OPTIMIZE BTK:

Orbital vessel PreparaTIon to MaximIZe dcb Efficacy in calcified below the knee (BTK) lesions- A pilot study

[redacted]

NCT02561299

[redacted]

May 20, 2016

Sponsor:

Cardiovascular Systems, Inc.

[redacted]

PROTOCOL SUMMARY

Title	OPTIMIZE BTK: Orbital vessel PreparaTIon to MaximIZe dcb Efficacy in calcified below the knee (BTK) lesions- A pilot study
Devices Used in the Study	• Peripheral Orbital Atherectomy System (OAS) manufactured by Cardiovascular Systems, Inc. (Minnesota, USA) • Lutonix® 014 Drug Coated Balloon (DCB) manufactured by C. R. Bard, Inc. (New Jersey, USA)
Primary Objective	To prospectively evaluate acute and long term clinical results of orbital atherectomy (OA) with adjunctive DCB angioplasty versus DCB angioplasty alone for treatment of Peripheral Artery Disease (PAD) in BTK lesions.
[redacted]	[redacted]
Study Design	This prospective, randomized, multi-center, post-market pilot study will include 50 subjects with calcified lesions of the distal popliteal (POP), anterior tibial (AT), posterior tibial (PT), tibialperoneal trunk (TPT) or peroneal (PR) arteries with ≥ 70% diameter stenosis (DS) by angiography. Subjects will be randomized 1:1 to OA with adjunctive DCB angioplasty versus DCB angioplasty alone. [redacted]
Follow-up Visits	Post-procedure follow-up visits will occur at 30 days and 24 months by phone; and at 3 months, 6 months, and 12 months in clinic.
Study Population	Subjects age 18 or older who present with ≥ 70 % DS of the arteries (distal POP, AT, PT, TPT, or PR) by angiography will be recruited for the study.

Outcome Measures	[redacted] Patency of the target lesion by Duplex Ultrasound (DUS*) at 6 months and 12 months post-procedure *Limited to patent versus occluded status Freedom from Major Adverse Events (MAEs) at [redacted] 6 months, 12 months, [redacted] post-procedure MAEs include: clinically-driven TLR; unplanned, unavoidable major amputation of the index limb; and death within 30 days of the index procedure Freedom from clinically driven target lesion revascularization (TLR**) [redacted] 6 months, 12 months, [redacted] post-procedure **Angiographic images must be sent to the Angiographic Core Lab for adjudication of TLR versus Target Vessel Revascularization (TVR) Freedom from unplanned, unavoidable major amputation of the index limb at [redacted] 6 months, 12 months, and 24 months post-procedure Change in Rutherford Category at [redacted] 6 months, 12 months, [redacted] post-procedure from baseline [redacted] Device success (per each DCB used during the index procedure), defined as the ability to achieve successful delivery and deployment of the DCB to the target lesion as described per Instructions for Use (IFU) within 3 minutes of insertion without removal and use of an additional device [redacted]

	[redacted]
Inclusion Criteria	Subject's age ≥ 18 years Rutherford Clinical Category 3 – 5 Lesions [except in-stent restenosis (ISR)] of the distal POP (POP segment below the anatomical knee *joint*), AT, PT, TPT, and PR arteries with ≥ 70 % DS by angiography Presence of clearly visible calcification in two views (both sides of vessel at the same location) evaluated angiographically - Computerized tomography (CT) angio images may substitute to confirm distribution of calcium, if available as standard of care Length of calcium ≥ 25 % of total lesion length or ≥ 2 cm total length Target lesion length up to 20 cm
Exclusion Criteria	• Subject or subject's legal representative is not willing to sign an Ethics Committee approved informed consent form or comply with the study protocol requirements • Contraindicated by either device, per IFU • Presence of inflow lesion (≥ 50 % DS) or inflow not successfully treated (≥ 50 % DS and/or unresolved significant angiographic complication) • Compromised outflow distal to the target lesion (≥ 70 % DS) or presence of lesion(s) or occlusion(s) located from 5 cm above the ankle to below the ankle joint space • Subject has more than 2 target vessels requiring treatment • The guide wire cannot be passed across the target lesion(s) and/or guide wire position distal to target lesion(s) outside vessel lumen • Pre-dilatation of the target lesion prior to randomization and OA treatment • Presence of significant (≥ 70 % DS) lesion(s) or occlusion(s) not meeting the study criteria which were not successfully treated during the index procedure (≥ 50 % DS and/or significant angiographic complication) • Subject has planned amputation (including minor) of the index limb or previous major amputation of the contralateral limb • Creatinine > 2.5 mg/dL, unless on dialysis • Subject has any significant medical condition which, in the Investigator's opinion, may interfere with the subject's optimal participation in the study • Subject is participating in an investigational drug or device study that has the potential to clinically interfere with the study outcome measures

	• Subject is pregnant or planning to become pregnant within the study period • Subject has an unresolved severe systemic infection • Subject has an anticipated life span of less than one year • Subjects with known hypersensitivity to paclitaxel or paclitaxel related compounds • Subjects who cannot receive recommended anti-platelet and/or anticoagulant therapy
Core Labs	• SynvaCor- Angiographic Core Lab, [redacted] • VasCore- Duplex Ultrasound Core Lab, [redacted] • [redacted]
National Principal Investigators/ Steering Committee Members	• Professor Marianne Brodmann, MD, Medical University of Graz Austria • Professor Gunnar Tepe, MD, Klinikum Rosenheim Germany • Professor Thomas Zeller, MD, Herz-Zentrum Bad Krozingen Germany [redacted]
Sponsor Contact Information	Cardiovascular Systems, Inc. (CSI) Clinical Affairs [redacted]

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1. ABBREVIATIONS

[redacted]	[redacted]
ACO	Anticoagulation
ADE	Adverse Device Effect
AE	Adverse Event
ASA	Aspirin
AT	Anterior Tibial
ATK	Above the Knee
BA	Balloon Angioplasty
BTK	Below the Knee
CLI	Critical Limb Ischemia
CSI	Cardiovascular Systems, Inc.
CTA	Clinical Trial Agreement
DAP	Data Analysis Plan
DCB	Drug Coated Balloon
DS	Diameter Stenosis
DUS	Duplex Ultrasound
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
[redacted]	[redacted]
EU	European Union
IC	Intermittent Claudication
[redacted]	[redacted]
ICF	Informed Consent Form
IFU	Instructions for Use
ISR	In-stent restenosis
LLL	Late Lumen Loss
MAE	Major Adverse Event
OAS	Orbital Atherectomy System
OA	Orbital Atherectomy
PAD	Peripheral Artery Disease
PI	Principal Investigator

POBA	Plain Old Balloon Angioplasty
POP	Popliteal
PR	Peroneal
PT	Posterior Tibial
PTA	Percutaneous Transluminal Angioplasty
[redacted]	[redacted]
[redacted]	[redacted]
QVA	Quantitative Vascular Angiography
RBP	Rated Burst Pressure
[redacted]	[redacted]
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
TPT	Tibial Peroneal Trunk
USADE	Unanticipated Serious Adverse Device Effect
[redacted]	[redacted]

2. DEFINITIONS

Term	Definition
Clinically-driven target lesion revascularization (TLR)	A repeat procedure (percutaneous or surgical) performed for ≥ 50% DS confirmed by angiography within all or part of the target lesion after documentation of recurrent clinical symptoms of PAD following the initial procedure.
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.
Device Success (per each DCB used during the index procedure)	The ability to achieve successful delivery and deployment of the DCB to the target lesion as described per IFU within 3 minutes of insertion without removal and use of an additional device.
Dissection classification[1]	Type 0: None 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 *Note: Type A and B are generally considered benign and minor dissections.*
Distal popliteal	The popliteal (POP) segment located below the anatomical knee joint.
Enrolled Subjects	Subjects who met all of the general inclusion and none of the general exclusion criteria and signed an Ethics Committee-approved informed consent form.
[redacted]	[redacted]
Inflow	Arterial flow proximal to the protocol defined target area.
Outflow	Arterial flow distal to the protocol defined target area extending through the foot.
Major adverse events (MAEs)	Clinically-driven TLR; unplanned, unavoidable major amputation of the index limb; and death within 30 days of the index procedure.
Major amputation	Above ankle amputation.
Maximum balloon inflation pressure	Balloon inflation pressure used during pre-dilatation to achieve full balloon expansion with no visible waist.

Term	Definition
[redacted]	[redacted]
[redacted]	[redacted]
Randomized Subjects	Enrolled subjects who met all of the angiographic inclusion and none of the angiographic exclusion criteria as reported by the Investigator (Core Lab review/adjudication optional) and the sealed randomization envelope was opened.
Rutherford classification[2]	**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.
[redacted]	[redacted]
Target area	Arterial anatomy extending from the distal POP through the tibial arteries to 5 cm above the ankle.
Target lesion	The stenotic segment treated with the study devices. **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 $\geq$ 3 cm apart.
Target lesion revascularization (TLR)	A repeat procedure occurring after the index procedure (percutaneous or surgical) which includes all or part of a target lesion treated during the index procedure.
Target vessel revascularization (TVR)	A repeat procedure occurring after the index procedure (percutaneous or surgical) which includes all or part of a target vessel treated during the index procedure.

Term	Definition
Target vessel(s)	The entire vessel(s) in which the target lesion(s) is located.
[redacted]	[redacted]
Tibial arteries	Anterior tibial (AT), posterior tibial (PT), tibial peroneal trunk (TPT) and peroneal (PR).
[redacted]	[redacted]
Unplanned, unavoidable amputation	Unplanned amputation where surgical reconstruction is not possible.

3. INTRODUCTION

Standard (uncoated) PTA catheters, otherwise known as Plain Old Balloon Angioplasty (POBA) are commonly used to treat peripheral artery disease (PAD); however, the high restenosis rate following treatment is problematic and repeat interventions may be required.[1] POBA has been shown to have higher restenosis rates below the knee (BTK) than in the femoro-popliteal segment above the knee (ATK).[2] In long lesions in BTK arteries, the one-year restenosis rate after POBA may be as high as 70%.[3] For long-segment BTK disease, drug-coated balloons (DCBs) are intended to reduce the restenosis rate.[4] Initial clinical experience with DCB angioplasty for BTK occlusive disease showed a significantly lower restenosis rate when long-segment infrapopliteal lesions were treated with DCB. [5]

One of the limiting factors that may impair DCB efficacy is the presence of calcium. Calcified lesions are challenging to treat due to increased risk of plaque rupture, embolization, and dissection;[6] unfortunately, most randomized controlled studies excluded patients with severe calcification due to these problems.[7] In their most recent study, Fanelli et al. found that calcium presents a barrier to optimal drug absorption.[8] In patients with such complicated lesions, the combination of DCB with plaque modification devices may lead to optimized therapeutic approaches.[2] For example, it has been shown that combined use of directional atherectomy and DCB is safe in the treatment of severely calcified lesions of the femoro-popliteal tract and is associated with a low restenosis rate.[7]

We propose a well-designed hypothesis generating pilot study evaluating patient outcomes after revascularization of calcified lesions below the knee (BTK). This population is often difficult to treat due to multiple comorbidities and challenging vascular anatomy. Previous BTK DCB vs. POBA studies such as Biolux P-II have failed to see the same previously established (Biolux P-I, LEVANT, etc.) effects of paclitaxel on longer-term patient outcomes ATK. No clear answer exists as to why BTK DCB trials fail to see the paclitaxel working as well in the vessel. One theory as to why this is the case suggests BTK lesions are more often heavily calcified which may reduce or block the drug form reaching the vessel wall at the targeted location. We hypothesize that calcified lesion preparation (removing or reducing the atherosclerotic tissue) using orbital atherectomy (OA) will improve outcomes, potentially due to increased drug uptake at the targeted location subsequent to decreased plaque burden.

[redacted]

4. PRIMARY OBJECTIVE

The primary objective of the study is to prospectively evaluate acute and long term clinical results of orbital atherectomy (OA) with adjunctive DCB angioplasty alone for treatment of PAD in BTK lesions.

5. DEVICES USED IN THE STUDY

Only devices that have CE marking will be utilized in this study according to their intended use:

- Peripheral Orbital Atherectomy System (OAS) manufactured by Cardiovascular Systems, Inc. (Minnesota, USA)
- Lutonix® 014 Drug Coated Balloon (DCB) manufactured by C. R. Bard, Inc. (New Jersey, USA)

Please refer to each applicable Instructions for Use (IFU).

6. STUDY DESIGN AND STATISTICAL METHODOLOGY

6.1. STUDY DESIGN

This prospective, randomized, multi-center, post-market pilot study includes subjects with calcified lesions of the distal popliteal (POP), anterior tibial (AT), posterior tibial (PT), tibial peroneal trunk (TPT) or peroneal (PR) arteries. Target lesions must be located entirely within the protocol defined target area, which extends from the distal popliteal (popliteal segment below the anatomical knee joint) to 5 cm above the ankle.

[redacted]

[redacted]

6.2. STATISTICAL METHODOLOGY

Study outcome measures will be analyzed and reported using descriptive statistics.

7. SAMPLE SIZE, SUBJECT ENROLLMENT, AND SUBJECT RANDOMIZATION

7.1. SAMPLE SIZE

[redacted] the study is expected to enroll approximately 65 TOTAL subjects.

[redacted]

7.3. SUBJECT RANDOMIZATION

Subjects who have signed the ICF and have met all of the inclusion criteria and none of the exclusion criteria as determined by the Investigator (Core Lab review of angiographic criteria is optional pre-procedure) will be randomized (1:1) to treatment with OA + DCB vs. DCB alone. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8. SUBJECT SELECTION

8.1. SUBJECT SELECTION

Subjects must meet ALL of the inclusion criteria and NONE of the exclusion criteria to be eligible to participate in this study.

8.2. INCLUSION CRITERIA

- Subject's age ≥ 18 years
- Rutherford Clinical Category 3 – 5
- Lesions [except in-stent restenosis (ISR)] of the distal POP (POP segment below the anatomical knee *joint*), AT, PT, TPT, and PR arteries with ≥ 70 % DS by angiography
- Presence of clearly visible calcification in two views (both sides of vessel at the same location) evaluated angiographically

  -Computerized tomography (CT) angio images may substitute to confirm distribution of calcium, if available as standard of care

- Length of calcium ≥ 25 % of total lesion length ≥ 2 cm in total length
- Target lesion length up to 20 cm

8.3. EXCLUSION CRITERIA

- Subject or subject's legal representative is not willing to sign an Ethics Committee approved informed consent form or comply with the study protocol requirements
- Contraindicated by either device, per IFU
- Presence of inflow lesion (≥ 50 % DS) or inflow not successfully treated (≥ 50 % DS and/or unresolved significant angiographic complication)
- Compromised outflow distal to the target lesion (≥ 70 % DS) or presence of lesion(s) or occlusion(s) located from 5 cm above the ankle to below the ankle joint space
- Subject has more than 2 target vessels requiring treatment
- The guide wire cannot be passed across the target lesion(s) and/or guide wire position distal to target lesion(s) outside vessel lumen
- Pre-dilatation of the target lesion prior to randomization and OA treatment
- Presence of significant (≥ 70 % DS) lesion(s) or occlusion(s) not meeting the study criteria which were not successfully treated during the index procedure (≥ 50 % DS and/or significant angiographic complication)
- Subject has planned amputation (including minor) of the index limb or previous major amputation of the contralateral limb
- Creatinine > 2.5 mg/dL, unless on dialysis
- Subject has any significant medical condition which, in the Investigator's opinion, may interfere with the subject's optimal participation in the study
- Subject is participating in an investigational drug or device study that has the potential to clinically interfere with the study outcome measures
- Subject is pregnant or planning to become pregnant within the study period
- Subject has an unresolved severe systemic infection
- Subject has an anticipated life span of less than one year
- Subjects with known hypersensitivity to paclitaxel or paclitaxel related compounds
- Subjects who cannot receive recommended anti-platelet and/or anticoagulant therapy

8.4. OUTCOME MEASURES

[redacted]

- Patency of the target lesion by Duplex Ultrasound (DUS*) at 6 months and 12 months post-procedure

  *Limited to patent versus occluded status

- Freedom from Major Adverse Events (MAEs) at [redacted] 6 months, 12 months, [redacted] post-procedure

  MAEs include: clinically-driven TLR; unplanned, unavoidable major amputation of the index limb; and death within 30 days of the index procedure

- Freedom from clinically driven target lesion revascularization (TLR**) at [redacted] 6 months, 12 months, [redacted] post-procedure

  **Angiographic images must be sent to the Angiographic Core Lab for adjudication of TLR versus Target Vessel Revascularization (TVR)

- Freedom from unplanned, unavoidable major amputation of the index limb at [redacted] 6 months, 12 months, [redacted] post-procedure

- Change in Rutherford Category at [redacted] 6 months, 12 months, [redacted] post-procedure from baseline

[redacted]

- Device success (per each DCB used during the index procedure), defined as the ability to achieve successful delivery and deployment of the DCB to the target lesion

as described per Instructions for Use (IFU) within 3 minutes of insertion without removal and use of an additional device

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11. ADVERSE EVENT DEFINITIONS, COLLECTION, RELATEDNESS AND REPORTING

11.1. ADVERSE EVENT DEFINITIONS

Adverse Event definitions for the study are adopted from EN ISO14155:2011.

An **Adverse Event (AE)** is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

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

a) led to death
b) led to serious deterioration in the health of the subject, that either resulted in:
   1. a life-threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function, or
   3. in-patient or prolonged hospitalization, or
   4. 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 Protocol, 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.

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.

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 version of the risk analysis report.

11.2. ADVERSE EVENT COLLECTION

Adverse events must be documented starting from the time of randomization until study completion. Angiographic complications, including but not limited to:

- Bleeding complications
- Dissections
- Perforations
- Distal embolization
- Abrupt closure
- Slow flow/no flow
- Spasm
- Thrombus

will be considered AEs and must be recorded accordingly on the AE electronic Case Report Form (eCRF).

Following discharge, only events that meet any of the seriousness criteria must be collected (SAE, SADE, USADE).

11.3. ADVERSE EVENT RELATEDNESS

The relatedness of the AE to the treatment device(s) and procedure(s), index limb, and target lesion will be classified by the Investigator and reviewed by the Sponsor. The Investigator will use the following definitions in classifying the relationship of the AE:

- **Device Related**: AE is directly related to the device(s) used in treatment of the lesion.
- **Procedure Related**: AE is directly attributable to the index procedure.
- **Limb Related**: AE is related to the index limb.
- **Lesion Related**: AE is related to the target lesion.

11.4. ADVERSE EVENT REPORTING

Adverse events defined above must be reported to the Sponsor via the AE eCRF as well as to each reviewing regulatory body [e.g., Competent Authority(CA), EC, etc.] per policy, as required. Note: not all AEs collected in the study may be reportable to the reviewing EC/CA per policy (e.g., pre-planned interventions noted at baseline, minor dissections, etc.).

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.

[redacted]

13. RISKS AND BENEFITS

13.1. RISKS

All devices that will be used in this study have CE marking and will be used within their intended use. Clinical risks to subjects treated during the index procedure with the study devices are the same risks encountered if treated outside of the study. The Investigator should refer to the manufacturer's IFU for each technology used in the study for specific device-related risks, contraindications, restrictions, warnings and precautions.

[redacted]

13.2. BENEFITS

Pre-treatment with OA for calcified BTK arteries where the hard atherosclerotic plaque is removed or reduced prior to treatment with DCB may provide incremental benefits versus DCB angioplasty alone due to increased drug uptake at the targeted location subsequent to decreased plaque burden. The knowledge gained from this study will inform design of future trails in subjects with calcified lesions to help physicians choose the best care for patients and advance treatment of PAD.

14. PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the study is not conducted according to the protocol and applicable regulations. Protocol deviations that will be collected include, but are not limited to the following:

- Failure to obtain informed consent or failure to obtain informed consent prior to study procedures
- Enrolling a subject who did not meet inclusion criteria, or met exclusion criteria
- Not completing protocol-required examinations or evaluations

[redacted]

Protocol deviations are reportable to the Sponsor as soon as possible after their occurrence.

15. SITE NON-COMPLIANCE

If excessive protocol deviations are noted, the Sponsor reserves the right to suspend study enrollment until a sufficient system is in place at the site to reduce further deviations, or to withdraw the site from participation in the study.

16. SUBJECT STUDY EXIT

Active subject participation is expected to last for a maximum of 24 months follow-up. Subjects will be followed until completion of the study or death, whichever comes first. [redacted] 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 follow-up visits, 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:** [redacted]

- **Other:** Includes other possible reasons for exiting the Study which may not be outlined above, as determined by the Sponsor or Investigator.

17. STUDY MANAGEMENT

This study will be conducted in accordance with the study protocol, applicable laws and regulations, and in accordance with the policies and procedures of each Institution's reviewing EC and other applicable regulatory bodies (e.g. CA, Radiation Committee, etc.), as may be required.

17.2. EARLY TERMINATION/WITHDRAWAL

Early termination of the study by either the Sponsor or the Investigator, if applicable, will be communicated to the Ethics Committee and CA as appropriate.

Upon completion of subject participation in this study, the subject will be followed-up in accordance with institutional standards.

Possible reasons for early termination of the study and/or site's participation in the study may include, but are not limited to:

- Low subject enrollment
- Request from a study site's Principal Investigator
- Occurrence of serious device performance issue or effects which cannot be prevented in future cases
- Sponsor management decision to discontinue the study
- Request from reviewing regulatory bodies
- Site's noncompliance with the requirements of the study protocol and/or applicable laws and regulations
- Falsification of data or any other breach of ethics or scientific principles

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 and withdrawal from the study will not jeopardize their future medical care or their relationship with the Principal Investigator. Subjects will be asked what the reason for termination is but have the right not to answer.

The Principal Investigator may withdraw a subject from the study at any time if s/he believes it is in the subject's best interest.

The subject's future care will not be changed by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the clinical study.

Possible reasons for subject's termination or withdrawal include, but are not limited to, the following:

- Subject did not meet the inclusion or met the exclusion criteria
- Subject death (in case of subject death, cause should be documented)
- Subject and/or family request, if applicable
- Subject non-compliance
- Subject lost to follow-up defined as a minimum of three (3) documented attempts by the study site to contact the subject and/or family or emergency contact, and a letter sent to the last known address by traceable mail
- Subject's participation terminated by the Principal Investigator
- Study is discontinued
- Study site ends participation in the study

The study will be terminated according to locally applicable regulations.

If applicable, the study may be temporarily suspended or terminated, either at the local, national, or international level, at the request of the Ethics Committee or regulatory authorities. Justification and request for resuming the clinical study after suspension will be communicated to the reviewing EC other applicable regulatory bodies, as may be required.

18. DATA ANALYSIS

Study data will be analyzed as indicated in the Statistical Analysis Plan (SAP).

[redacted]

[redacted]

19. ADMINISTRATIVE RESPONSIBILITIES

19.1. ETHICAL BASIS OF STUDY

This clinical study will be performed in accordance with the World Medical Association Declaration of Helsinki, EN ISO 14155:2011 as applicable for studies involving on-label usage of commercially approved products, and applicable local and national legal and regulatory requirements.

19.2. ETHICS COMMITTEE (EC) APPROVAL

The study protocol and applicable supporting documentation must be submitted to each study site's reviewing EC and written approval obtained prior to each site being allowed to conduct the study. In addition, acknowledgment, review or waiver by the relevant national Competent Authority (CA) and other applicable regulatory bodies (e.g., Radiation Committee) may be required per each study site's country specific requirements.. Documentation certifying study approval must be provided to the Sponsor prior to enrolling subjects into the study. The Investigator and Sponsor are also responsible for fulfilling any conditions of approval imposed by the applicable regulatory bodies or EC (i.e., submission of progress reports or summaries) and maintaining continuation of approval over the duration of the study. The Investigator is responsible for maintaining copies of approvals and filing of study related correspondence.

Withdrawal of EC approval is reportable to the Sponsor within five (5) business days.

19.3. INFORMED CONSENT FORM (ICF) APPROVAL

The Sponsor will provide a template Informed Consent Form (ICF) to each site for EC submission prior to site initiation if a site ICF template is not available. This template may be modified to suit the requirements of the study site; however, the Sponsor must pre-approve all changes to the ICF template prior to submission to the reviewing EC. If changes to a submitted ICF are required prior to approval by the reviewing EC, changes must be reviewed and approved by the Sponsor and a copy of the final approved document must be provided by the Investigator to the Sponsor prior to enrollment of any study subjects. A copy of the final EC-approved ICF must be sent to the Sponsor prior to study start in addition to any subsequent revisions which are reviewed and approved by the EC.

Prior to enrolling in the clinical study, subjects shall be fully informed of the details of the participation as required by applicable regulations and the center's EC. Informed consent must be obtained from each subject, or a legally authorized representative (as allowed by the study Investigator/EC), prior to any participation, using the Informed Consent Form (ICF) approved by site's reviewing EC. The ICF must be signed and dated by the subject or legal representative and by the person obtaining the consent. All information pertinent to the clinical study shall be provided in writing and in native, non-technical language that is understandable to the subject or subject's legally authorized representative.

If a subject or legally authorized representative is unable to read or write, the informed consent (as allowed by the study Investigator/EC) shall be obtained through a supervised oral process. An independent witness shall be present throughout the process. Upon completion of the supervised oral process, the ICF must be signed and dated by the subject or legal representative and by the person obtaining the consent attesting that the information was accurately explained and that informed consent was freely given.

Prior to the subject or legal representative signing the ICF, the Investigator or authorized delegate will fully explain to the subject or legal representative the nature of the research, clinical study procedures, anticipated benefits, and potential risks of participation in the clinical study. The Investigator or delegate will allow adequate time for the subject or legal representative to read and review the ICF and ask questions.

The Investigator or authorized delegate must document in the subject's medical records that the subject was consented and the date on which the consent was obtained. The original signed consent form will be retained in the subject's clinical study records. A copy of the signed informed consent will be provided to the subject or legal representative and a copy placed in the subject's medical record.

19.4. 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 data will be used in a manner without identifiable reference to the subject. The Investigator consents to visits by the Sponsor or designee and authorized governmental body to review the

study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., angiogram).

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.

19.5. SPONSOR RESPONSIBILITIES

Sponsor responsibilities include but are not limited to:

- Protection of the rights, safety, and welfare of subjects by conducting the clinical study in accordance with the Declaration of Helsinki, the Study Protocol, all applicable laws and regulations, and any conditions of approval imposed by the reviewing EC and other applicable regulatory authorities (e.g., National Competent Authority, Radiation Committee, etc.) where the study is performed.
- Selection of qualified Investigators, study sites, and Core Labs who participate in the study;
- Training of participating study sites including the Investigator and staff conducting the study;
- Adverse Event/Incident reporting:
    - Relaying adequate information on AEs and SAEs to the regulatory authorities per country's applicable reporting requirements and complying with medical devices vigilance reporting per country-specific regulations.
- Providing financial support to each study site which is fair, reasonable, and equitable to fair market value;
- Following/promoting all applicable regulatory standards per applicable regulations at each study site; and,
- Ownership and control of the use of data, including review and approval of study-related publications/presentations, etc.

19.6. INVESTIGATOR RESPONSIBILITIES

Investigator responsibilities include, but are not limited to, the following:

- Protection of the rights, safety, and welfare of subjects by conducting the clinical study in accordance with the Declaration of Helsinki, the Study Protocol, all applicable laws and regulations, and any conditions of approval imposed by the reviewing EC and other applicable regulatory authorities (e.g., National Competent Authority, Radiation Committee, etc.) where the study is performed.
- Conduct of the study in accordance with the Clinical Trial Agreement (CTA) with the Sponsor, the Protocol, applicable laws and regulations and any conditions of approval imposed by the reviewing EC/CA or other applicable regulatory body.
- Delegation of study-related tasks to qualified personnel under their supervision as may be applicable; however, the Investigator remains responsible for the proper conduct of the clinical study.
- Not commencing enrollment until the Sponsor has received all required documentation, including but not limited to the signed CTA and required regulatory approvals.

- Following appropriate procedures to maintain subject confidentiality according to the applicable laws and regulations. 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 site's relevant patient privacy laws.
- Not transferring the study to other sites attended by the Principal Investigator unless prior approval is obtained from the reviewing EC and the Sponsor.
- Keeping records pertaining to this study for a minimum of two (2) years following the date on which the study is terminated or completed.

20. INVESTIGATOR RECORDS AND REPORTS

20.1. INVESTIGATOR RECORDS

Investigator responsibilities include, but are not limited to, preparation and/or retention of the following records:

- Subject's records including the signed/dated ICF, adverse event documentation, relevant medical history, results of study-related tests/exams, and dates and data collected during the study visits
- Protocol approvals with associated amendments
- Regulatory correspondence

20.2. INVESTIGATOR REPORTS

The Investigator is responsible for preparation and submission to the Sponsor of all eCRFs, adverse event reports, and deviations from the protocol. If any action is taken by the EC/CA or other applicable regulatory body, the information must be forwarded to the Sponsor in a timely manner.

Note: reviewing regulatory bodies may impose additional requirements and/or require a different notification timeframe.

21. PUBLICATION OF STUDY DATA

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 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, with the help of the Steering Committee, reserves the right to review and approve all publications and presentations utilizing the study data. The Investigator may proceed with the publication or presentation only when approved by the Sponsor.

22. REFERENCES

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