Abbott	Clinical Investigation Plan Cover Page

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KAIZEN
KAIZEN: Safety and Effectiveness Evaluation of Peripheral Orbital Atherectomy
Study Document No: [redacted]
Version G
Date: 17-APR-2023

Sponsor Abbott

[redacted]

[redacted] [redacted]

[redacted]

Clinical Protocol

KAIZEN: Safety and Effectiveness Evaluation of Peripheral Orbital Atherectomy

Protocol [redacted]

Rev. G

17Apr2023

Sponsored By:

Cardiovascular Systems, Inc.

[redacted]

In-Country Clinical Caretaker:

[redacted]

Notwithstanding the contents of this protocol, this clinical study will be conducted in accordance with local regulations in Japan.

CONFIDENTIAL INFORMATION

[redacted]

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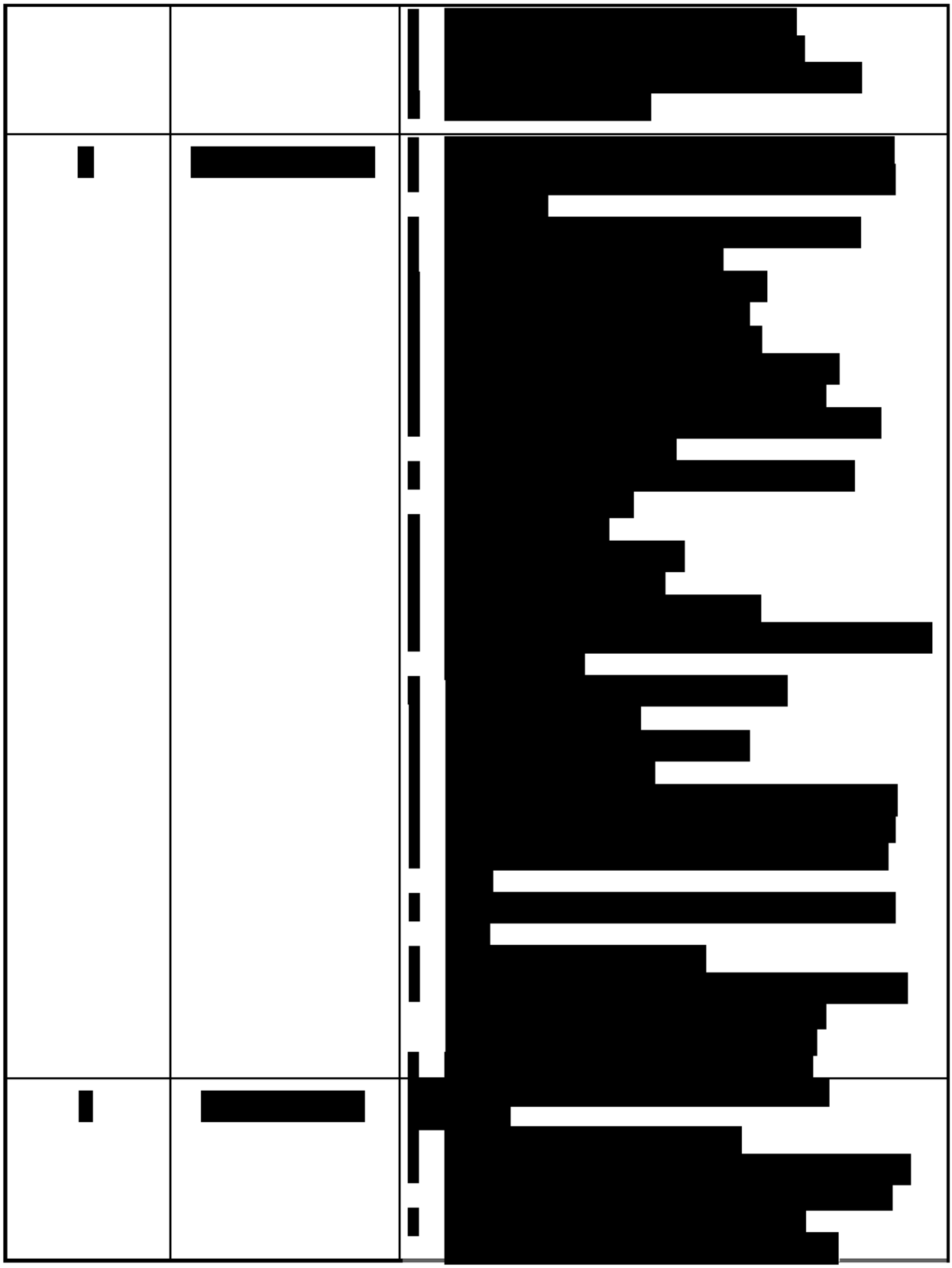
CONTACT INFORMATION

Title	Contact Information
Study Sponsor/Project Management	[redacted]
In-Country Clinical Caretaker (Japan)	
Principal Investigator for the Study	[redacted]
Independent Physician Reviewer	[redacted]
Core Lab – Angiography, IVUS, Duplex Ultrasound	[redacted]
Monitor	ICON JAPAN K.K. [redacted]
Clinical Events Committee	[redacted]
Data Monitoring Committee	[redacted]

1. WORKING VERSION HISTORY

Version	Version Date	Description
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]



2. STUDY SUMMARY

Protocol Section	Description
Title	KAIZEN: Safety and Effectiveness Evaluation of Peripheral Orbital Atherectomy
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.
Study Population	Patients with a *de novo* calcified occlusive atherosclerotic lesion in the superficial femoral artery (SFA) and/or popliteal (POP) artery, with symptoms classified as Rutherford classification (RC) 2-4. Patients must also be acceptable candidates for Percutaneous Transluminal Angioplasty (PTA).
Objective	To collect safety and effectiveness data to support potential commercialization of the peripheral OAS device in Japan.
Device Name	CSI Peripheral Orbital Atherectomy System (OAS) – 1.25, 1.50, 2.00 Solid Crown.
Number of Sites	Approximately twelve (12) active sites in Japan.
Study Sample Size	A sample of 62 subjects meeting Independent Physician Review is required to reject the null hypothesis. [redacted]: [redacted] This study includes an Independent Physician Reviewer who will verify the treating physician's assessment of eligibility criteria. [redacted] [redacted] Each investigator will also be permitted a maximum of three (3) roll-in subjects with an anticipated roll-in rate of 1-2 subjects per investigator. In order to minimize bias, a maximum of 25% of subjects may be enrolled at a single site, not including roll-in subjects.

Endpoint	[redacted]	[redacted]	[redacted]	[redacted]	**Sample Size**
Acute Device Success	[redacted]	[redacted]	[redacted]	[redacted]	62

Protocol Section	Description
Primary Endpoint	Acute Device Success defined post-procedure as the percentage of subjects with: a) ≤50% residual stenosis post Orbital Atherectomy Device (OAD) + Plain Old Balloon Angioplasty (POBA) [Angiographic Core Lab assessed] and, b) No OAS-related severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]
Secondary Endpoints	1. Reduction in lesion stenosis post-OAD and post-OAD+POBA [Angiographic Core Lab assessed] 2. 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] 3. DCB Device Success defined as the ability to achieve successful delivery and deployment of all DCB 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. 4. 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 Lab 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] 5. Rate of severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated] 6. Acute procedure success defined as both acute technical success and absence of death, stroke, myocardial infarction (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] 7. Major Adverse Event Rate at 30 days and 6 months [CEC adjudicated] defined as: a) All-cause death through 30-days or b) Major amputation of the target limb or c) Clinically-driven TLR 8. Adverse Event rates at 30 days and 6 months [CEC adjudicated] 9. Distribution of Rutherford Classification compared to baseline at 30 days and 6 months 10. Change in Ankle Brachial Index (ABI) after clinical trial treatment compared to baseline
Follow-Up Visits	All Enrolled subjects will have a 30-Day and 6-Month in-hospital follow-up visit or telephone follow-up assessment for adverse events. All Enrolled and Treated subjects will have a 30-Day in-hospital follow-up visit or telephone follow-up assessment. The 6-month visit will be an in-hospital follow-up visit.
Duration of Study	The duration of this study is expected to be approximately two (2) years.

Protocol Section	Description
General Inclusion	1. Subject is 18 years of age or older 2. Subject has signed the approved KAIZEN study Informed Consent Form (ICF) prior to any study-related procedures 3. Subject has chronic, symptomatic lower limb ischemia defined as Rutherford classification (RC) 2-4 4. Subject has a clinical indication for percutaneous transluminal angioplasty (PTA) intervention in the native SFA and/or POP (P1 and/or P2) artery via femoral access
General Exclusion	5. Subject is female who is pregnant and/or breastfeeding 6. Subject is currently participating in another investigational clinical study that has not completed the primary endpoint at the time of enrollment or that clinically interferes with the current study endpoints 7. Subject is unwilling to follow the Investigator's instructions or follow-up requirements 8. Subject has had any non-diagnostic peripheral vascular intervention that was unsuccessful or had complications within 30 days before clinical trial treatment, per the following definition: a) >50% residual stenosis and/or b) Presence of angiographically assessed dissection (type D-F), perforation, distal embolization, thrombus and/or slow flow/no reflow 9. Subject has had or requires any non-diagnostic coronary intervention within 30 days before clinical trial treatment 10. Subject requires any planned non-diagnostic vascular (coronary or peripheral) intervention(s) within 30 days after- clinical trial treatment 11. Subject has any planned procedures or other medical conditions which, in the Investigator's opinion, may interfere with the study result and/or subject's optimal participation in the study 12. Subject has had a prior major amputation within one year of the clinical trial treatment procedure on either limb 13. Subject has a planned major amputation on either limb 14. Subject has life expectancy of ≤6 months 15. Subject has history of coagulopathy or hypercoagulable bleeding disorder 16. Subject has history of MI, or stroke/cerebrovascular accident (CVA) within 6-months prior to the clinical trial treatment 17. Subject has unstable angina pectoris at the time of the clinical trial treatment 18. Subject has untreatable hemorrhagic disease or platelet count <80,000mm^3 or >600,000mm^3 at baseline assessment 19. Subject has evidence of active infection on the day of clinical trial treatment requiring oral or intravenous antibiotics

<table>
<tr><th>Protocol Section</th><th>Description</th></tr>
<tr><td></td><td>20. Subject has known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated or cannot be exposed to the radiation required per the KAIZEN protocol
21. Subject has known hypersensitivity/allergy to the investigational atherectomy system or protocol-related therapies (e.g., CSI OAS lubricant, soybean oil, egg yolk phospholipids, glycerin, nitinol, stainless steel, other stent materials, paclitaxel, anticoagulant, or thrombolytic medications)
22. Subject has known contraindication to antiplatelet therapy
23. Subject has serum creatinine > 2.5 mg/dL, unless on dialysis</td></tr>
<tr><td>Clinical Trial Treatment Inclusion</td><td>24. De novo target lesion in the native SFA and/or POP (P1 and/or P2) artery
25. All guidewires cross the Target Lesion within the true lumen without a sub-intimal course
26. Target lesion with ≥70% stenosis [confirmed by visual estimate via angiography]
27. Target reference vessel diameter (RVD) ≥3.0 mm and ≤6.0 mm [confirmed by visual estimate via angiography]
28. Target lesion length ≤150 mm [confirmed by visual estimate via angiography]
29. Subject has at least one patent tibial vessel (anterior tibial artery, posterior tibial artery, or peroneal artery) on the target leg, defined as having both:
a) Blood flow to the foot, and
b) No stenosis >50%
30. Target lesion has visual evidence of calcification based on the KAIZEN calcification definition:
<table>
<tr><th>IVUS Calcium Assessment</th><th>Angiographic Calcium Assessment</th></tr>
<tr><td>a) ≥ 270° of calcification</td><td></td></tr>
<tr><td>b) ≥180° to 269° calcification</td><td>i) ≥ ½ of target lesion length calcified OR
ii) > 50mm of calcium</td></tr>
<tr><td>c) IVUS cannot cross lesion after one attempted pass</td><td>i) Bilateral calcification AND ≥ ½ of target lesion length calcified OR
ii) Bilateral calcification AND >50mm of calcium</td></tr>
</table></td></tr>
<tr><td>Clinical Trial Treatment Exclusion</td><td>31. Subject has had any Inflow treatment (ipsilateral iliac and/or common femoral artery) that was unsuccessful or had complications prior to OAS guidewire insertion per the following definition:
a. >50% residual stenosis and/or
b. Presence of angiographically assessed dissection (type D-F), perforation, distal embolization, thrombus and/or slow flow/no reflow
32. Target lesion is a chronic total occlusion (CTO) [confirmed by visual estimate via angiography]
33. Subject has presence of any other hemodynamically significant lesions or asymptomatic lesions in the target limb requiring a planned surgical intervention or endovascular procedure 30-days after clinical trial treatment</td></tr>
</table>

Protocol Section	Description
	34. Presence of aneurysm in the target vessel 35. Acute ischemia and/or acute thrombosis of the SFA and/or POP (P1 and/or P2) artery 36. Angiographic evidence of perforation prior to insertion of the CSI Peripheral OAS Guide Wire 37. Angiographic evidence of severe (type D-F) dissection prior to insertion of the CSI Peripheral OAS Guide Wire 38. Planned use of atherectomy (other than CSI Peripheral OAS), laser, other debulking devices, CTO devices, cutting balloons, scoring balloons, specialty balloons or similar devices in the target limb

3. ABBREVIATIONS

ABI	Ankle Brachial Index
ADE	Adverse Device Effect
AE	Adverse Event
ATK	Above the Knee
BTK	Below the Knee
BA	Balloon Angioplasty
CAPA	Corrective Action Preventive Action
CEC	Clinical Events Committee
CLI	Critical Limb Ischemia
CRF	Case Report Form
CRO	Clinical Research Organization
CSI	Cardiovascular Systems, Inc.
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
CVA	Cerebrovascular Accident
DCB	Drug Coated Balloon
DMC	Data Monitoring Committee
DS	Diameter Stenosis
DUS	Duplex Ultrasound
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

FAS	Full Analysis Set
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ID	Identity
IFU	Instructions for Use
IRB	Institutional Review Board
ISR	In-stent Restenosis
ITT	Intent to Treat
IV	Intravenous
IVUS	Intravascular Ultrasound
MAE	Major Adverse Event
MI	Myocardial Infarction
mITT	Modified Intent to Treat
OAD	Orbital Atherectomy Device
OAS	Orbital Atherectomy System
OA	Orbital Atherectomy
PAD	Peripheral Artery Disease
PACSS	Peripheral Artery Calcification Scoring System
PARC	Peripheral Academic Research Consortium
PI	Principal Investigator
POBA	Plain Old Balloon Angioplasty
POP	Popliteal
PP	Per Protocol
PTA	Percutaneous Transluminal Angioplasty
QVA	Quantitative Vascular Analysis
RBP	Rated Burst Pressure
RC	Rutherford Classification
RCT	Randomized Controlled Trial
RMA	Returned Materials Authorization
RVD	Reference Vessel Diameter

SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFA	Superficial Femoral Artery
SOC	Standard of Care
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
USADE	Unanticipated Serious Adverse Device Effect

4. DEFINITIONS

Term	Definition
Acute Device Success	The percentage of patients with the following, post-procedure: a) ≤50% residual stenosis post OAD + POBA [Angiographic Core Lab assessed] and, b) No OAS-related severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]
Acute Procedural Success	Both acute technical success and absence of death, stroke, myocardial infarction (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 [CEC adjudicated]
Acute Technical success[1]	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]
Adverse Device Effect (ADE)	An adverse event-related to the use of an investigational medical device (per ISO14155:2020) **Note 1:** This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment,

Term	Definition
	implantation, installation, or operation, or any malfunction of the investigational medical device. **Note 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **Note 3:** This includes 'comparator' if the comparator is a medical device.
Adverse Event	Any disease or injury, or its clinical signs occurring in a subject who has been treated with an investigational device or post-marketing study device.
Before Clinical Trial Treatment	Begins when procedural visit window begins. Ends when OAS Guide Wire enters the body.
Clinically-driven target lesion revascularization (TLR)	A 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 [CEC adjudicated]
Clinically-driven target vessel revascularization (TVR)	A repeat procedure (percutaneous or surgical) performed for ≥ 50% DS confirmed by angiography within all or part of the target vessel after documentation of recurrent clinical symptoms of PAD following the initial procedure.
Clinical Trial Treatment	Begins when OAS Guide Wire enters the body. Ends when the patient exits the Cath Lab.
De Novo Lesion	A native lesion not previously treated
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator. (per ISO 14155:2020)
Dissection classification	Type 0: None

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>Type A: Small radiolucent area within lumen of the vessel
Type B: Linear, non-persisting extravasation of contrast
Type C: Extraluminal, persisting extravasation of contrast
Type D: Spiral shaped filling defect
Type E: Persistent lumen defect with delayed ante/retrograde flow
Type F: Filling defect accompanied by total arterial occlusion</td></tr>
<tr><td>Enrolled Subjects</td><td>Subjects who met all of the Inclusion and none of the Exclusion criteria, signed an Institutional Review Board (IRB) approved ICF, and had the CSI Peripheral OAS Guide Wire enter the body.</td></tr>
<tr><td>Enrolled and Treated Subjects</td><td>An Enrolled subject and the OAD enters the body.</td></tr>
<tr><td>Inflow</td><td>Arterial flow proximal to the protocol defined target area.
For this study, the iliac and common femoral are considered in-flow to the target area.</td></tr>
<tr><td>KAIZEN Calcification</td><td>
<table>
<tr><th>IVUS Calcium Assessment</th><th>Angiographic Calcium Assessment</th><th>Eligibility</th></tr>
<tr><td>≥ 270° of calcification</td><td></td><td>Eligible</td></tr>
<tr><td>≥180° to 269° of calcification</td><td>• ≥ ½ of target lesion length calcified OR
• > 50mm of calcium</td><td>Eligible</td></tr>
<tr><td>IVUS cannot cross lesion after one attempted pass</td><td>• Bilateral calcification AND ≥ ½ of target lesion length calcified OR
• Bilateral calcification AND >50mm of calcium</td><td>Eligible</td></tr>
<tr><td><180° of calcification</td><td></td><td>Not Eligible</td></tr>
</table>
Definitions for calcium based on PARC Severe[1]; PACSS Grade 4[2]
</td></tr>
<tr><td>Major adverse events (MAEs)</td><td>All-cause death through 30-days of the clinical trial treatment, major amputation of the target limb, clinically-driven TLR.</td></tr>
<tr><td>Major amputation</td><td>Amputation of the ankle joint and/or above.</td></tr>
<tr><td>Malfunction</td><td>Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB (per ISO 14155:2020)</td></tr>
</table>

Term	Definition
Maximum balloon inflation pressure	Balloon inflation pressure used during pre-dilatation to achieve full balloon expansion with no visible waist.
Myocardial Infarction (MI) (Fourth Universal definition)	Type 1: Detection of a rise and/or fall of cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: • Symptoms of acute myocardial ischemia; • New ischemic electrocardiographic (ECG) changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; • Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy. Type 2: Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: • Symptoms of acute myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology. Type 3: Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increase in cardiac biomarkers can be identified, or MI is detected by autopsy examination. Type 4a: Percutaneous coronary intervention-related MI is defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required: • New ischemic ECG changes;

Term	Definition
	• Development of new pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; • Angiographic findings consistent with a procedural flow-limiting complications such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization. Type 4b: MI related to stent/scaffold thrombosis documented by angiography or autopsy. Type 4c: MI due to restenosis (≥50%) after an initially successful PCI defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL. Type 5: MI related to coronary artery bypass grafting (CABG) is arbitrarily defined by elevation of cardiac biomarker values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. In addition, one of the following elements is required: • Development of new pathological Q waves; • Angiographic documented new graft or new native coronary artery occlusion, • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Outflow	Arterial flow distal to the protocol defined target area extending through the foot.
PACSS degree of lesion calcification[2]	**Grade 0:** No visible calcium at the target lesion site **Grade 1:** unilateral calcification <5cm **Grade 2:** unilateral calcification ≥5cm **Grade 3**: bilateral calcification <5cm **Grade 4:** bilateral calcification ≥5cm
PARC degree of lesion calcification[1]	**Focal:** <180° (1 side of vessel) and less than one-half of the total lesion length **Mild:** <180° and greater than one-half of the total lesion length

Term	Definition
	Moderate: ≥180° (both sides of vessel at same location) and less than one half of the total lesion length **Severe:** >180° (both sides of the vessel at the same location) and greater than one-half of the total lesion length
Popliteal artery[1]	**P1 segment:** from Hunter's canal to proximal edge of patella **P2 segment:** from the proximal part of patella to center of knee joint **P3 segment:** from the center of knee joint space to origin of anterior tibial artery
Roll-in	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
Rutherford classification[3]	**Class 0**: Asymptomatic; no hemodynamically significant occlusive disease. **Class 1**: Mild Claudication; there is no limitation with ordinary physical activities (e.g., walking several blocks, climbing stairs). Limiting symptoms may occur with marked exertion (e.g., strenuous, rapid or prolonged exertion at work or recreation). **Class 2**: Moderate Claudication; there is a slight limitation of ordinary physical activities (e.g., walking uphill, or more than two level blocks, or climbing stairs rapidly). Subject is comfortable at rest. **Class 3**: Severe Claudication; there is marked limitation of ordinary physical activities (e.g., walking 1-2 level blocks or climbing one flight of stairs). Subject is comfortable at rest. **Class 4**: Ischemic rest pain. **Class 5**: Minor tissue loss, non-healing ulcer, focal gangrene with diffuse pedal ischemia. **Class 6**: Major tissue loss extending above transmetatarsal level; functional foot no longer salvageable.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (per ISO14155:2020).

Term	Definition
Serious Adverse Event	An adverse event that (per ISO14155:2020): a) Led to death, b) Led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: o A life-threatening illness or injury, or o A permanent impairment of a body structure or a body function including chronic diseases, or o In-patient or prolonged hospitalization, or o Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) 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 CIP, without serious deterioration in health, is not considered a serious adverse event.*
Severe angiographic complications	Severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]
Stroke	An acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Classification: a) **Ischemic Stroke:** An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke. b) **Hemorrhagic Stroke:** An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. c) **Undetermined Stroke:** An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but

Term	Definition
	with insufficient information to allow categorization as either ischemic or hemorrhagic.
Target area	Area between the SFA and POP (including P1 & P2)
Target lesion	The stenotic segment treated with the study devices. Only one (1) target lesion is allowed in this study. ***Note:*** *A target lesion treated as part of the study must be contained entirely within the protocol-defined target area. Target lesions are generally considered to be separate lesions when stenotic segments are ≥ 3 cm apart.*
Target lesion revascularization (TLR)	A repeat procedure occurring after the clinical trial treatment (percutaneous or surgical) that includes all or part of a target lesion treated during the clinical trial treatment.
Target vessel revascularization (TVR)	A repeat procedure occurring after the clinical trial treatment (percutaneous or surgical) that includes all or part of a target vessel treated during the clinical trial treatment.
Target vessel	A target vessel is any vessel that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire length of native vessel upstream and downstream from the target lesion, including side branches. For the arteries of the leg, the vasculature is divided into 3 vessel "levels:" aorto-iliac, femoral-popliteal, and tibial-crural.
Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment (per ISO14155:2020). ***Note***: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Unstable Angina Pectoris	1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring a) At rest, OR b) In an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

Term	Definition
	AND 2. At least one of the following: a) resting ECG evidence of acute myocardial ischemia; b) exercise or pharmacological stress testing evidence of inducible myocardial ischemia that is believed to be responsible for the ischemic symptoms/signs; c) angiographic evidence of new or worsening obstructive coronary artery disease and/or intracoronary thrombus that is believed to be responsible for the ischemic symptoms/signs; OR d) need for coronary revascularization of the presumed culprit lesion(s), as defined in c; **AND** 3. Negative cardiac biomarkers and no evidence of acute myocardial infarction (MI)
Use Error	User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Note 1 to entry: Use error includes the inability of the user to complete a task. Note 2 to entry: Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Note 3 to entry: Users might be aware or unaware that a use error has occurred. Note 4 to entry: An unexpected physiological response of the patient is not by itself considered a use error. Note 5 to entry: A malfunction of a medical device that causes an unexpected result is not considered a use error. (Per: ISO 14155:2020)

5. INTRODUCTION

In 2015, an estimated 8.1 to 10.3 million Japanese had peripheral artery disease (PAD).[4] The prevalence of this disease, often referred to as arteriosclerosis obliterans (ASO), is expected to increase up to 11.9 million by 2030.[4] PAD of the lower extremities is caused by atherosclerosis and the prevalence of atherosclerotic risk factors, such as advanced age, diabetes, kidney disease, and smoking which are on the rise in Japan.[4,5] Compared to non-PAD patients, within the first year of diagnosis PAD patients have a significantly higher risk of adverse cardiovascular events, including ischemic stroke and myocardial infarction, and significantly greater health care utilization and total annual healthcare costs.[6] Thus, PAD poses a significant clinical and economic burden in Japan.

Revascularization is a crucial component for the treatment of patients with PAD, including those with claudication and the more advanced form of the disease, critical limb ischemia (CLI).[7] Endovascular intervention may reduce limb pain, improve quality of life, and prolong walking distance for patients with claudication and has been associated with lower amputation rates in patients with CLI.[8] However, the disease severity and anatomical location strongly influence the technical challenges and expected outcomes of the treatment.[7] In particular, calcification represents a significant challenge to current endovascular device strategies and is associated with increased procedure-related adverse events, as well as poor long-term clinical outcomes[2,9]. In the CODE Study, severe calcification in a ≥180° arc prevented successful dilation of superficial femoral artery (SFA) lesions with either plain balloon angioplasty or a nitinol stent.[10] Balloon angioplasty (BA) of calcified lesions is limited by acute vessel recoil, frequent flow-limiting dissections, high rate of perforation, and poor primary and secondary patency rates.[2,11,12] For example, in a small study of 67 patients with 62% of them having severely calcified femoropopliteal lesions, the aggressive predilation of the calcified plaque led to a 59% perforation rate.[12] Furthermore, 40-50% of the BA cases require bailout-stenting; in the Resilient and Zilver trials, 48.3% and 57% of the lesions were moderately or severely calcified in the BA arm, respectively; of the patients in the BA arm, 40.3% and 50.4% required bail-out stenting.[13,14] It is known that calcification increases the risk of stent fractures [*with consecutive thrombosis and vessel occlusion*[15]], which is associated with a higher in-stent restenosis (ISR) and reocclusion rate.[16] In addition, the presence of rigid calcified plaques may result in incomplete and/or eccentric stent expansion and significant residual stenosis, which again increases the risk of in-stent restenosis and thrombosis.[2,15,17] Drug-coated balloons (DCB) could be the solution to stent-related adverse events in calcified lesions [*leaving nothing behind*], as well as in reducing the high restenosis rates after BA [*the antiproliferative drug reduces neointimal hyperplasia, resulting in a lower incidence of restenosis and target lesion revascularization*[18]]. However, Fanelli et al. found that calcium represents a barrier to optimal drug absorption.[19] Circumferential distribution seems to be the most influencing factor with the lowest primary patency rate and higher late lumen loss in 360° calcium presence. Based on the above, a new endovascular technique [*vessel preparation prior to DCB angioplasty*], such as CSI's OAS, is available for the treatment of severely calcified lesions. The findings of a recently published study suggest, that vessel preparation with orbital atherectomy prior DCB angioplasty may enhance the effect of DCBs in calcified lesions, reducing the need for stents and maintaining acceptable patency rates.[20]

Calcific plaque is common in lower extremity arteries; in a recent analysis of 394 Japanese PAD patients who underwent endovascular therapy for SFA lesions, calcification was present in 46% of the lesions.[9]

In the US, CSI currently has approval for its Peripheral OAS (Class II). The prospective multicenter Clinical Study of the OAS for the Treatment of Peripheral Vascular Stenosis (OASIS) was conducted to evaluate the safety and effectiveness of the orbital atherectomy (OA) in patients with symptomatic PAD. One hundred twenty-four (124) patients from seventeen (17) contributing centers were enrolled, and two hundred and one (201) lesions were treated with OA. For additional information about the OASIS study and other CSI peripheral studies, please refer to the study Investigator's Brochure (IB).

6. DEVICE DESCRIPTION

6.1 Device Name and Indications for Use

The CSI Peripheral Orbital Atherectomy System (OAS) is a percutaneous orbital atherectomy system indicated for use as therapy in patients with calcified occlusive atherosclerotic disease in peripheral arteries and who are acceptable candidates for percutaneous transluminal atherectomy.

6.2 Device History and Description

The orbital atherectomy device (OAD) consists of a diamond-coated abrasive head (referred to as a "crown") mounted on the driveshaft that is designed to track and spin over the CSI Peripheral OAS Guide Wire, which can be independently advanced and steered. The OAD ablates occlusive material (i.e., peripheral plaque) and improves luminal patency. The diameter of the crown's orbit is a function of crown mass and rotational speed. During rotation, centrifugal forces press the crown laterally against the peripheral plaque, reducing a thin layer of that plaque on the vessel wall.

The first-generation model of the CSI Peripheral OAS received CE Mark in February 2007 and US FDA 510(k) clearance in August 2007 for use as therapy in patients with occlusive atherosclerotic disease in peripheral arteries and who are acceptable candidates for percutaneous transluminal atherectomy. The Peripheral OAS is commercially available in the US, Germany, Austria, France, Malaysia, Singapore, and United Arab Emirates.

The current generation model of the CSI Peripheral OAS intended to be used in KAIZEN received US FDA clearance in July 2019. The components of the OAS are described below.

- CSI Peripheral Orbital Atherectomy Device (OAD) is a hand-held component of the OAS that provides the physician with independent control of the OAS. The OAD is a single use over-the-wire device consisting of a handle, and a saline line (**Table 1**).
    - The OAD handle includes a sheath-covered drive shaft and a diamond-coated crown. The OAD crown can pass in tight lesions, smaller than the crown size, due to its angular front sanding edge and the OAD's mechanism of action. The handle

includes control buttons for operating the OAD and contains the motor and electronics that power the rotation of the drive shaft. The crown is a diamond-coated, abrasive surface mounted on the driveshaft that is designed to track and spin over the guide wire and remove or reduce the occlusive tissue into microscopic particles (**Table 2**).

- CSI OAS Pump (OAS Pump model number SIP-3000) provides the saline/lubricant pumping mechanism and power to the device. The small, reusable, and portable OAS Pump attaches to a standard five-wheel rolling intravenous (IV) pole and plugs into a wall power outlet. The OAS Pump includes a built-in audible 25 second spin time notification, system power and priming buttons, and status indicators.
    - ***Note:*** *OAS Pump was approved for use with CSI's Coronary OAS in Japan in June 2018.*
- CSI OAS Peripheral Guide Wires are single-use, smooth, stainless steel wires, with a silicone coating, and a radiopaque distal spring tip (**Table 3**). The OAS Peripheral Guide Wire allows for proper positioning of the OAD crown within peripheral arteries and provides a center of rotation for the OAD drive shaft. The OAS Peripheral Guide Wires are provided sterile.
- CSI OAS Lubricant (model number VPR-SLD2) is designed to reduce the friction between the flexible drive shaft of the CSI OAD and CSI Peripheral Guide Wire. The CSI OAS Lubricant is an emulsion composed of soybean oil, egg yolk phospholipids, glycerin, and water for injection. An addition of sodium hydroxide adjusts the pH resulting in a final pH of 8.0 with a pH range of 6.0 to 8.9. CSI OAS Lubricant is single use and provided sterile.
    - ***Note:*** *CSI OAS Lubricant was approved for use with CSI's Coronary OAS in Japan in March 2017.*

Table 1: CSI Peripheral OAD Information

Parameter	Value
Electrical cable length: OAD to OAS pump	3.4 m approximately (11 ft)
Electrical Connector type (OAD power)	Type CF applied Part –DC barrel (48 V DC)
Fluid connector type	Polycarbonate Luer fitting
Saline line tubing length (from pump to OAD port)	3.2 m approximately (10.5 ft) minimum
Visual alerts	Speed indicators
Sterilization	Ethylene oxide (EtO) cycle
Storage conditions	Room temperature in a clean environment.
Operating conditions	Typical operating room/catheterization laboratory environment (10-30° C)
Operating life	8 minutes of total therapy time
Water Ingress Protection	IPX1: Protection against water ingress
Approximate saline flow rate for 145 cm (4 Fr) OAD	6 mL/min to 16 mL/min
Approximate saline flow rate for 145 cm (5 Fr and 6 Fr) OAD	5 mL/min to 30 mL/min

Table 2: OAD Crown Information

Model Number	Crown Diameter (mm)	Crown Type	Shaft Length (cm)	Nose Length (mm)**	OAD Maximum Outer Diameter (mm)	Recommended Introducer Sheath Internal Diameter, Fr	Rotational Speeds (rpm) +/- 10%
DBP-125SOLID145	1.25	Solid	145	7	1.32	4	60,000 90,000 120,000
DBP-150SOLID145	1.50	Solid	145	10	1.60	5	60,000 90,000 120,000
DBP-200SOLID145	2.00	Solid	145	30	2.00	6	60,000 90,000 120,000

**Each crown size has a specific nose length. (Nose length is the length of the drive shaft from the crown to the shaft tip).

Table 3: CSI OAS Peripheral *Guide Wire Information*

Model	Guide Wire Length	Core wire diameter	Spring Tip Length	Spring Tip Diameter	OAD Device Shaft Length Compatibility
VPR-GW-14	335 cm	.014"	3 cm	.014"	145 cm
VPR-GW-17	335 cm	.014"	3 cm	.017"	145 cm

6.3 Principles of Operation

The OAS is designed to reduce occlusive material and improve lumen patency by using a rotating, diamond-coated crown. The combination of the off-set crown mass and rapid rotation of the crown creates centrifugal forces that press the diamond-coated crown against the stenotic lesion. With each pass of the crown, the diameter of the vessel lumen increases in relation to the reduction of stenotic material. As the lumen diameter increases the centrifugal force decreases until a maximum orbit diameter is achieved. Actual final orbit and lumen diameter will depend on a variety of factors including run time, rotation speed, the composition of the lesion, and individual subject anatomy. For additional information regarding the OAS, please reference the Instructions for Use (IFU) and study IB. Note the IFU is contained within the study IB.

6.4 Devices Used in the Study

The device under investigation in this study is the CSI Peripheral OAS. Approximately one device per subject will be used.

In addition, the following commercially available products will also be used in the study:

- Intravascular Ultrasound (IVUS) system using DICOM modality with a high-definition imaging catheter (e.g., Phillips Eagle Eye® Platinum IVUS Catheter)
- POBA: Per physician's standard of care, any approved POBA is allowed
- DCB: Medtronic IN.PACT™ Admiral™ (Applies to "Devices used in Clinical Trial" in this study.)

Please refer to the appropriate-device-related IFU.

6.5 Manufacturer

The Sponsor and manufacturer of the device under investigation is:

Sponsor Name	Cardiovascular Systems, Inc.
Address	[redacted]

6.6 Device Handling and Traceability

The investigational devices will be tracked from the time it is shipped from CSI until it is either used in a procedure on a study subject or returned to the Sponsor. To assist in the traceability of the investigational devices, each device is labeled with a Model number and Lot or Serial number.

6.7 Device Storage

All Investigational Devices must be stored in a locked/secure location with access limited only to applicable study staff. Refer to the IB for more information on device handling and storage.

6.8 Device Accountability

A Device Accountability Log and shipping records will be maintained at each study site. Investigational Devices allocated for site use will be recorded in the Device Accountability Log upon delivery to the study site until use. Each site will be responsible for tracking the receipt and disposition of all study devices. If there is a device accountability discrepancy, the Sponsor and site will work to reconcile the discrepancy. Documentation of reconciliation will be maintained.

The Device Accountability Log will be updated as devices are received, opened, used or returned.

Commercially available accessory products will not be required to be tracked on the Device Accountability Log.

6.9 Device Return

All unused/expired devices must be returned to CSI. Sites should contact their study representative to obtain further instruction on device return procedures. At the end of the study enrollment period, all remaining investigational devices and study supplies must be returned to CSI.

7. OBJECTIVE

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

8. STUDY ENDPOINTS

8.1 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:

a) ≤50% residual stenosis post OAD + POBA [Angiographic Core Lab assessed] and,

b) No OAS-related severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]

8.2 Secondary Endpoints

The following secondary endpoints will be evaluated:

1. 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 measured post-OAD and post-OAD+POBA)
2. 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]
3. DCB Device Success defined as the ability to achieve successful delivery and deployment of all DCB 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.
4. 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 Lab 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 [CEC adjudicated]
5. Rate of severe angiographic complications defined as severe dissections (D-F), perforation, or distal emboli requiring additional treatment during the procedure [CEC adjudicated]
6. 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 [CEC adjudicated]
7. Major Adverse Event (MAE) rate at 30 days and 6 months [CEC adjudicated] defined as:

a) All-cause death through 30 days **or**

b) Major amputation of the target limb **or**

c) Clinically-driven TLR

8. Adverse Event rates at 30 days and 6 months [CEC adjudicated]
9. Distribution of Rutherford Classification compared to baseline at 30 days and 6 months
10. Change in Ankle Brachial Index (ABI) after clinical trial treatment compared to baseline

9. STUDY DESIGN

9.1 Description of 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 SFA and/or POP arteries (**Figure 1**).

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 analyses.

The rationale for the single-armed study design is based on the significant amount of testing completed before human studies and the multiple human clinical trials that have assessed over 4000 subjects in the US. The peripheral OAS has a well-established safety and performance profile. The hypothesis-based performance goals chosen for this study are based on observed rates from previous study subjects and lesions similar to those expected to be enrolled in the KAIZEN study. It is expected that the results from this study will be similar to observed rates form other Peripheral OAS studies.

9.1.1 Study Duration

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

9.1.2 Enrollment Criteria

[redacted] ixty-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 (12) sites in Japan.

Additionally, KAIZEN includes an Independent Physician Reviewer who will verify the treating physician's assessment of eligibility criteria. The Independent Physician Reviewer will assess the angiographic and IVUS core laboratory results using objective computer-aided imaging to identify patients who will be included in the primary analysis of KAIZEN.

9.1.3 **Justification of Performance Goal**

[redacted]

[redacted]

[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

[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.

9.1.4 Study Hypothesis

The safety and efficacy of the OAS device will be evaluated by the rate of Acute Device Success (Section 8.1) against a pre-defined success criteria of 50% (Section 9.1.3). 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.

9.1.5 Justification of the Sample Size

A sample of 62 subjects meeting Independent Physician Review is required to reject the null hypothesis (**Table 5**). The sample size was determined based on the following:

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

Table 5: 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 6: 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.

10. DATA COLLECTION

10.1 Study Data Collection

The electronic case report forms (eCRF) for this study will be maintained in an electronic data capture (EDC) system. Site personnel who are trained and delegated the task will enter data from the subject's source documents stored in the subject's medical record into the eCRF accessed remotely via a secure internet connection. The PI will review and sign off on the data once entered into the eCRF. If changes are made to the data following PIs electronic signature, the eCRF will need to be re-signed. Data will be stored in a secure, password-protected database that will have the data archived daily.

Data will be reviewed by the study Sponsor for completeness, correctness and consistency using programmed and manual data checks. Data queries will be used to document data that are incomplete, inconsistent or unclear. Data queries may also be used to clarify if a deviation to the protocol had occurred. Data queries may be generated by the database, monitor, or Sponsor during data review. Table 7 below lists the tests and procedures required per protocol including timeframes.

Table 7: Summary of Required Tests and Procedures

Procedure / Test / Data Collection	Baseline	Before Clinical Trial Treatment	Clinical Trial Treatment[10]	Discharge	30-Day Follow-up Assessment[8]	6-Month Follow-up Visit[10]
Visit Window	**≤30 Days from Clinical Trial Treatment**	**Procedural (Values collected in Cath Lab)**		**After Clinical Trial Treatment and Before Discharge**	**+14 Days**	**+30 Days**
Informed Consent[1]	X					
General Inclusion / Exclusion Criteria	X					
Clinical Trial Treatment Inclusion / Exclusion Criteria		X				
Rutherford Classification	X				X[9, 12]	X[12]
ABI Assessment	X			X[12]		
Medical History with Demographics	X					
Physical Exam (Height/Weight)	X					
Medication Review	X			X	X[12]	X[12]
Angiography	X[3, 11]	X[5, 11]	X[11]			
IVUS	X[3]	X[5,6]	X			
Duplex Ultrasound						X[12]
Clinical Trial Treatment Details			X			
Study Exit						X
Clinical Laboratory Test						
Serum Creatinine	X					
Platelet	X					
Pregnancy Test	X[4]					
Other						
Adverse Events[2]			X[7]	X[7]	X[7]	X[7]
Complaints/Device Deficiencies			X			
Protocol Deviations	X	X	X	X	X	X

Notes:
1 Informed Consent must be collected prior to study-required testing or procedures that are not standard of care.
2 The reporting of adverse events will begin once the CSI Peripheral Guide Wire enters the body (enrollment).
3 Diagnostic images to determine General Inclusion Criteria can be taken ≤30 Days from Clinical Trial Treatment. All imaging needs to be reverified on the day of Clinical Trial Treatment.
4 Pregnancy Test must be conducted ≤24 hours of the Clinical Trial Treatment for female subjects of childbearing potential (urine or blood).

5 Verify Procedure eligibility, estimate treatment results, and determine complications (See Section 11 and 12 for further details). Subject must meet all Clinical Trial Treatment Inclusion/Exclusion Criteria prior to inserting the CSI Peripheral Guide Wire (enrollment).
6 IVUS must be attempted once; however, if IVUS cannot cross before clinical trial treatment, further procedural IVUS measurements are not required.
7 Submit appropriate source documents for review of Adverse Events.
8 30-Day Follow-up assessment can be in-hospital follow-up or telephone assessment.
9 Required if 30-day Follow-Up Assessment occurs in-hospital.
10 Subjects in whom a CSI Peripheral Guide Wire complication occurred while entering the body, or the OAD was never inserted, will have a 6-Month Follow-up visit or telephone follow-up assessment for adverse events only.
11 Angiographic images are required at all time-points noted in Appendix A: Imaging and Procedure Flow Chart even if angiography images are not used to determine Calcium Assessment.
12 Only required for Enrolled and Treated subjects.

11. STUDY ENROLLMENT

Institutional Review Board (IRB) approval of the KAIZEN protocol and Informed Consent Form (ICF) must be obtained prior to enrolling patients in the study. The Sponsor and/or Sponsor Representative will provide approval in writing to begin enrollment.

11.1 Baseline

Baseline assessments must be completed within 30 days of the Clinical Trial Treatment with exception of the Pregnancy Test for women of childbearing potentials which must be conducted within 24 hours of the start of the Clinical Trial Treatment. Refer to **Table 7** for Baseline assessment data collection requirements.

11.1.1 Study Medications

Appropriate antiplatelet and/or anticoagulation therapy should be administered per the individual institution's standard practice for intraoperative procedural management. Additional medications administered to the subject prior to the procedure, during the procedure, and after the procedure are at the discretion of the Investigator.

11.2 Verify General Inclusion and Exclusion Criteria

Screen the patient for General Inclusion and Exclusion Criteria.

11.2.1 General Inclusion Criteria

1. Subject is 18 years of age or older
2. Subject has signed the approved KAIZEN study Informed Consent Form (ICF) prior to any study-related procedures
3. Subject has chronic, symptomatic lower limb ischemia defined as Rutherford classification (RC) 2-4
4. Subject has a clinical indication for percutaneous transluminal angioplasty (PTA) intervention in the native SFA and/or POP (P1 and/or P2) artery via femoral access

11.2.2 General Exclusion Criteria

5. Subject is female who is pregnant and/or breastfeeding
6. Subject is currently participating in another investigational clinical study that has not completed the primary endpoint at the time of enrollment or that clinically interferes with the current study endpoints
7. Subject is unwilling to follow the Investigator's instructions or follow-up requirements
8. Subject has had any non-diagnostic peripheral vascular intervention that was unsuccessful or had complications within 30 days before clinical trial treatment, per the following definition:
    a) >50% residual stenosis and/or
    b) Presence of angiographically assessed dissection (type D-F), perforation, distal embolization, thrombus and/or slow flow/no reflow
9. Subject has had or requires any non-diagnostic coronary intervention within 30 days before clinical trial treatment
10. Subject requires any planned non-diagnostic vascular (coronary or peripheral) intervention(s) within 30 days after clinical trial treatment
11. Subject has any planned procedures or other medical conditions which, in the Investigator's opinion, may interfere with the study result and/or subject's optimal participation in the study
12. Subject has had a prior major amputation within one year of the clinical trial treatment on either limb
13. Subject has a planned major amputation on either limb
14. Subject has life expectancy of ≤6 months
15. Subject has history of coagulopathy or hypercoagulable bleeding disorder
16. Subject has history of MI, or stroke/cerebrovascular accident (CVA) within 6-months prior to the clinical trial treatment
17. Subject has unstable angina pectoris at the time of the clinical trial treatment
18. Subject has untreatable hemorrhagic disease or platelet count <80,000mm^3 or >600,000mm^3 at baseline assessment
19. Subject has evidence of active infection on the day of clinical trial treatment requiring oral or intravenous antibiotics
20. Subject has known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated or cannot be exposed to the radiation required per the KAIZEN protocol

21. Subject has known hypersensitivity/allergy to the investigational atherectomy system or protocol-related therapies (e.g., CSI OAS lubricant, soybean oil, egg yolk phospholipids, glycerin, nitinol, stainless steel, other stent materials, paclitaxel, anticoagulant, or thrombolytic medications)
22. Subject has known contraindication to antiplatelet therapy
23. Subject has serum creatinine > 2.5 mg/dL, unless on dialysis

11.3 Informed Consent

Patients will undergo a medical record screening. The investigator will pre-screen the patient for General Inclusion Criteria and General Exclusion Criteria. The investigator will perform the informed consent process. The patient will sign the study ICF. The investigator will verify the patient meets ALL General Inclusion and No General Exclusion Criteria.

The Sponsor will provide a template ICF to each site for IRB submission prior to the site initiation. This template may be modified to meet the requirements of the individual study site. The Sponsor must pre-approve all changes to the ICF prior to initial submission to the IRB except for administrative changes (e.g., name of Investigator or institution, version date, etc.). If the ICF is amended by the reviewing IRB, a copy of the approved documents must be provided to the Sponsor prior to enrollment of subjects in the study.

The Investigator or assigned designee must administer the approved ICF to each prospective study subject and obtain the subject's signature along with the date of consent prior to enrollment in the study. Subjects unwilling to provide consent will not be enrolled in this study. The ICF must be obtained in accordance with Ordinance 36, GCP, and any additional applicable regulations and/or local regulations and laws, whichever represents the greater protection of the individual. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. The subject must be informed that withdrawal from the study will not jeopardize their future medical care. The subject must be informed about that the Principal Investigator could also withdraw the subject from the trial at any time if it was felt to be in the subject’s best interest. The subject must be given the opportunity to make inquiries about the content of the written information and other study-related matters. A copy of ICF must be given to each subject enrolled in the study. The institutional standard subject consent form does not replace the KAIZEN study ICF. Subjects are not considered enrolled until the CSI Peripheral OAS Guide Wire enters the body. Informed consent is required at the Baseline visit (within 30 days of clinical trial treatment); however, does not expire unless specified per site requirements.

If an Investigator uses the OAS and/or performs any study-related procedure(s) without first obtaining informed consent from the subject, **the Investigator must report this to the study Sponsor within twenty-four (24) hours and to the reviewing IRB per IRB reporting**

guidelines after the use occurs. The ICF will be updated as appropriate based on new information and/or amendments to the protocol. The updated ICF will be approved by the Sponsor and IRB prior to administering to subjects.

11.4 Verify Clinical Trial Treatment Inclusion and Exclusion Criteria

After the ICF is signed, confirm subject meets the Clinical Trial Treatment Inclusion and Exclusion criteria. See **Section 12** for Clinical Trial Treatment process.

11.4.1 Clinical Trial Treatment Inclusion Criteria

24. *De novo* target lesion in the native SFA and/or POP (P1 and/or P2) artery
25. All guidewires cross the Target Lesion within the true lumen without a sub-intimal course
26. Target lesion with ≥70% stenosis [confirmed by visual estimate via angiography]
27. Target reference vessel diameter (RVD) ≥3.0 mm and ≤6.0 mm [confirmed by visual estimate via angiography]
28. Target lesion length ≤150 mm [confirmed by visual estimate via angiography]
29. Subject has at least one patent tibial vessel (anterior tibial artery, posterior tibial artery, or peroneal artery) on the target leg, defined as having both:
    c) Blood flow to the foot, and
    d) No stenosis >50%
30. Target lesion has visual evidence of calcification based on the KAIZEN calcification definition:

IVUS Calcium Assessment	Angiographic Calcium Assessment
a) ≥ 270° of calcification	
b) ≥180° to 269° of calcification	i) ≥ ½ of target lesion length calcified OR ii) > 50mm of calcium
c) IVUS cannot cross lesion after one attempted pass	i) Bilateral calcification AND ≥ ½ of target lesion length calcified OR ii) Bilateral calcification AND >50mm of calcium

11.4.2 Clinical Trial Treatment Exclusion Criteria

31. Subject has had any Inflow treatment (ipsilateral iliac and/or common femoral artery) that was unsuccessful or had complications prior to OAS guidewire insertion per the following definition:
    a) >50% residual stenosis and/or
    b) Presence of angiographically assessed dissection (type D-F), perforation, distal embolization, thrombus and/or slow flow/no reflow

32. Target lesion is a chronic total occlusion (CTO) [confirmed by visual estimate via angiography]
33. Subject has presence of any other hemodynamically significant lesions or asymptomatic lesions in the target limb requiring a planned surgical intervention or endovascular procedure 30-days after clinical trial treatment
34. Presence of aneurysm in the target vessel
35. Acute ischemia and/or acute thrombosis of the SFA and/or POP (P1 and/or P2) artery
36. Angiographic evidence of perforation prior to insertion of the CSI Peripheral OAS Guide Wire
37. Angiographic evidence of severe (type D-F) dissection prior to insertion of the CSI Peripheral OAS Guide Wire
38. Planned use of atherectomy (other than CSI Peripheral OAS), laser, other debulking devices, CTO devices, cutting balloons, scoring balloons, specialty balloons or similar devices in the target limb

11.5 Before Clinical Trial Treatment

- **NON-TARGET LIMB** Non-target limb treatment must occur either greater than 30 days prior to the clinical trial treatment or greater than 30 days after the clinical trial treatment in the study according to **Section 12.4**.
- **INFLOW LESIONS IN THE TARGET LIMB** Inflow lesions (ipsilateral iliac and/or common femoral artery) in the target limb may be treated on the same day as the clinical trial treatment provided.
    - The inflow lesion must be successfully treated defined as residual stenosis ≤ 50% without complications prior to insertion of the OAS guidewire in the target lesion to be revascularized. - **Refer to Clinical Trial Treatment Exclusion Criteria 31.**
    - The inflow lesion may only be treated with POBA or stenting.
    - Atherectomy, laser, other debulking devices, CTO devices, cutting balloons, scoring balloons, specialty balloons or similar devices cannot be used for the inflow treatment. **- Refer to Clinical Trial Treatment Exclusion Criteria 38.**
- **NON-INFLOW, NON-TARGET LESIONS IN THE TARGET LIMB**
    - Treatment of lesion(s) not considered Inflow or Target Lesion cannot occur on the day of the clinical trial treatment.
    - Non-target lesion treatment on the target limb must occur greater than 30 days after the clinical trial treatment in the study. **- Refer to General Exclusion Criteria 8 and 10.**
- Access artery by operator's preferred methodology for target limb treatment.

- Cross the lesion using the operator's preferred wire (CSI Peripheral OAS Guide Wire cannot be used at this point).
- Assess Clinical Trial Treatment Inclusion/Exclusion criteria including Calcium Assessment using IVUS and/or angiography – **Refer to Appendix A** to determine when IVUS and angiography images are taken.
    - IVUS Catheter – refer to IVUS IFU to determine appropriate IVUS catheter size.
    - One pass of the IVUS Catheter will be attempted in order to perform Calcium Assessment. If IVUS cannot cross the lesion, do not attempt crossing with IVUS again.
    - Ensure angiographic images have been collected.
    - To complete the Calcium Assessment, **Refer to Appendix B** to determine how to use data from IVUS and/or angiography to determine Calcium Assessment.
- Based on feedback from physician experts, there are no differences in patient characteristics that impact outcomes if calcium is measured by IVUS or angiography.
- Refer to **Figure 1** for the defined treatment area.
    - If the subject, target lesion, or vessel does not meet ALL Clinical Trial Treatment Inclusion Criteria and/or meets ANY Clinical Trial Treatment Exclusion Criteria, the subject will not be included in the study and is considered a screen fail. The subject will be treated per physician's standard of care and will not be followed in the study or included in the analysis cohorts.
    - Recommended use of ruler to assess lesion length
- Refer to **Table 7** for Before Clinical Trial Treatment data collection requirements.

12. CLINICAL TRIAL TREATMENT

12.1 CSI Peripheral OAS Guide Wire Insertion

- CSI Peripheral OAS Guide Wire **must be delivered via a femoral artery.**
    - A subject is **Enrolled** once the CSI Peripheral OAS Guide Wire enters the body.
- The CSI Peripheral OAS Guide Wire must cross the Target Lesion within the true lumen without a sub-intimal course.
    - If the CSI Peripheral OAS Guide Wire crosses the Target Lesion without complication, the OAD can be inserted and proceed with Clinical Trial Treatment. per **Section 12**. **Do not pre-dilate lesion prior to treatment with the OAD.**
    - If the CSI Peripheral OAS Guide Wire is inserted with complications and/or does not cross the Target Lesion and/or does not cross the true lumen, the OAD must not be used. These subjects are treated per standard of care and will continue to be followed through the 6-Month Follow-up Visit. Refer to **Section 14** for follow up instructions for these subjects.

12.2 **OAD, POBA, DCB Procedure**

Attempt to insert the OAD.

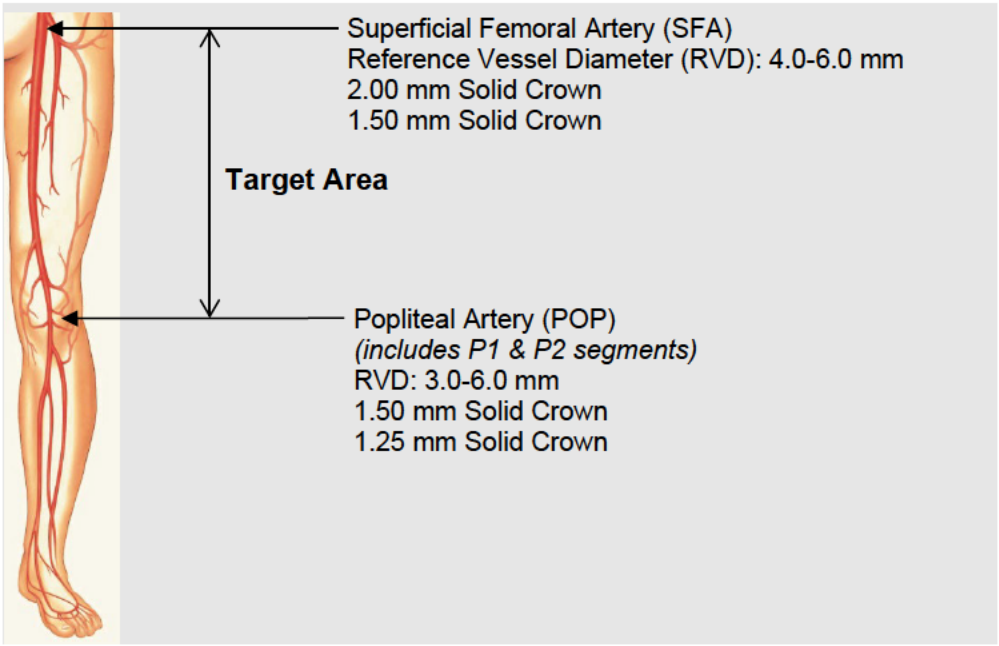
If the OAD cannot be inserted, the treating physician should treat the subject per standard of care and follow the subject through the 6-Month Follow-Up Visit. Refer to **Section 14** for follow-up instructions for these subjects.

If the OAD is inserted, the subject is considered **Enrolled and Treated**.

- Treat with OAD. Refer to the CSI Peripheral OAS, CSI Peripheral OAS Guide Wire, and CSI OAS Lubricant IFUs for treatment instructions.
- Refer to **Figure 1** for Solid Crown sizing to vessel size.
- Pre-dilate with uncoated PTA catheter (POBA). Refer to the appropriate device IFU for further instruction (e.g., balloon sizing, nominal pressure). The balloon diameter should be sized appropriately to the reference vessel diameter. The balloon length should correspond to the length of the area treated with OAD. Do not use high pressure balloons with nominal pressure 20 atm or greater.
    - Inflate the balloon at controlled low-pressure.
    - Continue to inflate to nominal pressure. Do not exceed nominal pressure.
        - If waist is seen at nominal pressure, recommend repeating OAD treatment (unless a complication occurs).
    - Continue inflation as needed.
- Once POBA pre-dilation treatment is complete, deploy DCB (Medtronic IN.PACT™ Admiral™). Refer to the appropriate device IFU for further instruction. (e.g., balloon sizing, nominal pressure).

Refer to **Table 7 and Appendix A** for Clinical Trial Treatment data collection and imaging requirements. Required imaging time points are described for Clinical Trial Treatment, however additional imaging per standard of care should be collected.

Figure 1: Protocol Defined Treatment Area and Crown Sizing Guide



12.3 Role of CSI Representatives During the Procedure

Personnel representing CSI may attend the procedure to provide technical support relative to the use of the OAD. All of these actions will be done under the careful direction of the Principal Investigator.

12.4 Non-Target Limb Treatment

If subject presents with bilateral disease with one eligible lesion in both legs, the target limb will be determined by physician's discretion. Non-target limbs requiring PTA treatment must be treated either >30 days prior to clinical trial treatment or > 30 days after clinical trial treatment.

The investigational OAS cannot be used in a non-target limb. The non-target limb should be treated per treating physician's standard of care.

13. DISCHARGE

Refer to **Table 7** for Discharge data collection requirements.

13.1 Discharge Medications

Subjects are recommended to follow an antiplatelet therapy protocol at the discretion of the investigator

14. FOLLOW-UP

The following sections describe follow-up requirements for all enrolled subjects in the KAIZEN study. All follow-up assessments and visits must be performed by someone who is study-trained and delegated to perform study follow-up.

- If the subject is seen by the Investigator between scheduled follow-up visits (i.e., not a study required assessment or visit), the assessment/visit should not be recorded on an CRF. However, if any adverse events are noted, an Adverse Event (AE) CRF needs to be completed for each event.
- If a revascularization occurs, images are required to be submitted for CEC review. The subject will still be required to return for the next scheduled follow-up visit if the unscheduled visit is out of the compliance follow-up window.

14.1 30-Day In-hospital Follow-up Visit or Telephone Follow-up Assessment

All Enrolled / Enrolled and Treated subjects are required to have a follow-up assessment occur at 30 days (+14 days) after enrollment. The 30-Day assessment can be an in-hospital follow-up visit or may occur by telephone assessment.

Refer to **Table 7** for 30-Day In-hospital Follow-up Visit or Telephone Follow-up Assessment data collection requirements.

14.2 6-Month Follow-up Visit

All Enrolled subjects are required to have a 6-Month (+30 days) Follow-up assessment phone call or in-hospital visit to monitor for adverse events.

All Enrolled and Treated subjects are required to have a Follow-up assessment occur at 6-Months (+30 days) after clinical trial treatment. The 6-Month visit must be an in-hospital visit.

Refer to **Table 7** for 6-Month Follow-up Visit data collection requirements.

All subjects will be exited from the study following the 6-month Follow-up visit.

15. OVERVIEW OF IMAGING DATA FLOW

Perform, record, and submit angiography, IVUS, and DUS images per the appropriate core lab guidelines. Refer to **Appendix A** and **Table 7** for imaging requirements. Diagnostic images taken ≤30 days prior to Clinical Trial Treatment may be requested in supplement to Clinical Trial Treatment images to verify Inclusion/Exclusion Criteria.

16. ADVERSE EVENTS

16.1 Adverse Event Requirements

For the purposes of this study the following events will be collected:

- All Clinical Trial Treatment Adverse Events
- All SAEs
- All ADEs, SADEs, USADEs
    - For both the CSI Peripheral OAS and the Medtronic IN.PACT™ Admiral™ DCB

16.2 Adverse Event Definitions

An **Adverse Event (AE)** is any disease or injury, or its clinical signs occurring in a subject who has been treated with an investigational device or post-marketing study device (Per Ordinance of the Ministry of Health and Welfare No.36)

A **Serious Adverse Events (SAE)** is an adverse event that (per ISO14155:2020):

a) Led to death,

b) Led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function including chronic disease, or
    - In-patient or prolonged hospitalization, or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) 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 CIP, without serious deterioration in health, is not considered a serious adverse event.*

An **Adverse Device Effect (ADE)** is an adverse event-related to the use of an investigational medical device (per ISO14155:2020).

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes 'comparator' if the comparator is a medical device.

A **Serious Adverse Device Effect (SADE)** is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (per ISO14155:2020).

An **Unanticipated Serious Adverse Device Effect (USADE)** is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment (per ISO14155:2020).

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

16.3 Adverse Event Relatedness

The relatedness of the AE will be classified by the Investigator for both the CSI Peripheral OAS and the Medtronic IN.PACT™ Admiral™ DCB and adjudicated by the CEC for the CSI Peripheral OAS. The Investigator will use the following definitions in classifying the relationship of the AE:

- **Peripheral Orbital Atherectomy System-Related**: AE is directly related to the investigational device(s) used in treatment of the lesion.
- **Clinical Trial Treatment Procedure-Related**: AE is directly attributable to the clinical trial treatment.
- **Target Limb-Related**: AE is related to the limb in which OA was performed.
- **IN.PACT Admiral Balloon-Related:** AE is directly related to the IN.PACT Admiral device used in treatment of the lesion

16.4 Reporting Adverse Events and Follow-Up

Adverse events should be reported throughout the subject's participation in the trial and not only at study mandated visits. Any subject who has unresolved adverse events at the end of their study participation will continue to be followed by the investigator per their standard of care. Source documents should be submitted to the Sponsor for review of the Adverse Event. Prior to submission to the Sponsor the source documents are to be appropriately redacted to remove the subject's name, and any other identifying information and the subjects unique Subject ID should be inserted on every page.

All adverse events, including subject deaths, must be reported on the AE CRF. In the event an adverse event cannot be submitted through the electronic database in a timely fashion, submission may be made to the Sponsor via email to [redacted] This does not replace the EDC reporting system; however, all information must still be entered in the EDC system as soon as feasible.

All efforts should be made to notify the Sponsor as soon as possible after first learning of an SAE. Additional information, obtained after the initial SAE, must also be reported as soon as possible to the study Sponsor. Deaths must be reported on the Study Exit CRF. If available, a copy of death records, medical records for the events that led to the subject's death, death

certificate and an autopsy report must be sent to the Sponsor as soon as they become available. Adverse event information will be collected up until each subject's study exit or study completion.

All AEs will be reviewed by the Sponsor and determined whether the AE meets regulatory reporting requirements. These events will be reported to the country's regulatory authorities according to the requirements of the country by the Sponsor or designee. The Investigator is responsible for reporting to the IRB, as applicable. In cases where the CEC does not agree with the Investigator's final assessment/classification of an adverse event, the Sponsor shall communicate both opinions to the regulatory authorities, if applicable.

Adverse events meeting the definition of SAEs, SADEs, or USADEs that result in death are to be reported to the Sponsor within 24 hours of becoming aware of the event. Documentation of AE on the CRF is sufficient for Sponsor reporting; however, if the CRF cannot be completed within the specified timeframe, reporting can be completed via email to [redacted]. If the event is reported outside of the required timeframe, a protocol deviation must be reported.

16.5 Device Deficiencies

All device deficiencies of the study device and Medtronic IN.PACT™ Admiral™ DCB must be documented on the CRF and reported to Sponsor, preferably within 24 hours of knowledge of the event. Reporting of device deficiencies includes reporting malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. Documentation of device deficiencies on the CRF is sufficient for Sponsor reporting. However, if the CRF cannot be completed within the specified timeframe, reporting to the Sponsor can be completed via email or phone. In the event of a device deficiency relating to the study device, return the suspected device to the Sponsor for analysis. All device deficiencies will be reported to regulatory authorities as required and included in the clinical results (e.g., final report).

If the investigator or site staff becomes aware of death or any SAE suspected to be attributable to device deficiencies of the study device or Medtronic IN.PACT Admiral™ DCB, the principal investigator shall immediately notify the Sponsor and the IRB. In such cases, the principal investigator shall provide additional relevant information upon the request of the Sponsor, the head of the medical institution, or the IRB.

17. PROTOCOL DEVIATIONS

A protocol deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. The Investigator is not allowed to deviate from the protocol except:

- With prior approval from the study Sponsor, and the local IRB if applicable, or
- Under emergency circumstances to protect the rights, safety and well-being of the subjects, or

- Inadvertent protocol deviations (e.g., missed lab test) or deviation outside the control of the Investigator/site (e.g., subject does not show up for a scheduled follow-up visit, etc.), are not expected to have prior Sponsor approval;

All deviations must be documented separately on a CRF. Documentation of the deviation should include a description of the deviation, the reasons thereof. Protocol Deviations should be reported to the Sponsor and reviewing IRB according to their requirements. If the investigator has failed to comply with the protocol to eliminate immediate hazards to subjects or for other inevitable medical reasons the investigator shall document the deviation and immediately report it to the Sponsor and head of medical institution. Documentation of the Protocol Deviation on the CRF is sufficient for Sponsor reporting, however if the CRF cannot be completed within the specified timeframe, reporting to the Sponsor can be completed via email or phone.

The Sponsor may implement measures to reduce the number of deviations such as, but limited to, a site Corrective Action Preventive Action plan (CAPA), protocol amendment or additional site training. Repeated and serious non-compliance by the site that is not adequately addressed by the PI or his/her staff may lead to corrective action taken by Sponsor including requesting the site's withdrawal from the study.

18. STUDY EXIT

Active subject participation is expected to last for a maximum of 6 months. The Study Exit CRF must be completed when a subject exits the study early or completes the required follow-up visits. Reasons for exiting the study include, but are not limited to the following:

- **Subject Lost to Follow-up:** If a subject fails to comply with the Protocol requirements to attend the follow-up visit, the study site should make at least three (3) documented attempts to contact the subject and/or family or emergency contact and send a letter to the last known address of the subject by traceable mail before considering the subject lost to follow-up.
- **Voluntary Withdrawal:** A subject may voluntarily withdraw from the study at any time. If the subject had an adverse event, where possible, the subject should be followed until the resolution of the adverse event.
- **Investigator Withdrawal:** An Investigator may withdraw a subject for reasons, which may include failure to keep appointments, termination or cancellation of the study by the Sponsor, etc.
- **Study Completion:** This will be after the last scheduled follow-up visit has occurred as defined by the Protocol or subsequent amendments.
- **Death:** The Adverse Event CRF must also be completed.
- **Other:** Includes other possible reasons for exiting the study which may not be outlined above, as determined by the Sponsor or Investigator.

19. STUDY TERMINATION

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study Principal Investigators and applicable reviewing bodies. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient adherence to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Sponsor management decision to discontinue the study

20. STUDY RESPONSIBILITIES AND MANAGEMENT

20.1 Conduct of Study

The study shall be conducted in accordance or compliance with the:

- Protocol;
- Study agreement;
- Conditions of approval imposed by the IRB
- Ethical principles that have their origin in the Declaration of Helsinki;
- Any local or national regulations, as appropriate, including ICH E6: Good Clinical Practices (GCP) and Ordinance 36: Ministerial Ordinance on Good Clinical Practice (GCP) for Medical Devices

The study cannot begin until approval from the Sponsor, applicable IRB, and regulatory authorities are obtained. In addition, appropriate insurance for the study to cover the cost of treatment of subjects in the event of a study-related injury, will be obtained prior to the start of the study, according to Japan requirements.

20.2 Investigator Selection and Responsibilities

20.2.1 Investigator Training

All treating physicians must be experienced in peripheral artery treatment (e.g., balloon angiography, stenting, atherectomy, etc.). The Sponsor will be responsible for ensuring that physicians are properly trained in the use of the CSI Peripheral OAS and on the protocol prior to enrolling subjects in this study. Training will be performed by qualified personnel from the Sponsor or designee.

Each investigator must complete at least one (1) roll-in. This will ensure proper device training, and procedural and data collection adherence. 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.

20.2.2 Investigator / Investigational Site Delegation

Only site personnel delegated in writing by the Investigator will conduct study-related functions. All individuals delegated study-related functions must have documented training, at a minimum, on the study protocol.

20.2.3 Investigator Responsibilities

The Principal Investigator (PI) is responsible for protecting the rights, safety, and welfare of study subjects. In addition, the Investigator is responsible for:

- Providing agreement on the content of the protocol and conduct the study in compliance with the protocol and applicable regulations
- Providing adequate oversight of all study-related activities
- Maintaining control over the investigational devices, ensuring the devices are used solely by authorized users under his or her direct supervision, tracking the receipt and disposition of all study devices, and returning all devices upon the completion of termination of the study
- Disclosing financial, or other information, that may constitute a potential conflict of interest
- Maintaining source documents throughout the study and making them available/ providing direct access as requested during monitoring visits, audits/inspections, and IRB review
- Providing a current signed and dated curriculum vitae (CV). If any changes affecting the PI's qualification, an updated CV is required to be sent to the Sponsor
- Avoiding improper influence on, or inducement of the subject, monitor and Sponsor or other parties participating in, or contributing to, the study by complying with the informed consent process for the subject, study agreements and IRB approval of the study
- Obtaining IRB approval of the protocol, ICF and any other study-related documents prior to enrolling subjects. The Investigator will also be responsible for notifying the Sponsor within five (5) working days of becoming aware of the IRB withdrawing their approval of the study.
- Explain the appropriate use of the investigational devices to each subject.

- If a subject is receiving treatment by another primary physician, the investigators etc. shall inform the primary physician, with prior consent of the subject, that the subject will participate in the clinical trial.
- The head of the medical institution and the investigators etc. shall beforehand take necessary measures to ensure that adequate medical care is provided to a subject for any adverse event.
- The investigator shall promptly notify the subjects if the study is prematurely terminated or suspended and shall provide appropriate medical care to the subjects and take other necessary measures.
- The investigators etc. shall inform subjects of the fact that medical care is needed for adverse event(s) of which the investigator becomes aware, if applicable.
- Upon completion of a clinical trial, the investigator shall report the completion in writing and submit a written summary of the trial's outcome to the head of the medical institution.

The Investigator for each site may not begin enrollment until Sponsor receives and approves (when necessary) required documents, including a signed Study Agreement, IRB protocol and ICF approvals.

It is acceptable for the Investigator to delegate study-related functions to an associate or Sub-Investigator or trained Study Coordinator; however, the Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, maintaining applicable study records, etc.

At each site, appropriate procedures must be followed to maintain the security and confidentiality of individually identifiable health information, and will comply with all applicable health information confidentiality laws and regulations, including as applicable, the U.S. HIPAA Standards for Privacy of Individually Identifiable Health Information, Title 45 of the U.S. Code of Federal Regulations, Part 160 and 164, and the applicable health information privacy laws of any state or foreign jurisdiction (including Japan's Act on the Protection of Personal Information and applicable circulars published by Japan's Ministry of Health, Labor and Welfare. Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant subject privacy laws.

21. MONITORING

The study Sponsor, or designate, will monitor the study to ensure proper conduct and progress of the study including adequate protection of human subjects and the integrity of the clinical study data is of the highest quality. This will include routine, periodic visits to study sites to confirm reported results are consistent with source documentation, appropriate subject enrollment,

accurate investigational device accountability, compliance with all applicable laws and regulations, and compliance with the protocol, and may also include qualification, initiation and close-out visits. Remote monitoring may also occur. A risk-based monitoring approach will be utilized and the data points that are source data verified as well as the frequency of monitoring visits will be based upon enrollment, data integrity, and site compliance.

Each monitoring visit will be documented via a monitoring report and a letter will be sent to the site's PI to document the study status at his/her site. The PI will be responsible for ensuring that all action items identified during the monitoring visit are resolved in a timely manner.

A Monitoring Plan will be written for the study outlining the strategy, methods, responsibility, and requirements for monitoring the study. The Monitoring Plan will be kept separate from the protocol. Each investigational site will allow monitoring activities to be conducted at their site, including visits by the study Sponsor or their designate. Therefore, access to the subjects' files must be allowed as per the informed consent at the Investigator's site.

22. INDEPENDENT PHYSICIAN REVIEWER

Subjects will be enrolled in KAIZEN based on treating physician's assessment. An Independent Physician Reviewer will use Before Clinical Trial Treatment images, quantified core lab assessments of the images, including quantitative vascular analysis (QVA), and his expert judgement to verify the treating physician's assessment of eligibility criteria listed in **Section 11.4**. A charter or operating procedures will be written to define the responsibilities of the Independent Physician Reviewer including format and documentation to be maintained, etc. The Independent Physician Reviewer will be an independent vascular surgeon, interventional cardiologist, interventional radiologist or cardiologist who has experience with review of peripheral arteries using IVUS and angiography. The Independent Physician Reviewer will not be affiliated with the Sponsor, study/data management, or a site that is actively participating in the study.

23. CLINICAL EVENTS COMMITTEE (CEC)

A Clinical Events Committee (CEC) will be established for this clinical study to adjudicate adverse events reported during the study using angiographic imaging and site reported source documents. IVUS imaging will not be used to adjudicate adverse events. The CEC will consist of a minimum of three (3) physicians with vascular experience who are not affiliated with the Sponsor or actively participating in the study and are independent to an institution conducting this study. A charter will be written to define the responsibilities of the CEC including the events to be adjudicated, documentation to be maintained, meeting format, etc. Committee membership rosters will be maintained at CSI and will be made available upon request.

24. DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee (DMC) will be established for this clinical study to assess at intervals during the study, the safety data and to recommend to the Sponsor whether to continue, suspend, modify or terminate the study early for safety reasons. The DMC will consist of at least two (2) physicians with vascular experience (one (1) of which may be a non-

interventional physician) and one (1) statistician. The DMC will not be affiliated with the Sponsor or actively participating in the study and are independent to an institution conducting this study. A charter will be written to define the responsibilities of the DMC including deliberations, format of the meetings, documentation to be maintained, etc. Committee membership rosters will be maintained at CSI and will be made available upon request.

25. STATISTICAL METHODS

An overview of statistical methods and analyses are included below. Detailed analyses are outlined in a separate Statistical Analysis Plan (SAP).

25.1 Data Analysis

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 [redacted] The following analysis sets are specified for KAIZEN.

25.1.1 Full Analysis Set (FAS)

[redacted]

25.1.2 Intent to Treat (ITT) Analysis Set

[redacted]

25.1.3 Modified Intent to Treat (mITT) Analysis Set

[redacted]

25.1.4 Per Protocol (PP) Analysis Set

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

25.1.5 Roll-in Analysis Set

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

25.2 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]

25.3 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).

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.

25.4 Endpoint Analyses

The following analyses will be performed on the populations indicated.

25.4.1 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:

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

b) 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. The rate of Acute Device Success and the corresponding 95% confidence interval will be

presented. The lower confidence bound of the acute device success rate will be compared against the performance goal of 50%.

25.4.2 Primary Endpoint Sensitivity Analysis

Sensitivity analyses will be performed by assessing the observed rate of Acute Device Success in the ITT, FAS, and PP analysis sets.

25.4.3 Secondary Endpoint Analysis

There are no formal hypothesis tests associated with the secondary endpoints. Secondary endpoints will be assessed with the appropriate statistical method appropriate for the type of data analyzed (e.g., rates, changes over time, Kaplan-Meier).

25.4.4 Roll-in Analysis

All primary and secondary endpoint analyses will be performed for the roll-in subjects and will be reported separately.

26. RISK ANALYSIS

26.1 Risks Associated with OAS

Study subjects will be informed of all known potential side effects and complications associated with the study treatment and evaluations prior to enrollment in the study.

Potential adverse events that may occur and/or require intervention as a result of the use of this device include, but are not limited to:

- Allergic reaction to medication/media/OAD components
- Amputation
- Anemia
- Aneurysm
- Bleeding complications which may require transfusion
- Cerebrovascular accident (CVA)
- Death
- Distal embolization (air, tissue, thrombus, device)
- Entry site complications
- Hemolysis
- Hypotension/hypertension
- Infection
- Myocardial infarction
- Pain
- Pseudoaneurysm
- Restenosis of treated segment that may require revascularization

- Renal insufficiency/failure
- Slow flow or no reflow phenomenon
- Thrombus
- Vessel closure, abrupt
- Vessel injury, including dissection and perforation that may require surgical repair
- Vessel spasm
- Vessel occlusion

Possible complications that may be associated with use of the OAS Peripheral Guide Wire are similar to those that may occur during percutaneous transluminal angioplasty and during other types of atherectomy procedures including:

- Bleeding at the vascular access site
- Perforation
- Dissection
- Acute vessel closure
- Slow flow
- Contrast media reaction
- There may also be complications associated with kinks, distortion, fracture or other damage to the guide wire that could lead to patient injury or death.

26.2 Risk Associated with DCB

Medtronic IN.PACT™ Admiral™ DCB will be used in this clinical study. A systematic review and meta-analysis of randomized controlled trials (RCT)investigating paclitaxel-coated devices in the femoral and/or popliteal arteries was performed using data from 28 RCTs with 4663 patients.[21] The analysis showed that the mortality rate was greater in patients treated with paclitaxel devices compared to control at the 2-year and 5-year follow-up suggesting a possibility of an increased mortality risk. However, there was no difference at the 1-year follow-up. Risk assessment has been continued carefully in Japan and overseas and have not found suggestions of higher mortality among patients treated with paclitaxel.

26.3 Risk Minimization

The Peripheral OAS undergoes rigorous bench and animal testing to ensure device safety. In addition, the device and patient risks are reviewed and mitigated as far as possible following CSI Risk Management procedures which are compliant with Application of risk management to medical devices - ISO14971. The first-generation model of the peripheral OAS received CE Mark in February 2007 and US FDA 510(k) clearance in August 2007. The current generation model of the Peripheral OAS intended to be used in KAIZEN received US FDA clearance in July 2019. The Peripheral OAS is commercially available in the US, Germany, Austria, France, Malaysia, Singapore, and United Arab Emirates. Peripheral OAS has been studied extensively by CSI in over 4,000 subjects and has a well-established safety profile in the US population. In addition, KAIZEN study investigators will undergo training, and subjects will be screened and

evaluated for medical histories/conditions that may compromise successful performance of the device.

26.4 **Minimization Bias**

Potential sources of bias in the KAIZEN study that may compromise the outcome of the study may result from the selection of subjects, treatment of subjects, and evaluation of study data. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

1. Subjects will be screened to confirm eligibility for enrollment with defined inclusion and exclusion criteria prior to enrollment.
2. A minimum of 1, but up to 3 roll-in subjects per Investigator will be permitted. This will ensure proper device training, and procedural and data collection adherence. Roll-in subjects will be consented and followed per protocol, and their data will be reported separately.
3. Critical outcome variables, including endpoints, are objectively measured. Electronic data collected to support the primary endpoint will be verified against source documents.
4. An independent core lab will perform assessment of all IVUS and angiographic images
5. An Independent Physician Reviewer will verify the treating physician's assessment of eligibility criteria using objective computer-aided imaging. Only subjects who meet the Independent Physician review will be included in the primary analysis population.
6. All study clinicians and CSI personnel and their delegates will be trained on their respective aspects of the KAIZEN study using standardized training materials.
7. No single site can contribute more than 25% of the study enrollments, not including roll-in subjects.
8. A pre-specified statistical analysis plan will be developed prior to analyzing data which will document ~~all~~ analyses and analysis methods.
9. An independent statistician will complete analysis per statistical analysis plan.
10. Classification rules are defined for important subjective variables such as device-related, procedure-related, and target limb-related events
11. An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported adverse events and will be considered final adverse event disposition.
12. An external, international CRO, will lead study related activities in Japan.

In summary, potential sources of bias that may be encountered in the KAIZEN study have been considered and minimized by careful study design.

26.5 **Benefits**

Subject's participation in this study is voluntary. There is no direct additional benefit to the subjects enrolled in the study. Information gathered from this study will help confirm the safety and efficacy of the OAS in treating *de novo*, moderate to severe calcific atherosclerotic lesions

in the lower limbs. Ultimately, this knowledge may provide physicians additional information which may help improve the care for future subjects.

27. CONFIDENTIALITY

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

The Investigator agrees to visits by Sponsor staff, and/or designee, and applicable regulatory authorities to review the study-related documents and subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., angiographic cines).

28. RECORD KEEPING

28.1 Medical Institution

Per Article 61 of Ordinance 36, the medical institution shall appoint a record-keeping manager.

The record keeping manager specified in the preceding paragraph shall retain the following records (including documents) until the day on which marketing approval of the test device is obtained (or the day 3 years after the date of notification in the case of a notification pursuant to Article 32, Paragraph 3 or Article 43, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later:

1) Source documents
2) The contract or Approval Document, informed consent forms, written information and other documents prepared by persons engaged in the clinical trial at the medical institution in accordance with this Ministerial Ordinance, or their copies
3) The protocol, documents obtained from the IRB etc. pursuant to Article 51, Paragraphs 1 through 3 (IRB documentation), and other documents obtained in accordance with this Ministerial Ordinance
4) Records of trial-related duties such as control/accountability of investigational devices

28.2 Sponsor

Per Article 34 of Ordinance 36, the Sponsor shall appropriately retain the following records (including documents and data) related to the clinical trial until the day on which marketing approval of the test device is granted (or the day 3 years after the date of notification in the case of a notification pursuant to Article 32, Paragraph 3) or the day 3 years after the date of premature termination or completion of the clinical trial, whichever comes later:

1) Protocol, contracts, clinical trial reports, and other documents prepared by the Sponsor in accordance with this Ministerial Ordinance, or copies thereof.

2) Case report forms, the written notification pursuant to Article 51, Paragraph 6, and other records obtained from the heads of medical institutions or investigators etc. in accordance with this Ministerial Ordinance

3) Records of the duties related to sponsoring and managing the clinical trial, such as monitoring and audits (excluding those specified in the preceding two items and Items (5))

4) Data generated in conducting the clinical trial

5) Records specified in Article 24, Paragraph 5

The Sponsor who resides outside Japan shall have a clinical trial in-country representative retain the records specified in Article 24, Paragraph 5, during the period specified in the preceding paragraph.

29. PROTOCOL AMENDMENTS

The protocol, IB, CRFs, ICF and other subject information, or other study documents shall be amended as needed throughout the study whenever important new information becomes available that may be relevant to the proper conduct of the clinical study, such as information on the quality, efficacy and safety of the test device.

The study Sponsor will submit any significant change to the protocol, including a justification for the change, to the appropriate regulatory authorities and to the Investigator to obtain approval from the local IRB. The Investigator will only implement the protocol amendment after approval of the IRB, and regulatory authority, if applicable. Administrative changes to the protocol will be submitted to the IRB for notification. Investigators shall sign any approved protocol amendment to indicate agreement with the amendment.

30. PUBLICATION OF STUDY DATA

Any previously unpublished information provided to the Investigator by the Sponsor, such as patent applications, manufacturing processes and basic scientific data, is considered confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the Sponsor's written consent.

A complete manuscript describing the results of this study is considered the primary publication for the study. Study publications and authorship will be determined by the Sponsor based upon the submission of ideas, significant contributions to the study design, study enrollment, publication development, etc. An Investigator may also want to publish the study experience from his/her own site. In either case, these secondary publications can only be published after the complete multi-center study publication is published.

The Sponsor reserves the right to review and approve all publications and presentations utilizing the study data. The Investigator may proceed with the publication when notified by the Sponsor.

31. BIBLIOGRAPHY

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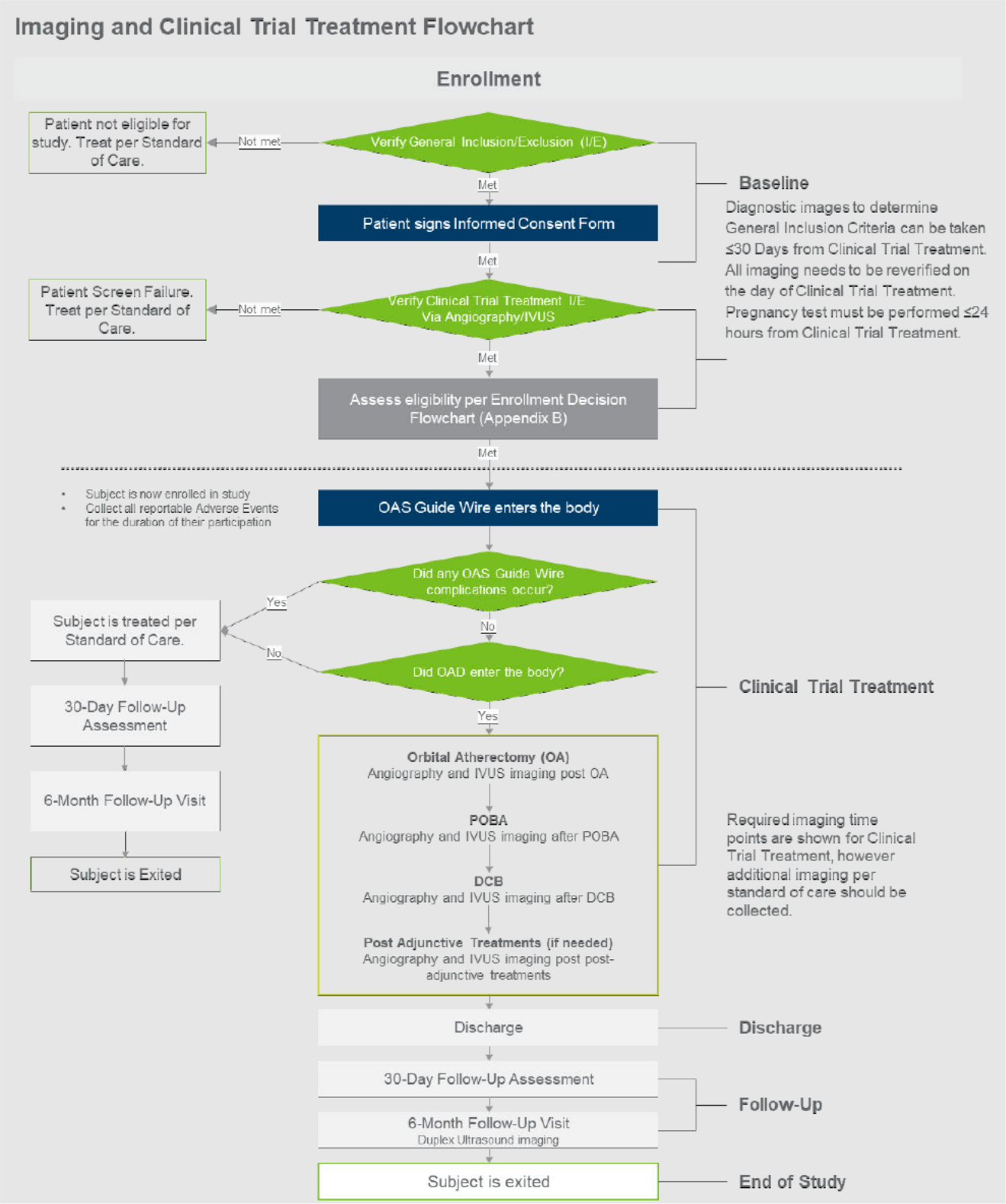
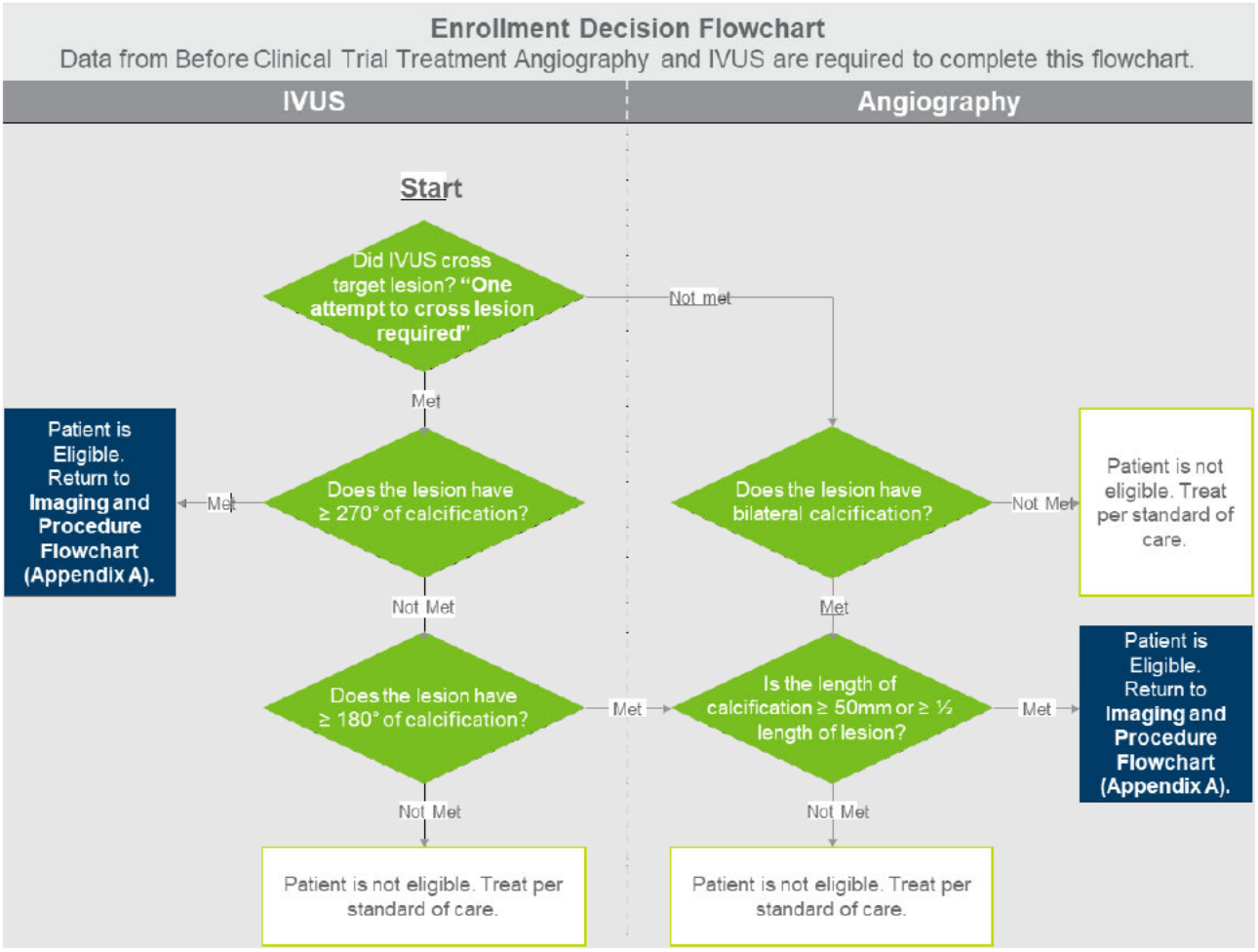
Appendix A: Imaging and Procedure Flow Chart



Appendix B: Enrollment Decision Flow Chart



Appendix C: Investigator's Brochure

The KAIZEN Investigator's Brochure is provided under separate cover

Appendix D: Participating Sites and Investigators

A complete list of participating sites and investigators will be provided under separate cover upon request.