoroscopy.

7. STUDY EVALUATIONS/PROCEDURES

7.1 Clinical Evaluations

Data including demographics, CHA2DS2VASc score and HASBLED risk score and other medical history, surgical history, routine laboratory investigations, and medications will be collected during the screening.

7.2 Laboratory Evaluations and Specimen Collection

Not applicable. All blood investigations are as for routine clinical practice.

7.3 Case Report Form (CRF)

Please refer to Appendix.

7.4 Permitted or Non-permitted Medication

Medication assessments will be conducted at pre-discharge and all follow-ups. Patients will be assessed whether to be prescribed with anticoagulant or/and antiplatelet medications such as aspirin, clopidogrel, unfractionated heparin, LMW heparin, warfarin, dabigatran, rivaroxaban, apixaban and endoxaban, at various duration. The dose and planned duration will be determined by the investigator. There is no non-permitted medication which needs to be avoided by the patient after the implant.

All concomitant cardiac medications, at the time of screening, loading dose, and each visit will be recorded in the Case Report Form (CRF).

8. STATISTICAL CONSIDERATIONS

8.1 Details of statistical analysis

Descriptive statistics includes percentage, mean with standard deviation, or median with interquartile range will be reported, whichever appropriate. Categorical variables will be analysed using chi-square test or Fisher's exact test. Continuous variables will be analysed using independent (two variables only) or ANOVA test (more than two variables), or Mann-Whitney test (two variables only) or Kruskal-Wallis test (more than two variables) depending on the nature of underlying distributions. Time dependent outcome data will be analysed using Kaplan-Meier survival analysis.

8.2 Sample size

A sample size of 100 patients for the study. This is based on the estimated number of recruitments from the participating centers.

9. ASSESSMENT OF SAFETY

The investigator will monitor the occurrence of Serious Adverse Events (SAEs) for each subject during the study. For the purpose of this protocol, adverse events will be assessed from the date of informed consent form is signed until up to the end of follow-up.

9.1 Serious Adverse Events (SAEs) Definitions

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Lack of drug effect is not an adverse event.

An AE is classified as "serious" if the event:

- Led to death;
- Led to serious deterioration of a patient that:
  - Resulted in a life-threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required in subjects hospitalization or prolongation of existing hospitalization;
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical study protocol, without serious deterioration in health, is not considered a serious adverse event.

9.2 Anticipated Adverse Device Effects
Anticipated adverse device effects are described in the Instruction For Use.

9.3 Reporting of SAE
The investigator must record all serious adverse events, regardless of treatment or relationship to study therapy, as soon as he/she is informed of the event. Investigators must report immediately to the Principal Investigator any serious adverse events.

9.4 Follow-up of SAE
Any serious and or unexpected adverse event should be medically well documented, and the information made available as soon as possible.

10. ETHICS AND REGULATORY CONSIDERATIONS

A copy of the protocol (including protocol amendments), all versions of informed consent forms, other information to be completed by participants such as survey instruments or case report forms, and any proposed advertising/ recruitment materials must be reviewed and approved by the REB/IRB approval and annual Continuing Review throughout the duration of the study.

11. INFORMED CONSENT PROCESS

Informed consents will be obtained for all prospective data collection. Consent forms describing in detail the study intervention, study procedures and risks will be given to each participant and written documentation of informed consent is required prior to starting study intervention. Participants must sign an informed consent document that has been approved by a participating centre's IEC/IRB if he/she agrees to participate in this study. Each participant should have sufficient opportunity to discuss the study and consider the information in the consent process

prior to agreeing to participate. Participants may withdraw consent at any time during the course of the trial. The informed consent form will be signed and dated by the participant and the person who conducted the informed consent discussion. Two informed consent form to be signed. One to be kept by the investigators, one to be kept by patients. No photocopy of informed consent form.

12. CONFIDENTIALITY

Subject's personal details and medical information obtained in this study is considered confidential and will not be disclosed to the funder or third parties other than for the reasons below:

a. Requirement from regulatory authority
b. Requirement from ethic committee members

The study results might be published or presented. However, none of the subject's personal information will be revealed in any of the publications or presentations.

13. DATA MANAGEMENT

13.1 Data Collection

All data generated and gathered during the study will be entered into the case report forms (CRF) directly and accurately. Every entry must be recorded legibly in black ink. If a correction is needed, strikethrough the mistake with a single line, initial and date at the side of the correction. Designated staff at participating sites shall enter data required by the protocol into the eCRF. The eCRF system is a validated system and conforms to 21 CRF part 11.

13.2 Study documentation and record keeping

All the documents in the study will be filed and kept in a locked room with limited access. All electronic data will be stored in a password-protected database. The study data and documents will be kept up to 7 years after the completion of study. Study data is destroyed after period of storage. Only personnel involved in the study and regulatory representatives will have the access to the data. The subjects may not access the study data directly.

13.3 Database management and structure

All the data will be managed and handled by the study team (the Sponsor) and InnoSignum. InnoSignum functions as a CRO-SMO (Site Management Organization) and acts as an intermediary to the funder and the Sponsor-site in running the study. The patient's medical information obtained in this study is confidential and will not be disclosed to the funder or other third parties. The funder will not involve in the study design or influence/interfere with the conduct

of the study. The funder will not have access to the study data or clinical database directly or indirectly.

14. PROCEDURE OF HANDLING WITHDRAWAL

Study coordinator will explore the reason of withdrawal from study. The reason will be recorded. Patients who withdraw from the study will continue their management under the respective hospital. Patients who withdraw from the study will be replaced with new patients.

15. RISK OF PROCEDURE

Not applicable. The study is an observational study which involve data collection for the LAAO implantation.

16. STUDY FUNDING

This is an investigator-initiated research where the investigator or the study site, which is Sarawak Heart Centre serves as the Sponsor. The study was supported by an educational research grant from St. Jude Abbott Medical (the funder). The funds supported by the funder is mainly used to manage the data management and to support the purpose of this study, which is to collect the data both retrospectively and prospectively. The LAA occluders that were implanted are funded by pensioner Tabung Bantuan Perubatan, Ministry of Health (MoH) or self-paying by the patients.

17. PUBLICATION POLICY

At the conclusion of the Amulet-SEA-01 study, a manuscript will be prepared for publication in a reputable scientific journal regardless of positive or negative results. The scientific validity and timing of publications will be evaluated in order to maximize the benefits derived from the publication of the clinical data of the study. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Permission from the Director General of Health will be obtained for the publication of this study.

17.1 Authorship Selection

Authors will be selected on the basis criteria of the following:

- A significant contribution to the design of the clinical study;
- A significant contribution to patient enrollment in the clinical study;
- High quality of data as determined by the clinical study requirements;

- Demonstration of a high level of interest in the performance of the product and/or the unique product feature, and the ability to write, review, edit and present the publication;
- A demonstration of a good publication history;
- A willingness to contribute to the publication.

17.2 Review and Communication Guidelines

Investigators will receive communication regarding the authorship selection, the publication co-authors and to which scientific platform the publication will be submitted. Prior to submission of a publication, the Publication Committee and all co-authors will review and authorize the publication.

18. REFERENCES

1. Brachmann J, Lewalter T, Akin I, Sievert H, Geist V, Zeymer U, et al. Interventional occlusion of left atrial appendage in patients with atrial fibrillation. Acute and long-term outcome of occluder implantation in the LAARGE Registry. J Interv Card Electrophysiol. 2020;58(3):273-80.

2. Hildick-Smith D, Landmesser U, Camm AJ, Diener HC, Paul V, Schmidt B, et al. Left atrial appendage occlusion with the Amplatzer Amulet device: full results of the prospective global observational study. Eur Heart J. 2020;41(30):2894-901.

3. Phillips KP, Santoso T, Sanders P, Alison J, Chan JLK, Pak HN, et al. Left atrial appendage closure with WATCHMAN in Asian patients: 2year outcomes from the WASP registry. Int J Cardiol Heart Vasc. 2019;23:100358.

19. APPENDIX

Appendix A: Schedule of Events

Evaluation	Baseline	LAAO implant	Pre-discharge	1-3mo	6mo	12mo
Informed consent (For prospective data collection only)	X					
CRF form	X					
Demographics	X					
Indication	X					
Clinical examination and investigations	X		X	X	X	X
mRS, CHA2DS2-VASc, HASBLED	X					
Medications	X		X	X	X	X
CT Scan, TOE or ICE	X	X		X	X	
Procedural detail		X				
Safety Outcomes		X	X	X	X	X
Efficacy Outcomes		X	X	X	X	X

Signature Page Principal Investigator

Study title:	Left Atrial Appendage Occlusion with The Amplatzer™ Amulet™ Device: The Southeast Asia Observational Study
Short title:	Amulet-SEA-01
Version no:	1.2
Version date:	27 October 2022

I have read this protocol and/or amendment and appendices and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational product and the conduct of the study.

I will conduct the study in accordance with the protocol and local regulations.

Dr. Koh Keng Tat

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Signature Principal Investigator at the Site

27-Oct-2022

Date