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Statistical Analysis Plan Cover Page

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KAIZEN
KAIZEN: Safety and Effectiveness Evaluation of Peripheral Orbital Atherectomy
Study Document No: [redacted]
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Sponsor Abbott

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Statistical Analysis Plan (SAP)

KAIZEN: Safety and Effectiveness Evaluation of Peripheral Orbital Atherectomy

SAP-0005

Rev. E

22MAY2024

Sponsor:

Cardiovascular Systems, Inc.

[redacted]

CONFIDENTIAL INFORMATION

[redacted]

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1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of clinical study data collected under study protocol [redacted] KAIZEN: Safety and Effectiveness Evaluation of Peripheral Orbital Atherectomy. This SAP should be read in conjunction with the study protocol and Case Report Forms (CRF). This version of the plan has been developed with respect to KAIZEN study protocol revision G. Any changes to this protocol or the CRFs may necessitate updates to the SAP.

2 STUDY OBJECTIVE

The objective of this study is to collect safety and effectiveness data to support potential commercialization of the peripheral OAS device in Japan.

2.1 Primary Endpoint

The primary endpoint will demonstrate OAS safety and efficacy via Acute Device Success.

Acute Device Success is defined post-procedure as the percentage of subjects with:

- ≤50% residual stenosis post OAD + POBA [Angiographic Core Lab assessed] and,
- No OAS-related severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]

2.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

Reduction in lesion stenosis both post-OAD and post-OAD+POBA [Angiographic Core Lab assessed] (absolute mean percentage change defined as the difference between the pre-procedure percent stenosis and the percent stenosis measurement post-OAD and Post-OAD+POBA)

Acute technical success defined per the PARC definition of achievement of a final residual stenosis <30% for stented and <50% for non-stented subjects by angiography at the end of the procedure [Angiographic Core Lab Assessed] without severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]

DCB Device Success defined as the ability to achieve successful delivery and deployment of all DCBs to the target lesion as described per the Instructions for Use (IFU) within 3 minutes of insertion without removal and use of an additional device

Target vessel patency at 6 months defined as absence of clinically driven Target Lesion Revascularization (TLR) and ≤2.4 peak systolic velocity ratio (PSVR) as assessed by Duplex Ultrasound [Duplex Ultrasound Core Laboratory assessed]. Clinically-driven TLR is defined as repeat procedure performed for ≥50% stenosis confirmed by angiography within all or part of the target lesion after documentation of recurrent clinical symptoms of PAD following clinical trial treatment procedure [CEC adjudicated]

Rate of severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]

Acute procedure success defined as both acute technical success and absence of death, stroke, MI, acute onset of limb ischemia, index bypass graft or treated segment thrombosis, and/or need for urgent/emergent vascular surgery within 72 hours of the clinical trial treatment procedure [CEC adjudicated]

Major Adverse Event (MAE) rate at 30 days and 6 months [CEC adjudicated] defined as:

All-cause death through 30-days **or**,

Major amputation of the target limb **or**,

Clinically driven TLR.

Adverse Event rates at 30 days and 6 months [CEC adjudicated]

Distribution of Rutherford Classification (RC) compared to baseline at 30 days and 6 months

Change in Ankle Brachial Index (ABI) after clinical trial treatment compared to baseline

3 STUDY DESIGN

This prospective, single-arm, multi-center study is designed to evaluate the performance of the peripheral Orbital Atherectomy System (OAS) in the treatment of the adult Japanese population with a *de novo* symptomatic calcified occlusive atherosclerotic lesion in the superficial femoral artery (SFA) and/or popliteal (POP) arteries.

The KAIZEN study will use objective criteria to identify patients to be enrolled. The initial enrollment criteria will be assessed by the treating physician. An Independent Physician Review of objective computer-aided imaging will determine final eligibility into the Primary Analysis.

3.1 Enrollment

[redacted] sixty-two (62) subjects who meet the

enrollment criteria after an Independent Physician Review using objective computer-aided imaging are required for a proper assessment of the Primary Endpoint. The study may enroll at approximately twelve (12) sites in Japan.

The Independent Physician Reviewer will assess the angiographic and IVUS core laboratory results to identify patients who will be included in the primary analysis of KAIZEN.

For a full list of criteria for subject eligibility, refer to the KAIZEN study protocol.

Roll-in subjects are considered to be initial cases by the investigator enrolled to ensure proper device training, and procedural and data collection adherence. Each investigator must complete at least one (1) roll-in. Up to three (3) roll-in subjects per Investigator (Principal Investigator and/or Sub-Investigator) are permitted. Roll-in subjects will be consented and followed per protocol, and their data will be reported separately..

3.2 Duration

[redacted]. Subject participation in the study may last about 6 months.

3.3 Justification of Performance Goal

[redacted]

- [redacted]

[redacted] [redacted]

[redacted] [redacted]

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[redacted], a rate of Acute Device Success in the KAIZEN population can be assumed to be 70%. [redacted] a performance goal of 50% has been defined. In other words, at least half of the subjects, who would otherwise not receive successful therapy, will benefit from orbital atherectomy.

3.4 Study Hypothesis

The safety and efficacy of the OAS device will be evaluated by the rate of Acute Device Success (see **Section 2.1 Primary Endpoint**) against a pre-defined success criteria of 50% (see **Section 3.3 Justification of Performance Goal**). Comparisons will be made based on the following hypothesis test:

Ho: $\pi_s \leq 50\%$
Ha: $\pi_s > 50\%$

Where:
π_s = the probability of Acute Device Success

For the Acute Device Success endpoint, if the lower bound of the 95% confidence interval is >50%, the null hypothesis will be rejected and the endpoint will be considered met.

3.5 Justification of the Sample Size

A sample of 62 subjects meeting Independent Physician Review is required to reject the null hypothesis (**Table 2**). The sample size was determined based on the following:

- [redacted]
- Approximately 90% power
- A one-sided α-level of 0.025

Table 2 Sample Size Parameters and Justification

Endpoint	Anticipated Performance	Performance Goal	Power	Alpha (one-sided)	Sample Size
Acute Device Success	0.70	0.5	0.90	0.025	62

Subjects who are enrolled and treated may not meet Independent Physician Review. In order to ensure a primary analysis population of at least 62 subjects, sites will need to enroll and treat patients in excess of the required 62. [redacted] Roll-in subject data will be reported separately.

Table 3 Sample Size Parameters and Justification

Endpoint	N	[redacted]	[redacted]
Acute Device Success	62	[redacted]	[redacted]

In order to minimize bias, a maximum of 25% of subjects may be enrolled at a single site, not including roll-in subjects. There is no minimum number of subjects required to be enrolled at each site.

4 DATA STORAGE

4.1 Raw Data Storage

The site reported and core lab data collected in the KAIZEN study will be housed in a [redacted]. The Clinical Events Committee (CEC) adjudication data will be housed in the [redacted]

[redacted]. Data collection for study data is performed directly by the site(s), core lab(s), and CEC through electronic representations of Case Report Forms (CRF) into tables related to each individual CRF.

4.2 Raw Data Exports

For analysis purposes, raw data must be extracted from the study data into a format compatible with the analysis software. Exports may be created at any time and will coincide with study milestones (e.g., 6-month endpoints) at a minimum. Data exports can consist of raw data and study metadata required to understand the export (e.g., table names, field names, and coding formats).

4.3 Analysis Data Sets

The raw data exports will be imported into SAS or other applicable statistical software packages for analysis. Analysis data sets will be created from the raw data in order to standardize formatting and when appropriate, create derived variables for the purpose of analysis.

4.4 Analysis Output

[redacted]Clinical Study Report Procedure outlines the process for generating output from clinical studies. CSI procedures also permit the use of external vendor standard operating procedures (SOPs) when performing statistical programming and validation. The vendor will follow their SOPs when performing any analysis external to CSI.

5 DATA ANALYSIS SETS

The Primary Analysis will be based on the Modified Intent to Treat (mITT) analysis set, unless otherwise noted. Enrolled subjects are those who met all of the Inclusion and none of the Exclusion criteria, signed an Institutional Review Board (IRB) approved Informed Consent Form (ICF), and had the Peripheral OAS Guide Wire enter the body (subjects are considered enrolled even if the OAD does not enter the body). [redacted]. The following analysis sets are specified for KAIZEN.

5.1 Full Analysis Set (FAS)

[redacted]

5.2 Intent to Treat (ITT) Analysis Set

[redacted]

5.3 Modified Intent to Treat (mITT) Analysis Set

[redacted]

5.4 Per Protocol (PP) Analysis Set

[redacted]

5.5 Roll-in Analysis Set

All roll-in subjects will be analyzed as part of the roll-in analysis set. The roll-in analysis set will be analyzed separately from the enrolled population.

6 DATA ANALYSIS METHODOLOGY & CONVENTIONS

The primary analysis of the KAIZEN clinical study subjects will be based on locked clinical data and the mITT analysis set unless otherwise noted.

Statistical analyses will be performed using [redacted] In the event an analysis is required that is better suited for a statistical package other than [redacted] the other package may be used.

6.1 Timing of Analysis

Analyses of all primary and secondary endpoints will be performed after all FAS subjects have completed the 6-month follow-up assessment and all data have been entered and verified in the database. [redacted]

6.2 Analysis Conventions

This section details the general conventions to be used for data analysis. Departures from these general conventions may be given in the specific detailed sections of this SAP. When this occurs, the rules set forth in the specific section take precedence over the general conventions. Departures from the plans laid out in this document will be explained and justified with appropriate scientific, clinical and/or statistical justification.

- [redacted]

[redacted]

6.3 Managing Missing Data

Although every effort will be made during study conduct to minimize missing data, missing data are expected for both general data and calculation of endpoints. The following activities may be performed to manage missing data:

- The impact of missing data will be minimized in any time-to-event analysis by the use of Kaplan-Meier estimates where subjects are censored at the time of their last known event-free time point (typically the time of their last assessed visit or date of last reported adverse event, whichever is later)
- [redacted]

[redacted]

6.4 Analysis Windows

Assessments will be made at baseline (≤ 30 days prior to procedure), during the procedure, and post-procedure/discharge. Follow-up visits (analysis windows) are scheduled as office visits or phone call at the following time points post-procedure: 30-days (+14 days) and 6-months (+30 days). All windows will be calculated in days (i.e. 6-months will be calculated as 180 days).

6.5 Identifying Target Lesions

The protocol permits treatment of only one (1) target lesion in this study. The protocol specifies that the target lesion must be contained entirely within the protocol-defined target area (SFA and POP including P1 and P2). For the purposes of analysis, in addition to the target lesion any lesion treated with the OAD, will be considered a target lesion regardless of the protocol definition.

Endpoint data assessed on a subject-level basis requires that all success/failure criteria be assessed on all target lesions (i.e., all lesions will need to meet the specified endpoint criteria to be qualified as a success).

7 REQUIRED DATA ANALYSES

In cases where treatment of multiple target lesions has been performed, or treatment has been performed outside of the target area, the subject will be excluded from the PP analysis set on the basis of an inclusion or exclusion criteria deviation.

The following analyses will be performed on the populations indicated.

7.1 Subject Disposition

Subject disposition data will be presented on the FAS set unless otherwise noted. Tabulated data will be provided for:

The number of subjects enrolled at each site that fall into each analysis set (e.g., FAS, ITT, mITT)

Compliance to the follow-up visit schedule for subjects in the FAS and mITT analysis sets

The number and percentage of subjects by discontinuation reason

The listing of reasons will be provided for subjects excluded from the mITT and PP analysis set

7.2 Baseline Summary

Baseline characteristics such as subject demographics, clinical history, risk factors, and history of peripheral intervention will be summarized using descriptive statistics on the ITT and mITT analysis sets.

7.3 Investigator Reported Procedure, Lesion, and Treatment Summary

Site reported procedure, lesion, and treatment characteristics such as target limb characteristics, procedure time, fluoroscopy time, pre-OAD+POBA target lesion characteristics, and device usage data will be summarized using descriptive statistics on the ITT and mITT analysis sets.

7.4 Core Lab Assessed Data Summary

Core lab assessed IVUS and angiographic characteristics of the treated lesion at the time-points specified in the protocol (pre-procedure, post OAS+POBA, and post-procedure) such as quantitative vascular angiography (QVA) and

lesion morphology, will be summarized using descriptive statistics on the ITT and mITT analysis sets.

7.5 Primary Endpoint Analysis

Analysis of the primary endpoint of Acute Device Success will be assessed post-procedure and performed on the mITT analysis set. Acute Device Success is a composite endpoint comprised of:

the number of subjects with an Angiographic Core Lab assessed post OAD+POBA (and prior to the DCB) residual stenosis of ≤50% and,

no OAS-related severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure as adjudicated by the CEC.

A subject is considered a success if the OAD crosses the lesion and both criteria are met. Subjects with missing data (e.g. no post-POBA imaging available) will be excluded from the primary analysis. The rate of Acute Device Success and the corresponding lower 97.5% confidence bound will be presented. The lower confidence bound of the acute device success rate will be compared against the performance goal of 50%.

7.6 Primary Endpoint Sensitivity Analysis

Acute Device Success will also be analyzed using a number of sensitivity analyses.

7.6.1 General Sensitivity Analyses

The rate of Acute Device Success will be analyzed based on the ITT and PP analysis sets.

7.6.2 FAS Sensitivity Analysis

To examine the effect of subjects for whom the *CSI Peripheral Guide Wire* was inserted but the OAD was not inserted, an analysis will be performed including the enrolled subjects that were not treated with OAD as having failed the primary endpoint.

7.6.3 Missing Data Sensitivity Analysis

A tipping point analysis will be performed on the mITT analysis set to assess outcomes in cases where the core lab is unable to assess outcomes due to missing or non-readable images. [redacted]

7.7 Secondary Endpoint Analyses

The following analyses will be presented on the analysis sets indicated.

7.7.1 Reduction in Lesion Stenosis

Reduction in lesion stenosis presented as an absolute mean percentage change (defined as the difference between the pre-procedure measurement to both the value assessed post-OAD and the value post-OAD+POBA (and prior to DCB)) will be presented on a lesion level for the ITT and mITT analysis sets. Angiographic Core Lab values will be used in all cases.

7.7.2 Acute Technical Success

Analysis of Acute Technical Success will be assessed post-procedure and performed on a subject level for the ITT and mITT analysis sets. Acute Technical Success is a composite endpoint comprised of:

- the number of subjects that have an Angiographic Core Lab assessed post-procedure (after all treatment is complete) residual stenosis of <30% if a stent has been used for any reason, and <50% if the subject was not stented and,
- no severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure as adjudicated by the CEC

A subject is considered a success if both criteria are met.

7.7.3 DCB Device Success

DCB Device success will be assessed on the ITT and mITT analysis sets. DCB device success will be assessed on a subject level and is defined as successful delivery and deployment of all DCB to the target lesion. Successful delivery must be performed per the Instructions for Use (IFU); deployment of each DCB must occur within 3 minutes of insertion. Removal of a DCB and use of any non-DCB therapy prior to delivery of a subsequent DCB or use of any adjunctive therapy (including stents) after DCB will be counted as a failure. DCB Device success is based on investigator reported data.

7.7.4 Target Vessel Patency

The rate of Target Vessel Patency will be presented on a lesion level for ITT and mITT analysis sets at the time-point of 6 months on subjects with a 6-month visit. Target Vessel Patency is a binary composite endpoint comprised of:

- CEC adjudicated absence of clinically driven repeat procedure performed for ≥50% stenosis confirmed by angiography within all or part of the target lesion after documentation of recurrent clinical symptoms of PAD following clinical trial treatment procedure (i.e. clinically-driven TLR) occurring at any time-point on, or prior to the 6-month visit date and,

- a Duplex Ultrasound Core Lab assessed PSVR value of ≤2.4 (or equivalent by visual assessment if the lesion is non-patent and the PSVR cannot be numerically calculated).

The vessel is considered patent if both criteria are met at the time of assessment.

7.7.5 Severe Angiographic Complications

The subject-level rate of Severe Angiographic Complications will be assessed post-procedure and presented on the mITT and FAS from CEC adjudicated presence of severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure.

7.7.6 Acute Procedure Success

Acute Procedure Success will be assessed 72 hours after the index procedure and presented on the mITT and FAS. Acute Procedure Success is defined as Acute Technical Success and absence of: death by any cause, stroke, MI, acute onset of limb ischemia, index bypass graft or segment thrombosis, and/or need for urgent/emergent vascular surgery within 72 hours of the clinical trial treatment as adjudicated by the CEC.

7.7.7 Major Adverse Event (MAE) Rate

The MAE Rate will be assessed on a subject level for the mITT and FAS at the time-points of 30 days and 6 months as a time-to-event analysis. The 6-month rates will be evaluated at 210 days (180 days + 30-day visit window). The MAE rate is a composite endpoint comprised of CEC adjudicated:

- death through 30-days (note: subjects with a death after 30-days will be considered censored on the date of death) or,
- major amputation of the target limb (note: major amputation is defined per the protocol as any amputation at or above the ankle joint) or,
- clinically driven TLR (defined as a clinically driven repeat procedure performed for ≥50% stenosis confirmed by angiography within all or part of the target lesion following index procedure)

A subject is considered to have an MAE if any of the above criteria are met. The component rates of MAE may be presented.

7.7.8 Adverse Event (AE) Rates

Adverse event rates will be assessed on a subject level for the mITT and FAS. All site reported and CEC adjudicated reportable adverse events specified in the protocol will be included in the analysis. Adverse events

are collected starting at enrollment through subject exit from the study. Adjudicated AEs will be summarized by AE term and overall for number and percent of subjects experiencing each event, and number of events.

Adverse events summaries will be provided for the time-points of enrollment to 30 days, and 31 days to study exit in the following groups:

- Serious Adverse Event (SAE): Any AE that the CEC has determined meets the protocol definition of serious
- Adverse Device Effect (ADE): Any AE the CEC has determined meets the protocol definition of related to the use of the OAS
- Serious Adverse Device Effect (SADE): Any ADE that the CEC has the protocol definition of serious
- Unanticipated Serious Adverse Device Effect (USADE): Any SAE that the CEC has determined that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

Any events for which the determination of seriousness and/or relatedness to the device cannot be determined by the CEC will count as serious and/or related for the purposes of this analysis.

In addition, a subject data listing of all reportable AEs will be presented from the time of enrollment to study completion and will include the following: adverse event term, AE onset date, days to event, seriousness, relationship to OAS and procedure, outcome, and date resolved (if applicable).

7.7.9 Distribution of Rutherford classification at 30 days and 6 months

The distribution of Rutherford Classification (RC) will be assessed on the ITT and mITT analysis sets at baseline, 30 days, and 6 months. RC will be summarized by visit using the investigator reported values. The change from baseline, calculated as the follow-up RC value minus the baseline RC value, will be summarized. A negative change indicates improvement.

7.7.10 Change in Ankle Brachial Index after clinical trial treatment compared to baseline

The change in ABI on the target limb will be assessed on the ITT and mITT analysis sets. The change in ABI after clinical trial treatment compared to the baseline value will be summarized using the investigator reported values. The change will be measured as post-procedure ABI minus baseline ABI. Subjects with a baseline or post-procedure non-compressible vessel (including ABI > 1.4) will be excluded from the calculation as non-compressible vessels cannot be meaningfully interpreted as a continuous variable; these subjects will be presented categorically.

7.8 Covariate Analyses

An analysis will be performed to assess covariates that may introduce a confounding effect for the primary endpoint of Acute Device Success. The analysis will be performed using logistic regression on the mITT population. Univariable analysis will be performed on the following covariates:

- Gender
- Moderate or severe calcium per PARC definition (per IPR assessment)
- Lesion length
- Renal Disease

[redacted]

7.9 Pooling Data Across Investigational Sites

The appropriateness of pooling data across sites will be assessed on the mITT analysis set. The primary endpoint will be presented separately for each investigational site using descriptive statistics. [redacted]

[redacted]

8 OTHER ANALYSES

No further analyses are planned outside those outlined in **Section** Error! Reference source not found. Error! Reference source not found.. Unless specifically requested, any ad hoc analyses, including those requested by the Pharmaceutical and Medical Devices Agency (PMDA), will follow the guidelines outlined in this document. Deviations from the SAP will be outlined in a dedicated section of any report.

9 VERSION CONTROL

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		[redacted]

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