Statistical Analysis Plan

A Study to evaluate the safety and effectiveness of the Left atrial appendage closure therapy Using BSJ003W for patients with non-valvular atrial fibrillation at increased risk of ThromboEmbolism in Japanese medical environment

SALUTE

92042733

APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

Lead Biostatistician – Tomoo Noguchi	Date (dd-mon-yyyy)
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Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
A	90702621 Rev/Ver AE			new version
B	90702621 Rev/Ver AE		Modified classification of covariates.	To adjust in detail

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1 PROTOCOL SUMMARY

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment	
Study Objective(s)	To confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese Clinical environment
Planned Indication(s) for Use	To reduce the risk of thromboembolism from the Left Atrial Appendage in patients with non-valvular atrial fibrillation who are at increased risk based on $CHADS_2$ or CHA_2DS_2-VASc scores
Test Device	BSJ003W LAA Closure Technology; three-component system consisting of the • BSJ003W Closure Device; WATCHMAN(Gen 2.5) • BSJ003W Delivery System (Delivery Catheter and BSJ003W Closure Device) • BSJ003W Access System (Access Sheath and Dilator)
Control Device	None
Device Sizes	21mm, 24mm, 27mm, 30mm, 33mm
Study Design	This is a prospective, multi-center, single-arm study to confirm the safety and effectiveness of BSJ003W for Japanese subjects with non-valvular atrial fibrillation who are eligible for long-term anti-coagulation therapy to reduce the risk of stroke but who have a rationale to seek a non-pharmacologic alternative in Japanese clinical environment.
Planned Number of Subjects	One Roll-in subject per site is required prior to enroll an analyzable subject at each site. One more Roll-in subject should be enrolled if necessary per Investigators' or a proctor's discretion. Number of analyzable patients: 40 patients. Maximum of 60 subjects (including 10-20 Roll-in subjects) will be enrolled in the study.
Planned Number of Investigational Sites	Up to 10 investigational centers in Japan

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Primary Endpoints	To assess safety and effectiveness of BSJ003W, the following three endpoints are established as Co-Primary Endpoints: 1. 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. 2. The occurrence of composite events* including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) . *All data collected up to the last patient's 6 months follow-up visit to be completed. 3. The rate of effective LAA closure* at 45 days and 6 months. Change in the rate between the two time points will also be analyzed. *The effective LAA closure is defined as peri-device flow $\leq$ 5mm demonstrated by TEE. TEE measurements will be assessed by independent Core Lab.

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Secondary endpoints	Safety endpoints: • The occurrence of major bleeding* at 0 – 45 days, 45 days – 6 months, 6 months – 24 months *Major bleeding is defined as per BARC bleeding definition type 3 or 5 • Frequency of the following bleeding events at 0 – 45 days, 45 days – 6 months and 6 months – 24 months: • Clinically overt non-fatal bleeding* • All bleeding events *Clinically overt non-fatal bleeding is defined as per BARC bleeding definition type 2. Effectiveness endpoints: • The occurrence of composite events* for effectiveness; stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) *All data collected up to the last patient's 12 months and 24 months follow-up visits to be completed. • Effective LAA closure at 12-month and its time course until then. • The occurrence of ischemic stroke or systemic embolism (excluding 7 days after implanting or day after hospital discharge whichever is later) at 6 months, 12 months and 24 months.
Additional Endpoints	Device performance: • Technical Success defined as successful delivery and release of BSJ003W into the LAA including successful recapture and retrieval if necessary. Safety endpoints: • Occurrence of reportable adverse events • Occurrence of all-cause mortality Effectiveness endpoints: • Individual occurrence of all-cause death, ischemic stroke,

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<table>
<tr><td></td><td>hemorrhagic stroke, systemic embolization, cardiovascular death (including unexplained cause) at 6-month, 12-month and 24-month.
• Warfarin discontinuation rate at 45 days, 6-month and 12-month
• Severity of stroke assessed by NIH Stroke Score, Modified Rankin Scale Score, and Barthel Index

Other endpoint:
• EQ-5D</td></tr>
<tr><td>Required Medication Therapy</td><td>
<table>
<tr><th>Visit</th><th>Medication</th></tr>
<tr><td>Implant through 45-day visit</td><td>ASA+ Warfarin</td></tr>
<tr><td>45-day visit through 6-month visit</td><td>ASA+ Thienopyridine</td></tr>
<tr><td>Following the 6-month visit</td><td>ASA</td></tr>
</table>
Warfarin therapy should be appropriately monitored and adjusted so as to achieve a therapeutic INR of 2.0- 3.0. For a subject who are 70 years old or older, a therapeutic INR of 2.0 – 2.6 is recommended considering the high risk of major bleeding. Subjects should remain on warfarin until the 45-day TEE evaluation has shown adequate seal of the LAA. If the LAA is not adequately sealed, the subjects should be on warfarin and Aspirin therapy.</td></tr>
<tr><td>Follow-up Schedule</td><td>Study procedures and follow-up visits will occur as follows:
• Informed consent
• Screening
• BSJ003W Implant
• 45-day Follow-up (45 ± 15 days)
• 6-Month Follow-up (180 ± 15 days)
• 12-Month Follow-up (365 ± 30 days)
• 18-Month Follow-up (540 ± 60 days)
• 24-Month Follow-up (730 ± 60 days)</td></tr>
<tr><td>Study Duration</td><td>The duration of the study is expected to last approximately 3 years. The duration of individual subject participation is expected to last approximately 2 years.</td></tr>
</table>

A study to confirm the safety and effectiveness of the BSJ003W in Japanese patients with non-valvular atrial fibrillation at increased risk of thromboembolism in Japanese clinical environment	
Key Inclusion Criteria	1. The subject is Japanese, over 20 years old and provides written informed consent to participate in the trial 2. The subject has documented paroxysmal, persistent or permanent non-valvular atrial fibrillation 3. The subject has a calculated CHA_2DS_2-VASc score of 2 or greater and is recommended for long-term oral anti-coagulation therapy 4. The subject is deemed by their physicians to be suitable for anticoagulant therapy and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin 5. The subject is eligible to come off warfarin therapy if the LAA is sealed (i.e. the subject has no other conditions that would require warfarin therapy).
Key Exclusion Criteria	1. The subject has a prior stroke (ischemic or hemorrhagic) or TIA within the 90days prior to consent 2. The subject has had a MI either non-ST elevation or ST elevation MI within 90days prior to consent with or without intervention 3. The subject had or is planning to have any cardiac (e.g. cardioversion, coronary angiogram, percutaneous coronary intervention, cardiac ablation, etc.) or non-cardiac invasive or surgical procedure (e.g. cataract surgery, endoscopy, etc.) within 30 days prior or 45 days after the BSJ003W implant 4. The subject has a history of atrial septal repair or has an ASD/PFO device 5. The subject has an implanted mechanical valve prosthesis in any position 6. The subject currently NYHA class IV CHF 7. The subject is contraindicated to aspirin 8. The subject is contraindicated or seriously allergic to thienopyridine 9. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician's discretion) 10. The subject is not able and willing to return for required follow-up visits and examinations 11. Subjects who are currently enrolled in another

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	investigational study (of which primary endpoint follow-up have not been completed yet). 12. The subject has other reason not to be eligible for this study per investigators' discretion.
ECHO Exclusion Criteria	1. The subject has LVEF < 30%. 2. The subject has intracardiac thrombus visualized by TEE within 2 days prior to implant. 3. The subject has an existing pericardial effusion with a circumferential echo-free space > 5mm, and/or the patient has signs/symptoms of acute or chronic pericarditis, and/or there is evidence (clinically or echocardiographically) of tamponade physiology. 4. The subject has a high- risk patent foramen ovale (PFO) with an atrial septal aneurysm excursion > 15mm or length ≥ 15mm. 5. The subject has a high-risk PFO with a large shunt defined as early, within 3 beats, and/or substantial passage of bubbles. 6. The subject has significant mitral valve stenosis (i.e., MV <1.5 cm^2). 7. The subject has complex atheroma with mobile plaque of the descending aorta and/or aortic arch. 8. The subject has a cardiac tumor.
Multiple Interventions During Index Procedure	No concomitant procedures are to be performed at the time of the BSJ003W implant procedure. This includes, but is not limited to, cardiac ablation procedures, transcutaneous valve procedures, cardioversions, pacemaker or ICD generator change, etc.
Statistical Methods	
Statistical consideration and Sample size justification	The primary safety endpoint (endpoint1) event rate observed in the PREVAIL study was 2.2%. Based on the PREVAIL data only, the exact 95% upper confidence bound for this rate is 4.4%. An additional margin of 5.6% is added to this upper confidence bound to create a performance target of 10.0%. In order to maintain >=95% probability that the observed estimate from this study is lower than the performance target of 10.0%, 40 subjects are required. The expected primary effectiveness endpoint (endpoint3) rate is 99.3%. Based on this expected rate, and the number of subjects in the PREVAIL study with 6-month TEEs, the corresponding exact 95% lower confidence bound is 97.3%. An additional margin of 3.3% is subtracted from this lower confidence bound to create a

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	performance target of 94.0%. Accounting for 10% attrition to 6-month TEE follow-up, 40 subjects are required to maintain >=95% probability that the observed estimate from this study is higher than the performance target of 94.0%.
Statistical Test Method	Similarities of this study results will be evaluated with foreign pivotal study results. Roll-in patients' data will be evaluated separately from the data of those patients enrolled after the Roll-in patients and will not be included in the endpoint analysis.

2 INTRODUCTION

This statistical plan addresses the planned analyses for the SALUTE Trial based on the protocol with PDM # 92042733. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

3 ENDPOINT ANALYSIS

If and only if the both of primary safety and efficacy endpoints are met Performance Targets (of safety based 10%, of efficacy based 94%), we say that the study objectives are met. So, no overall significant level adjustments are employed. Endpoint 2 is medically observed (no Performance Target).
Roll-in patients' data will be evaluated separately from the data of those patients enrolled after the Roll-in patients and will not be included in the endpoint analysis.

3.1 Primary Safety Endpoint (Endpoint 1)

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.

Similarities of this study results will be evaluated with foreign pivotal study results.

3.1.1 Hypotheses

Not applicable.

3.1.2 Sample Size

The primary safety endpoint event rate observed in the PREVAIL study was 2.2% and an additional margin was added to create a performance target of less than 10.0%. Considering that 1-2 events may occur by chance, equal or more than 40 subjects will allow at least 3 events or more to occur and with >=95% probability, observed estimate from this study is lower than the performance target.

3.1.3 Statistical Methods

Each event will be evaluated individually and occurrence rate and 95% CI will be calculated.

3.2 Primary Efficacy Endpoints (Endpoint2 and 3)

Followings are primary efficacy endpoints:

Primary efficacy endpoints are the occurrence of composite events including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) and the rate of effective LAA closure at 45 days, 6 months and change in rate between the two time points.

TEE measurements will be assessed by independent Core Lab.

3.2.1 Hypotheses

Not applicable.

3.2.2 Sample Size

A performance target of an effective LAA closure rate (endpoint3) of this study, 94.0%, was created by considering an additional margin with 99.3% of the effective LAA closure rate observed in PROTECT AF and PREVAIL studies. Accounting for 10% attrition to 6-month TEE follow-up, 40 subjects are required to maintain >=95% probability that the observed estimate from this study is higher than the performance target of 94.0%. This will allow up to 2 patients whose LAA may not be effectively closed for any reasons at 6 months.

Meantime, sample size of 40 patients were established taken into consideration that 10% of pivotal study sample size was reasonable from standpoint of the study feasibility and similarity comparison of outcomes of this study and the pivotal studies.

3.2.3 Statistical Methods

The occurrence of composite events including stroke (all/ ischemic/ hemorrhagic), systemic embolism and CV death (including unexplained cause) as well as effective LAA closure rate will be calculated and similarities of this study results will be

evaluated with foreign pivotal study results. All data collected up to the last patient's 6 month follow-up completion will be used for the analysis.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

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The analysis set for the Co-Primary Endpoints analysis includes implanted subjects with a completed 6-month visit, i.e. for subjects who withdrawn consent/ missing before 6 month time window will be excluded from the implanted analysis set. The analysis set for the other analyses will be the "intent-to-treat" analysis set, including all implanted or attempted subjects.

Roll-in patients' data will be evaluated separately from the data of those patients enrolled after the Roll-in patients.

Intention-to-Treat (ITT) subjects are included in primary analysis for primary safety and efficacy endpoints as well as secondary endpoints and other endpoints. In addition, Implant subjects alone will be evaluated as needed as reference.

ITT: A subject who signs informed consent and regardless of the study device implanted or not, being enrolled into the study.
IMPLANT and ATTEMPT subjects are included in ITT.

4.2 Control of Systematic Error/Bias

Selection of subjects for enrollment will be made from the Investigator's usual subject load. All subjects meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. To control for the potential bias that could be introduced via sponsor classification of adverse events, a Clinical Events Committee (CEC) will adjudicate important endpoints and relevant adverse events.

4.3 Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 20% of the 40 subjects (n = 8) per this protocol. Further enrollment will require advance agreement from sponsor.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

Baseline and other results (include other primary and secondary endpoints) will be analyzed descriptively with continuous variables (mean, standard deviation, number of patients, minimum, maximum, etc) and discrete values (frequency table and percentage). Similarities of this study results will be evaluated with foreign pivotal study results if necessary.

5.2 Interim Analyses

Interim analysis is not planned.

Initial analysis is planned at the last patient's 6 month follow-up completion (primary analysis for submission) and the second analysis (additional analysis) at 12 month follow-up completion. Final analysis (additional analysis) is planned once all follow-ups (24month follow-up) required by the study are completed.

5.3 Subgroup Analyses

Sub-group analysis will be completed, such as analysis by BSJ003W size, Sex, Age(<75, ≥75) and ability to discontinue Warfarin, $CHADS_2$ score(1-3, 4-6), CHA_2DS_2-VASc score (1-3, 4-9) ,and HAS-BLED score (1-3, 4-9), AF pattern (Paroxysmal, Persistent +Permanent +Paced), AF ablation, LVEF (Above Median, below Median), history of stroke/TIA, abnormal renal function, chronic dialysis, for the primary and secondary endpoints, appropriately. LAAC by Baseline covariates (raw category) will be displayed.

5.4 Justification of Pooling

Not applicable due to single-arm study.

5.5 Multivariable Analyses

Univariate and multivariate analyses will be performed to assess predictors for primary and secondary endpoints appropriately.

Unknown is counted as missing.

Planned covariates at start are followings listed;

AGE at IC (<75, ≥75),
Sex (Male, Female),
Body weight (<60kg, ≥60kg)
BSJ003W size (21mm+24mm+27mm, 30mm+33mm),
AF pattern（Paroxysmal, Persistent +Permanent +Paced）
AF onset (<1 year, ≥1year)
LVEF (Above Median, below Median)
Warfarin discontinuation (Yes/No),
History of Stroke/Ischemic stroke/Hemorrhagic stroke /TIA (Yes/No),
$CHADS_2$ score (1-3, 4-6)
$CHA2DS_2$-VASc score (1-3, 4-9)
HAS-BLED score (1-3, 4-9)
LAA ostium diameter (Above Median, below Median),
LAA length (Above Median, below Median),
Previous AF ablation (Yes/No),
MI (Yes/No)
Hypertension (Yes/No)
Congestive Heart Failure (Yes/No)
NYHA (I/II, III)
LV dysfunction (Yes/No)
Peripheral Artery Disease (Yes/No)
Diabetes (Yes/No),
Abnormal Renal Function (Yes/No),
Chronic Dialysis (Yes/No),

Warfarin naïve (Yes/No)

From those covariates, as a result, highly skewed or rare frequency cases are deleted, and correlated variables are combined to one variable and then entered into the model.

5.6 Sensitivity Analysis for Missing outcome data

Sensitivity analyses for the binary primary effectiveness and/or safety endpoints assessment will be conducted to assess the impact of missing data on the result's robustness, if necessary. In addition to the use of the worst-case analysis, the tipping point analysis will be performed for the ITT analysis set to consider all combinations of present/absent for all subjects with missing primary outcome. No imputation will be made to the other endpoints/parameters unless specified.

5.7 Handling of Missing Date

For the analysis of adverse events or medication usage, 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 1 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.

5.8 Other Analyses

- To explore the relationship between LAA closure rate and other endpoints, effective LAA closure rate at 45 days and 6 months will be used to classified other endpoints.
- Descriptive analysis will be used for other analysis.
- To explore the relationship between all bleedings, the descriptive of TTR (Time in Therapeutic Range), and an appropriate correlation of bleeding rate and TTR are calculated.

5.9 Changes to Planned Analyses

Any changes to the planned statistical analyses will be documented in an amended Statistical Analysis Plan approved prior to the change. Changes from the planned statistical methods after completion of the statistical analysis 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 Software

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

7.2 Format of Output

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

7.3 Rules and Definitions for Calculated Variables

Analysis approach:

7.3.1 Body Mass Index is calculated for each visit.

$$BMI = \frac{Weight\,(Kg) \times 10000}{\left(Height\,(cm)\right)^2}$$

7.3.2 Stroke/TIA definitions

See protocol Sec.26

7.3.3 Classification of Bleeding events

See protocol Sec.26

7.3.4 Effective LAA closure rate

The subjects with LAA imaging at a given follow-up who have residual jet size <= 5 mm. The denominator is target samples at risk.

7.3.5 Time in Therapeutic range (TTR)

To explore appropriateness of Warfarin control and/or explore the relationship between bleedings, TTR is calculated by Rosendaal Method. (under linear assumption of INR change, then percentage of total of "within therapeutic range time "out of "Time between visits" is calculated.)
The normal ranges of INR are refer to 2.0-3.0 for age less than 70 years, and to 1.6-2.6 for age 70 years old or older in accordance with JCS guideline, and also for a subject 70 years old or older, a recommended range is to 2.0-2.6 in SALUTE protocol consideration.

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