Chansu Vascular Technologies Everolimus-Coated Percutaneous Transluminal Angioplasty Catheter First-in-Human Clinical Investigation

The CVT-SFA Trial

PROTOCOL

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Lead Principal Investigator:	[redacted]
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I have reviewed this protocol, including the investigator's brochure, and agree to adhere to the requirements and responsibilities listed herein. I am trained to the contents of this protocol, percutaneous angioplasty procedures and the specific use of the device listed in this protocol. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practices, Declaration of Helsinki and all applicable regulatory requirements.

_____ _____
Site Investigator Signature Date

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Site Investigator Printed Name

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Sponsor Signature Date

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Sponsor Printed Name

REVISION HISTORY

Revision Level	DCO Number	Effective Date	Description of Change
01	0036	18-May-2021	N/A, Initial release
02	0048	09-Jun-2021	Update Section 5 for SAE definitions and notification per MDR 2017/745. Removed angiographic core lab references.
A	0134	11-Jan-2022	Add Core Lab documents to Appendix I. Add Appendix M with Core Lab Guidelines. Edit section 4.3 which previously allowed stent placement before procedure. Remove DUS at Post Procedure (section 4.3). Add risk analysis information to section J.
B	0159	15-Mar-2022	Added walking test or treadmill test to baseline functional status to assess walking distance (section 4.1); added completion of walking test or treadmill test to 6 month and 12 month follow up (section 4.6); added walking test or treadmill test to Table 2 schedule of events. Updated planned enrollment schedule in protocol summary section.
C	0162	24-Mar-2022	Added stent post-dilatation clarification to use CVT device to section 4.3 “Criteria for Bail-Out Stenting”.
D	0168	28-Apr-2022	Revise Appendix M (angiographic core lab guideline) to include complete distal runoff images
E	0189	02-Aug-2022	Corrected Appendix F (Schedule of Events) to include Walking/Treadmill Test at 6M/12M follow up. This change reflects the requirements in the body of the protocol and the Schedule of Events in Table 2.

PROTOCOL SUMMARY

Investigational Device	CVT Everolimus-coated Percutaneous Transluminal Angioplasty (PTA) Catheter (CVT EVE-PTA Catheter)
Study Objective	To assess the safety and inhibition of restenosis of the CVT Everolimus-coated PTA Catheter in the treatment of subjects with de-novo occluded/stenotic or re-occluded/restenotic lesions in superficial femoral or popliteal arteries.
Study Design	Prospective, multi-center, open, single arm study
Number of Subjects	A total of 75 subjects will be enrolled
Number of Sites	Up to eight (8) sites in Europe
Primary Safety Endpoint	Freedom of Major Adverse Event (MAE) rate at 6 months post-procedure, defined as a composite rate of cardiovascular death, index limb amputation and ischemia-driven target lesion revascularization (TLR).
Primary Effectiveness Endpoint	Patency at 6 months post procedure, defined as freedom from restenosis as determined by duplex ultrasonography (DUS) (peak systolic velocity ratio (PSVR) ≤2.4 or ≤50% stenosis) and freedom from ischemia-driven target lesion revascularization (TLR).
Secondary Safety Endpoints	• Rate of Major Adverse Event (MAE) rate in hospital and at 30 days, 1-, 2- and 3-years post-procedure, defined as a composite rate of cardiovascular death, index limb amputation and ischemia-driven Target Lesion Revascularization (TLR). • Rate of occurrence of arterial thrombosis of the treated segment. • Rate of ipsilateral embolic events of the study limb. • Rate of clinically-driven target lesion revascularization at 6, 12, 24 and 36 months. • Patency rate at 12 months post procedure defined as freedom from clinically driven TLR and duplex ultrasonography detected restenosis (ultrasound peak systolic velocity ratio ≤ 2.4 or stenosis ≤50%) • Rate of vascular access site complication defined as the combined rate of hematoma, AV fistula or a pseudoaneurysm that required intervention, such as surgical repair or transfusion, prolonged hospital stay, or required a new hospital admission. • Lesion success (per device), defined as achievement of a final in-lesion residual diameter stenosis of <50% (by QA), using any device after wire passage through the lesion. Pre- and post-dilatation of the lesion with a non-study device is considered part of assigned device treatment.

Secondary Endpoints *(continued)*	• Technical success (per device), defined as achievement of a final in-lesion residual diameter stenosis of <50% (by QA), using the CVT Everolimus-coated PTA Catheter without a device malfunction after wire passage through the lesion. Pre- and post-dilatation are considered part of assigned device treatment. • Clinical success (per subject) defined as technical success without the occurrence of major adverse events during the procedure. • Procedural success (per subject) defined as lesion success without the occurrence of major adverse events during procedure. • Ankle-Brachial Index (ABI) changes before procedure compared with ABI at discharge and at 6 and 12 months. • Change in WIQ (walking impairment questionnaire) from pre-intervention at 6 and12 months follow-up. • Change in walking distance from pre-procedure at 6 and 12 months. • Change in Rutherford classification grades of chronic limb ischemia from pre-intervention at 6 and12 months follow-up for the treated limb.
Subject Population	Subjects with documented symptomatic occlusion and/or >70% stenosis of the superficial femoral or popliteal (P1 segment) artery.
Inclusion Criteria	Study subjects must fulfill the following criteria: 1. Subject must be at least 18 years of age. 2. Subject or his/her legally authorized representative provides written informed consent prior to any clinical investigation related procedure, as approved by the appropriate Ethics Committee of the respective clinical site. 3. Subject must agree to undergo all clinical investigation plan-required follow-up visits and examinations. 4. Subjects with symptomatic leg ischemia, requiring treatment of SFA or popliteal (P1 segment) artery. 5. *De novo* or restenotic lesion(s) >70% within the SFA and popliteal arteries in a single limb which are ≥3 cm and ≤15 cm in cumulative total length (by visual estimation). Lesion must be at least 2 cm from any stented area. 6. Subject is willing to provide informed consent and comply with the required follow up visits, testing schedule and medication regimen. 7. Successful wire crossing of lesion. 8. Target vessel reference diameter ≥4 mm and ≤6 mm (by visual estimation). 9. Target lesion(s) can be treated with a maximum of two (2) CVT Everolimus-coated PTA Catheters.

	10. At least one patent (less than 50% stenosis) tibio-peroneal run-off vessel confirmed by baseline angiography or prior MR angiography or CT angiography. 11. Life expectancy >1 year 12. Rutherford classification of 2, 3 or 4
Exclusion Criteria	Subject with **any** of the following should be excluded: 1. Pregnant or lactating females. 2. Co-existing clinically significant aneurismal disease of the abdominal aorta, iliac or popliteal arteries. 3. Significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy. 4. Known intolerance to study medications, everolimus or contrast agents. 5. Doubts in the willingness or capability of the subject to allow follow-up examinations. 6. Subject is actively participating in another investigational device or drug study. 7. History of hemorrhagic stroke within 3 months of procedure. 8. Previous or planned surgical or interventional procedure within 30 days of index procedure. 9. Prior vascular surgery of the target lesion. 10. Lesion length is <3 cm or >15 cm or there is no normal proximal arterial segment in which duplex ultrasound velocity ratios can be measured. 11. Known inadequate distal outflow. 12. Significant inflow disease. 13. Acute or sub-acute thrombus in target vessel. 14. Use of adjunctive therapies (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy, lithotripsy). 15. Outflow arteries (distal popliteal, anterior or posterior tibial or peroneal arteries) with significant lesions (≥ 50% stenosis) may not be treated during the same procedure. 16. Treatment of the contralateral limb during the same procedure or within 30 days of the study procedure. 17. Rutherford classification of 0, 1, 5 or 6 18. Presence of prohibitive calcification that precludes adequate PTA treatment. 19. Subjects held in custody in an institution by official or court order.

Treatment Strategy	• Target lesion pre-dilatation will be performed to determine lesion treatability and prevent the need for stent implantation for treatment of flow limiting dissection. • In the absence of flow limiting dissection and if no stent has been needed, the target lesion will be treated with the CVT Everolimus-coated Balloon Catheter from healthy-to-healthy segments.
Planned Schedule	• First subject enrolled: February - 2022 • Last subject enrolled: October - 2022 • Last subject last contact: November - 2025

1. STUDY OVERVIEW AND RATIONALE

1.1. Study Overview

The CVT-SFA study is a prospective, multi-center, open, single arm study which will include seventy-five (75) subjects at up to eight (8) sites in Europe and will evaluate an everolimus-coated percutaneous transluminal angioplasty (PTA) catheter for the treatment of de-novo occluded/stenotic or re-occluded/restenotic superficial femoral or popliteal arteries.

Study enrollment will be offered to all subjects who are suitable candidates for balloon PTA to correct occlusive or stenotic lesions of the superficial femoral or popliteal P1 segment artery. Subjects who fail to match the inclusion criteria or who present with any of the exclusion criteria should not be included into this study.

To comply with regulatory requirements, subjects will be required to give written informed consent prior to their participation in the study.

1.2. Background and Literature Review

Peripheral artery disease (PAD) is associated to incident cardiovascular morbidity and mortality[1] and would have affected in 2015 about 236 million people aged 25 years and older worldwide; women accounted around 52% of this population.[2] Total disease prevalence has been estimated at between 3% and 10%, increasing to 15 to 20% in subjects over 70 years.[3] Only about 25 percent of affected individuals undergo treatment for the disease.[4]

The most common symptom of PAD is difficulty in walking (intermittent claudication); less common is critical limb ischemia (CLI) which includes severe, persistent rest pain (requiring treatment with analgesics), ulceration or gangrene of the distal extremity. Lower extremity arterial disease can lead to reduced mobility, limb pain, gangrene and amputation, as well as increased mortality[3, 5, 6, 7] Subjects with PAD generally also present with cardiovascular disease (CVD) which may explain the increased risk of mortality from myocardial infarction (MI) and stroke for these patients,[6, 8, 9] with mortality rates at five years ranging from approximately 30% to 44%.[10, 11]

The superficial femoral artery (SFA) is the most commonly diseased artery in the peripheral (lower limb) vasculature. Available therapies for patients with PAD remain controversial. Treatments include watchful waiting, medical management, endovascular treatment and surgical reconstruction.[12]

Medical management comprises risk factor modification (i.e. diabetes control, smoking cessation, hyperlipidemia lowering), exercise therapy, pharmacological therapy.[13, 14, 15]

Risk factor modification therapy is recommended to improve claudication and decrease the morbidity and mortality associated with the progression of PAD. Exercise therapy can produce clinical improvements in walking ability and reductions in claudication pain.[19-21] Pharmacological options include antiplatelet and anticoagulant therapies.[16, 17, 18]

Surgery is typically reserved for subjects with CLI and is associated with risks such as wound complication, death, MI, infection and leg edema.[18, 23] Patency rates for surgical

revascularization of the lower extremities have been reported to be 23-74%.[18, 23, 24]

During the past decade, endovascular therapy has become the primary therapy in SFA interventions.[25]

Multiple studies have been published reporting on the short and long-term results of percutaneous angioplasty interventions and/or stenting for PAD.[26-46] Patency rates were reported to range between 29-93%.[26-46] A meta-analysis of percutaneous angioplasty with provisional stenting compared to stenting alone for treatment of SFA lesions showed similar rates of target vessel revascularization, making both reasonable choices as endovascular treatments.[47]

However, restenosis remains as a major limitation of the clinical usefulness of PTA and stenting. Poor long-term results, especially after the treatment of longer lesions in the femoropopliteal region, were reported.[48-59]

The local application of anti-proliferative drugs (e.g., sirolimus, zotarolimus, everolimus, paclitaxel) for prevention of restenosis in coronary arteries via a stent delivery system has shown that these therapies successfully inhibit or reduce restenosis.[60-74] The use of drug-eluting stents in the superficial femoral and proximal popliteal arteries had promising early results that have not been sustained over the long-term.

The SIROCCO I and SIROCCO II trials evaluated the local application of sirolimus for prevention of restenosis in the superficial femoral artery in 95 subjects comparing use of an uncoated nitinol stent to a drug-coated nitinol self-expanding stent. At 24 months there were no significant differences in ABI or in-stent restenosis as measured by peak systolic velocity ratio using duplex ultrasound. Both groups showed an improvement in Rutherford classification post procedure which was sustained over 24 months.[75, 76]

Since the mid-2010s, drug-coated balloons (DCBs) have emerged as the first-line treatment option of obstructive SFA disease. These devices are essentially coated with paclitaxel. However, after promising results of several randomized controlled trials of paclitaxel-coated balloons (PCBs)[77-100], a meta-analysis of randomized controlled trials published in December 2018 by Katsanos et. al. identified an increased risk of late mortality at 2 years and beyond for patients treated with paclitaxel-coated devices compared to patients treated with uncoated devices[102]. Consequently, and further to its meta-analysis of long-term follow-up data from premarket trials, FDA made recommendations in August 2019 on the potential late mortality signal after treatment with paclitaxel-eluting devices in the femoropopliteal artery.[101] In June 2020, the French Competent Authority, ANSM (Agence Nationale de Sécurité du Medicament et des Produits de Santé) [103], the German Authority BFARM (Bundesinstitut für Arzneimittel und Medizinprodukte) requested all manufacturers to add a warning and clinical summary related to the meta-analysis data to European IFUs.[104]

In February 2021, the UK Competent Authority issued a similar statement recommending to not use paclitaxel drug-coated balloons (DCBs) or drug-eluting stents (DESs) in the routine treatment of patients with intermittent claudication, as the mortality risk generally outweighs the benefits.[105]

1.3. Study Rationale

Whereas the concerning long-term outcomes of paclitaxel-coated PTA catheters have led to controversy in the interventional vascular community, CVT has developed an possible catheter-based treatment alternative by combining 1) a proven percutaneous transluminal angioplasty (PTA) balloon catheter designed to treat lesions within the peripheral vasculature with 2) a drug coating using a proven drug, everolimus, as the active pharmaceutical agent to benefit from the proven long history of safety and efficacy of the use of this drug for coronary applications.

Everolimus [40-O-(2-hydroxyethyl)-rapamycin], is a semisynthetic macrolide immunosuppressant, which is in the same family as rapamycin (i.e., the "limus family of drugs") that inhibits mammalian target of rapamycin, and it is known to exert much higher interaction with rapamycin complex 2 leading to a blockage of protein synthesis. This interaction stops cell cycle progression, inhibits smooth muscle cell proliferation and reduces stent restenosis. In addition, everolimus has higher bioavailability and a shorter half-life than sirolimus, then it reduces vascular inflammation and stimulates rapid endothelialization[1].

Everolimus is a drug used worldwide in drug-eluting stents (DES) and is considered the percutaneous treatment of choice for coronary artery disease (CAD). The safety profile of everolimus-eluting stents is well established and safer than paclitaxel-eluting stents in long-term clinical follow-ups[2] .

Use of everolimus, a drug with an excellent safety profile and a very long proven history for cardiovascular use, with a proven PTA catheter was demonstrated by CVT in series of pre-clinical evaluations in the swine model. Extensive bench and pre-clinical studies have demonstrated that the CVT Everolimus-coated PTA Catheter is safe for its intended use with no adverse reactions associated to drug delivery for the treated vessel segment up to 30 days post-treatment in the animal model. The presence of everolimus in the vessel up to 30 days post-procedure, as demonstrated in pharmacokinetics studies, is associated with the possibility of prevention of a restenostic reaction in the treated vessel, characterized by signs of drug effect in the histopathology studies at that time point in the animal model.

The present trial will confirm the positive evaluations garnered to date in pre-clinical studies of the CVT Everolimus- coated PTA Catheter for its intended use of treating subjects with lesions in the SFA or popliteal (P1 segment) arteries.

2. DESCRIPTION OF THE STUDY DEVICE

The Chansu Vascular Technologies (CVT) Everolimus-coated PTA Catheter is an angioplasty

[1] Trimukhe R, Vani P, Patel A, Salgotra V. Safety and performance of the EverProTM everolimus-eluting coronary stent system with biodegradable polymer in a real-world scenario. World J Cardiol. 2020;12(12):615-625. doi:10.4330/wjc.v12.i12.615

[2] Meng, M., Gao, B., Wang, X. et al. Long-term clinical outcomes of everolimus-eluting stent versus paclitaxel-eluting stent in patients undergoing percutaneous coronary interventions: a meta-analysis. BMC Cardiovasc Disord 16, 34 (2016). https://doi.org/10.1186/s12872-016-0206-6

catheter designed to facilitate percutaneous treatment of subjects with documented symptomatic occlusion and/or >70% stenosis of the SFA or popliteal (P1 segment) artery.

The CVT Everolimus-coated PTA Catheter is comprised of two main components:

1) A CE-marked, commercially-available PTA balloon catheter (Ebony® 0.018" OTW PTA Balloon Catheter, Natec Medical Ltd. Reduit 72201, Mauritius) designed to treat peripheral vascular artery lesions. The PTA catheters are also previously cleared by FDA for peripheral (PTA) angioplasty indications (FDA classification LIT, K143041).
2) A drug coating comprised of an approved, commercially-available active pharmaceutical agent (API) mixed with an approved commercially-available excipient. The active pharmaceutical agent is the drug everolimus, in crystalline form, and it is applied onto the balloon using a glycerol ester excipient. Everolimus, like sirolimus, is an mTOR inhibitor drug with cytostatic properties. Everolimus is currently used in CE mark and FDA approved coronary drug-eluting stents [Promus (Boston Scientific), Xience (Abbott Vascular), Synergy (Boston Scientific)].

2.1. Basic Catheter Specifications

- Guidewire: 0.018"
- Sheath Compatibility: 6 French or greater
- Shaft length: 120 cm

The product size offerings and total dose content for the CVT Everolimus-coated PTA Catheter are listed in **Table 1**. The available sizes are 4.0, 5.0 and 6.0mm diameters and balloon lengths 40, 80 and 120mm. The nominal drug dose on all sizes is 3.0 µg/mm^2.

Table 1. CVT Everolimus-coated PTA Catheter Size Matrix and Total Drug Content

Balloon Diameter (mm)	Balloon Length (mm) and Total Drug Content (µg)		
	40	**80**	**120**
4.0	1508	3016	4524
5.0	1885	3770	5655
6.0	2262	4524	6786

2.2. Indication

The CVT Everolimus-coated PTA Catheter is intended for the treatment of patients with de-novo or post-PTA occluded/stenotic or re-occluded/ restenotic lesions (excluding in-stent lesions) ≤150mm in length in femoropopliteal arteries with reference vessel diameters of 4-6mm to establish blood flow and to maintain vessel patency.

For additional information, refer to the Instructions for Use provided as **Appendix E**.

3. STUDY DESIGN

The CVT-SFA Trial investigates the inhibition of restenosis using the CVT Everolimus-coated PTA Catheter in the treatment of de-novo occluded/ stenotic or re-occluded/ restenotic superficial femoral or popliteal arteries. The clinical study will be a prospective, multi-center, open, single-arm study.

Each subject will be followed for at least 3 years (36 months) after treatment. All subjects will have a follow-up contact or an optional office/hospital/clinic visit at 30 days. A follow-up office/hospital/clinic visit will occur at 6 and 12 months and a follow up phone call will occur at 24 and 36 months.

To participate in this study, the site will need the resources necessary for conventional vascular surgery as well as for fluoroscopy-guided catheter-based procedures with high quality imaging.

The study participation flow chart is provided in **Figure 1**.

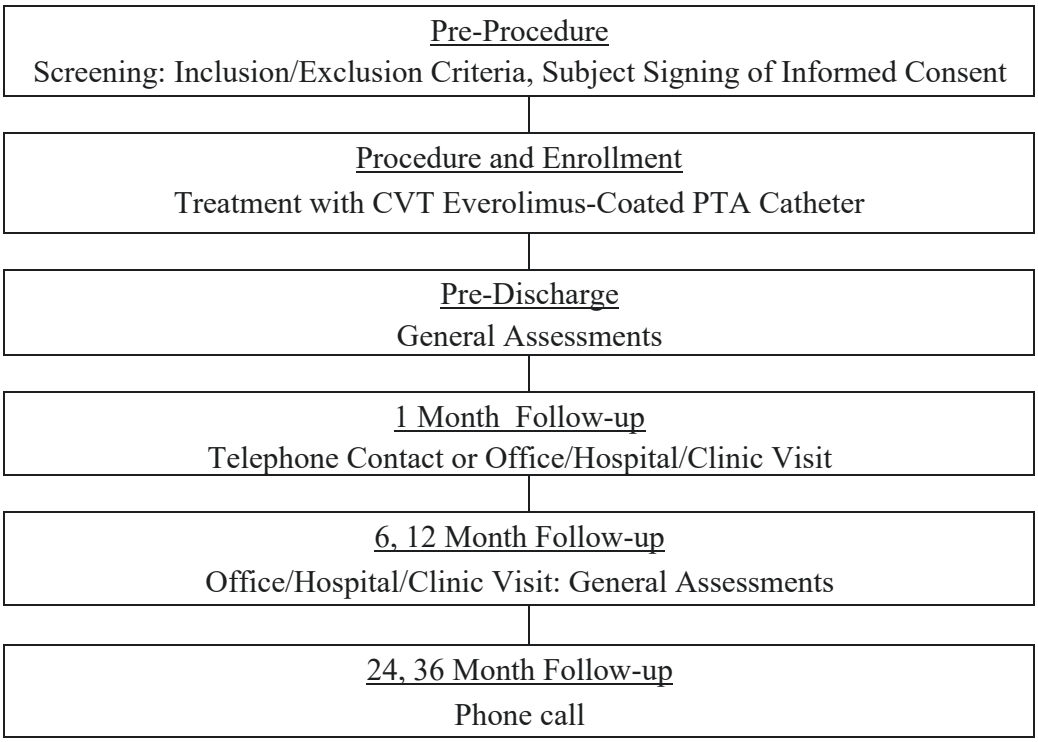

Figure 1. CVT-SFA Study Participation Flow Chart

3.1. Primary Endpoints

Primary Safety Endpoint

The primary safety endpoint for the study is freedom of major adverse event (MAE) rate at 6 months post-procedure, defined as a composite rate of cardiovascular death, index limb amputation and ischemia-driven target lesion revascularization (TLR).

Primary Effectiveness Endpoint

The primary effectiveness endpoint for the study is patency at 6 months post-procedure, defined as freedom from restenosis as determined by duplex ultrasonography (DUS) (peak systolic velocity ratio (PSVR) ≤ 2.4 or restenosis ≤ 50%) within 6 months and freedom from ischemia-driven target lesion revascularization (TLR).

Restenosis is determined by either PSVR >2.4, as assessed by an independent DUS core laboratory, or >50% stenosis, as assessed by an independent angiographic core laboratory in the event an angiogram has been recorded.

3.2. Secondary Endpoints

The following endpoints will be also evaluated as secondary endpoints:

- Rate of Major Adverse Event (MAE) Rate in hospital and at 30 days, 1, 2 and 3 years post-procedure, defined as a composite rate of cardiovascular death, index limb amputation and ischemia-driven Target Lesion Revascularization (TLR).
- Rate of occurrence of arterial thrombosis of the treated segment.
- Rate of ipsilateral embolic events of the study limb.
- Rate of clinically-driven target lesion revascularization at 6, 12, 24 and 36 months.
- Patency rate at 12 months post-procedure, defined as freedom from clinically driven TLR and duplex ultrasonography restenosis (ultrasound peak systolic velocity ratio ≤ 2.4 or stenosis ≤50%)
- Rate of vascular access site complication defined as the combined rate of hematoma, AV fistula or a pseudoaneurysm that required intervention, such as surgical repair or transfusion, prolonged hospital stay or required a new hospital admission.
- Lesion success (per device), defined as achievement of a final in-lesion residual diameter stenosis of <50% (by QA), using any device after wire passage through the lesion. Pre- and post-dilatation of the lesion with a non-study device is considered part of assigned device treatment.
- Technical success (per device), defined as achievement of a final in-lesion residual diameter stenosis of <50% (by QA), using the CVT Everolimus-coated PTA Catheter without a device malfunction after wire passage through the lesion. Pre- and post-dilatation are considered part of assigned device treatment.
- Clinical success (per subject), defined as technical success without the occurrence of major adverse events during the procedure.
- Procedural success (per subject), defined as lesion success without the occurrence of major adverse events during procedure.
- Ankle-Brachial Index (ABI) changes before procedure compared with ABI at discharge and at 6 and 12 months.

- Change in WIQ (walking impairment questionnaire) from pre-intervention at 6 and 12-months follow-up.
- Change in walking distance from pre-procedure at 6 and 12 months.
- Change in Rutherford classification grades of chronic limb ischemia from pre-intervention at 6 and 12-months follow-up for the treated limb.

3.3. Study Population

Subjects included in this study will be comprised of male and female subjects derived from the general interventional radiology or angiology population. The study will include seventy-five (75) subjects with a superficial femoral and/or popliteal (P1 segment) artery target lesion(s) eligible to be treated by interventional therapy and who meet all the inclusion criteria and none of the exclusion criteria of this study.

3.4. Ethical Considerations

The trial will be conducted in accordance with this Clinical Investigational Plan (CIP), the Declaration of Helsinki, BS EN ISO 14155:2020 standards and Good Clinical Practices. The conduct of the trial will be approved by the appropriate Medical Ethics Committee (MEC) of the respective clinical site and as specified by local and country specific regulations.

3.5. Subject Inclusion Criteria

Study subjects must fulfill the following clinical criteria:

1. Subject must be at least 18 years of age.
2. Subject or his/her legally authorized representative provides written informed consent prior to any clinical investigation related procedure, as approved by the appropriate Ethics Committee of the respective clinical site.
3. Subject must agree to undergo all clinical investigation plan-required follow-up visits and examinations.
4. Subjects with symptomatic leg ischemia, requiring treatment of SFA or popliteal (P1 segment) artery.
5. *De novo* or restenotic lesion(s) >70% within the SFA and popliteal arteries in a single limb which are ≥3 cm and ≤15 cm in cumulative total length (by visual estimation). Lesion must be at least 2 cm from any stented area.
6. Subject is willing to provide informed consent and comply with the required follow up visits, testing schedule and medication regimen.
7. Successful wire crossing of lesion.
8. Target vessel reference diameter ≥4 mm and ≤6 mm (by visual estimation).
9. Target lesion(s) can be treated with a maximum of two (2) CVT Everolimus-coated PTA Catheters.
10. At least one patent (less than 50% stenosis) tibio-peroneal run-off vessel confirmed by baseline angiography or prior MR angiography or CT angiography.

11. Life expectancy >1 year
12. Rutherford classification of 2, 3 or 4

3.6. Subject Exclusion Criteria

Subjects with **any** of the following criteria should be excluded:

1. Pregnant or lactating females.
2. Co-existing clinically significant aneurismal disease of the abdominal aorta, iliac or popliteal arteries.
3. Significant gastrointestinal bleeding or any coagulopathy that would contraindicate the use of anti-platelet therapy.
4. Known intolerance to study medications, everolimus or contrast agents.
5. Doubts in the willingness or capability of the subject to allow follow-up examinations.
6. Subject is actively participating in another investigational device or drug study.
7. History of hemorrhagic stroke within 3 months prior to treatment
8. Previous or planned surgical or interventional procedure within 30 days of index procedure.
9. Prior vascular surgery of the target lesion.
10. Lesion length is <3 cm or >15 cm or there is no normal proximal arterial segment in which duplex ultrasound velocity ratios can be measured.
11. Known inadequate distal outflow.
12. Significant inflow disease.
13. Acute or sub-acute thrombus in target vessel.
14. Use of adjunctive therapies (i.e. laser, atherectomy, cryoplasty, scoring/cutting balloons, brachytherapy, lithotripsy).
15. Outflow arteries (distal popliteal, anterior or posterior tibial or peroneal arteries) with significant lesions (≥ 50% stenosis) may not be treated during the same procedure.
16. Treatment of the contralateral limb during the same procedure or within 30 days of the study procedure.
17. Rutherford classification of 0, 1, 5 or 6.
18. Presence of prohibitive calcification that precludes adequate PTA treatment.
19. Subjects held in custody in an institution by official or court order.

3.7. Subject Enrollment Point

All subjects who are candidates for endovascular treatment of the SFA or popliteal artery will undergo screening for study eligibility and, if applicable, for study

enrollment. For any subject enrolled, a signature of informed consent will be obtained. The subject will be considered enrolled into the study upon the completion of all the following:

- A signed subject informed consent.
- Angiographic criteria for enrollment have been met.
- Successful treatment of the inflow (iliac) artery without complication, if applicable.
- Target lesion is successfully crossed by a guidewire.
- CVT Everolimus-coated PTA Catheter has entered the vasculature.

3.8. Subject Discontinuation

Every subject should remain in the study until completion of the required follow-up period; however, a subject's participation in any clinical trial is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. The reason for withdrawal, when it occurs, must be documented in the subject's medical record. Following study discontinuation, the subject will be followed per the institution's standard of care. Conceivable reasons for discontinuation may include, but are not limited to, the following:

- Subject participation in a clinical trial is voluntary and the subject may discontinue participation (refuse all subsequent testing/follow-up) at any time.
- Investigator may terminate the subject's participation without regard to the subject's consent if the Investigator believes discontinuation in the study is medically necessary.
- Subject does not complete the scheduled follow-up but has not 'officially' withdrawn from the trial (e.g. "lost to follow-up"). This does not apply to missed visits.
- Medical conditions such as the following:
    - Reaction to acute treatment that requires alternative treatment or intervention (e.g. allergic reaction to everolimus, complication with non-study device) where study objectives cannot be objectively evaluated.
    - Unanticipated hospitalization requiring treatment or therapy conflictive with study objectives and preventing compliance with study requirements.

Site personnel should make all reasonable efforts to locate and communicate with subjects at each contact time point. A minimum of two (2) telephone calls to contact the subject should be recorded in the source documents, including date, time, and initials of site personnel trying to make contact. If these attempts are unsuccessful, a letter should be sent to the subject. If the subject misses two (2) consecutive scheduled contact time points and the above mentioned attempts at communicating with the subject are attempted but unsuccessful, the subject will be considered "lost to follow-up".

A study completion form must be completed when a) the subject is considered "lost to follow-up" (per the above criteria), b) the subject withdraws from the study or c) the investigator withdraws the subject from the study. In each case of subject discontinuation, CVT must be notified of the reason for subject discontinuation. The site will provide this information on the case report form (CRF) and in source documents.

3.9. Early Termination of the Clinical Study

CVT, the trial sponsor, reserves the right to discontinue the clinical study at any stage, with suitable written notice to the investigator. The investigator may also discontinue participation in the clinical trial with suitable written notice to CVT.

CVT and the Study Steering Committee will monitor the progression of the study. The study will be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population. Per definition, this would be the case in the event that the Major Adverse Event (MAE) rate reaches a level greater that the upper limit of the 95% confidence interval of the anticipated MAE. MAE is defined as a composite rate of cardiovascular death, index limb amputation and ischemia-driven target lesion revascularization (TLR).

Notification of study suspension or termination will occur no later than five (5) working days after the sponsor makes the determination. In the event of study suspension or termination, the sponsor will send a report outlining the circumstances to the IRB/EC and all investigators. A suspended or terminated study may not be re-initiated without approval of the reviewing IRB/EC (where applicable).

4. CONDUCT OF THE STUDY

Study conduct as well as detail of pre-procedure, procedural, discharge and follow up activities are presented in this section of the protocol. Refer to **Table 2** for a summary of pre-procedure, procedure, discharge and follow up activities.

4.1. Baseline Assessments

Subject preparation will occur in accordance with standard hospital policy for the care of interventional endovascular subjects. Baseline assessments will be documented in the subject medical record and on the case report form (CRF) as appropriate.

Subject History

Subject history will include, but not be limited to, the following risk factors and co-morbidities: age, height, weight, body mass index (BMI), gender, hypertension, hyperlipidemia, diabetes mellitus, smoking, ischemic heart disease (history of myocardial infarction, angina pectoris, previous percutaneous or surgical coronary revascularization), history of peripheral vascular disease (previous percutaneous or surgical revascularization), deep vein thrombosis, congestive heart failure, renal insufficiency, renal disease, liver disease, cerebrovascular disease (known carotid artery disease, history of minor or major stroke or transient ischemic attack), and chronic obstructive pulmonary disease (COPD).

Medication History

A medication history should be documented which includes chronic concomitant

medications and protocol-required medications.

Clinical Assessments

The dorsalis pedis and posterior tibial pulses for the treated limb should be documented. The distal ipsilateral extremity should be examined to ensure no gangrene or ischemic ulcers are present.

Hemodynamic Evaluation

Ankle brachial index (ABI) measurement will be obtained for the target limb.

Functional Status

Functional status using the Rutherford Becker Clinical Categories will be determined for the target limb.

Subject-perceived walking performance will be evaluated utilizing a walking impairment questionnaire (WIQ).

Walking distance will be evaluated using either the Walking Test or the Treadmill Test.

Claudication at rest and after walking will be noted.

Laboratory Assessments

A pregnancy test should be administered to all female subjects of childbearing potential within 14 days of the procedure.

The following laboratory tests should be obtained for all subjects within 7 days of the index procedure.

- Hemoglobin
- Hematocrit
- White Blood Cell Count
- Absolute Platelet Count
- Serum Creatinine
- Coagulation tests as per standard of care of the hospital (e.g., Prothrombin Time (PT) and activated Prothrombin Time (aPTT).

Duplex Ultrasonography Assessment (Optional)

At the discretion of the investigator, duplex ultrasonography may be performed according to the ultrasound core laboratory guidelines.

4.2. Concomitant Medical Therapy

Prior to the study procedure, it is required that subjects receive aspirin (ASA) and either clopidogrel or ticlopidine (only if subject has known allergy to clopidogrel or prasugrel) per hospital standard of care (either antiplatelet medication 3 days pre-procedure or loading dose on the day of intervention). Recommended aspirin dose is 100 mg daily; for clopidogrel the recommended dose is 75 mg daily and for ticlopidine 250 mg twice a day.

4.3. SFA PTA Procedure

Procedural Medications

During the procedure, subjects will receive appropriate anticoagulation and other therapy according to standard hospital practice. The use of any medication for the treatment of vessel spasm, subject agitation or discomfort, hypotension, arrhythmias and hemodynamic changes during the procedure is at the discretion of the investigator.

Baseline Angiography

The diagnostic and interventional procedure can be conducted via either contralateral or antegrade approach at the investigator's discretion. A pelvic angiogram (digital subtraction angiography, Magnetic Resonance (MR) angiography, or Computed Tomography (CT) angiography) with run-off must have been performed prior to the PTA procedure (run-off should include popliteal and distal vessels) to confirm patent inflow and outflow as well as run-off required within the inclusion criteria.

Treatment Strategy

This study allows for treatment of *de novo* occluded/stenotic or re-occluded/restenotic superficial femoral (SFA) or popliteal artery (P1 segment) lesions in a single limb that are ≥3 cm (30 mm) and ≤15 cm (150 mm) in cumulative length, with up to two (2) CVT Everolimus-coated PTA Catheters. The lesion(s) should be within 1 cm distal to the femoral bifurcation in the SFA and 3 cm from the proximal margin of the intercondylar fossa.

The timing and method of treatment of any contralateral non-target lesion(s) is at the discretion of the investigator; however, it should be >30 days before or after the study procedure. A contralateral non-target lesion(s) cannot be treated during the same procedure in order to avoid complications.

Subjects selected for treatment must have a patent inflow artery and outflow arteries free from significant lesions (≥50% stenosis) as confirmed by angiography. If the ipsilateral iliac artery is diseased, but not occluded, it may be treated prior to the treatment of the target SFA/popliteal lesion. Successful treatment of the inflow artery is defined as attainment of final residual diameter stenosis of <30% without residual dissection or complication during the treatment. Outflow arteries (distal popliteal, anterior or posterior tibial or peroneal arteries) with significant lesions (≥50% stenosis) may not be treated during the same procedure.

Pre-dilatation will be performed for all target lesions with a non-study balloon catheter. After pre-dilatation, the investigator will determine the suitability of the lesion for treatment by PTA alone.

The target lesion should be treated after meeting the general and angiographic inclusion and exclusion criteria. Additional treatment modalities, including but not limited to, rotational or directional atherectomy, cryoplasty, scoring/cutting balloons, laser, brachytherapy or lithotripsy must not be performed in conjunction with this procedure.

The balloons should be sized to ensure the full length of the lesion is treated and that the balloon, upon inflation, apposes the arterial wall without oversizing.

The initial inflation of the study device should be ≥ 1 minute.

For a residual stenosis >50% or significant dissection after study treatment, post-dilatation should be performed. A commercially available non-drug eluting nitinol stent may be used to treat a flow-limiting dissection or persistent residual stenosis if balloon inflation is unsuccessful. Post-dilatation of the stent, if required, should be done with the CVT Everolimus-coated PTA Catheter.

PTA Procedure

The appropriate balloon size will be selected after review of the subject's baseline angiogram and determination of the reference vessel diameter and lesion length.

Pre-dilatation will be performed on all subjects per the following sequence: after crossing of the target lesion with a guidewire, pre-dilatation will be performed with a non-study balloon catheter. Based on the suitability of the lesion, the investigator will determine if the lesion can be treated by PTA alone or if treatment with a stent is required (e.g. dissection, stenosis >50%). If a stent is required, the investigator will implant the stent and the patient cannot be included in the study (e.g. screen fail). If the lesion is suitable for PTA treatment alone, the CVT Everolimus- coated PTA Catheter will be used to treat the lesion.

All catheters, including the CVT Everolimus-coated PTA Catheter, should be delivered and deployed per their respective Instructions for Use (reference Appendix E for CVT Everolimus-coated PTA Catheter IFU). All balloon inflations and stent deployments, when applicable, should be captured per the angiographic core laboratory guidelines.

Criteria for Bail-Out or Alternative Procedures

For a post-treatment residual stenosis >50% or significant dissection after study treatment, post-dilatation should be performed. A commercially available nitinol stent may be used to treat a flow-limiting dissection or persistent residual stenosis >50% only after post-dilatation inflation is unsuccessful. If stent post-dilatation is performed, a CVT Everolimus-coated PTA Catheter should be used.

Angiography following PTA

Angiographic imaging is to be performed according to the angiographic core laboratory protocol and will include runoff into the distal extremity. Post-procedural images should be captured in a precise manner such as was used for the pre-procedure images.

4.4. Post-Procedure Subject Management

Following the treatment procedure, the subject will be treated in accordance with the hospital standard of care for PTA interventions.

Sheath Removal and Ambulation

Use of approved vascular closure devices are allowed, provided the device is used according to the manufacturer's instructions for use and the operator has been properly trained in the device use. The subject may be ambulated according to hospital standards after hemostasis of the access site is achieved.

Medications

The optimal duration of antiplatelet therapy for each subject is to be determined by the investigator.

All subjects enrolled into the trial are recommended to be maintained on 75 mg of clopidogrel bisulfate daily for a minimum of one (1) month following the angioplasty procedure, increased to three (3) months if a stent was used. All subjects will receive ≥ 100 mg of aspirin daily to be taken throughout the length of the study following the procedure. (for minimum of 12 months following procedure)

If a subject develops hypersensitivity to clopidogrel bisulfate, they may be switched to ticlopidine hydrochloride at a dose in accordance with standard hospital practice.

NOTE: Subjects receiving ticlopidine hydrochloride must have a complete blood cell count (CBC) and differential blood count done per the IFU for ticlopidine hydrochloride.

4.5. Pre-Discharge Assessments

Medication History

The medication history should be updated as needed to include modifications to the chronic concomitant medications and protocol-required medications.

Clinical Assessments

The dorsalis pedis and posterior tibial pulses for the treated limb should be documented.

The distal ipsilateral extremity should be examined to ensure be examined to ensure no gangrene or ischemic ulcers are present.

Laboratory Tests

If the subject presents with less than desired clinical outcome or symptoms of an adverse event laboratory tests should be obtained within 12-24 hours post procedure (or prior to hospital discharge). Should laboratory tests be required, the following tests are recommended:

- Hemoglobin
- Hematocrit
- White Blood Cell Count and differential
- Absolute Platelet Count
- Blood Urea Nitrogen
- Serum Creatinine
- Serum Glutamic-Pyruvic Transaminase (SGPT)
- Serum Glutamic-Oxaloacetic Transaminase (SGOT)
- Coagulation tests as per standard of care of the hospital (e.g., Prothrombin Time (PT) and activated Prothrombin Time (aPTT)

Hemodynamic Evaluation

An ankle brachial index (ABI) measurement will be obtained for the treated limb.

Duplex Ultrasonography Assessment/Rutherford Classification

Duplex ultrasound examination and Rutherford classification will be performed prior to hospital discharge of the treated limb in accordance with the ultrasound core laboratory requirements.

Adverse Events

Documentation of adverse events.

4.6. Subject Follow-up Post Hospital Discharge

Following hospital discharge, subjects will be followed at pre-determined time points during the study.

Subject Contact at 1 month (30 ± 7 days)

Subjects will be contacted at 30 days post hospital discharge via phone call for assessment of overall condition and medications. Alternatively, this contact can be performed in a site visit.

Subject Clinical Visit at 6 months (180 ±30 days)

- Assessment of ischemia
- Claudication at rest and after walking
- Completion of the walking impairment questionnaire (WIQ)
- Completion of either the Walking Test or Treadmill Test
- Rutherford Classification
- Ankle Brachial Index (ABI) measured at rest.
- Data regarding any emergent treatment and or serious adverse events and/or need for repeat angiography or interventions and results of such, if applicable
- Concomitant medication (name, dose, duration)
- Duplex ultrasonography examination per core laboratory guidelines
- Adverse event assessment
- Medications

Subject Clinical Visit at 12 months (365 ±30 days)

- Assessment of ischemia
- Claudication at rest and after walking
- Completion of the walking impairment questionnaire (WIQ)
- Completion of either the Walking Test or Treadmill Test
- Rutherford Classification

- Ankle Brachial Index (ABI), measured at rest
- Data regarding any emergent treatment and or serious adverse events and/or need for repeat angiography or interventions, and results of such if applicable
- Concomitant medication (name, dose, duration)
- Duplex ultrasonography examination
- Adverse event assessment
- Medications

Subject Phone call follow up at 24 Months (730 ± 30 days)

Subjects will be contacted at 24 months post hospital discharge via phone call for assessment of overall condition and medications. Alternatively, this contact can be performed in clinical visit with the referring physician.

Subject Phone call follow up at 36 Months (1095 ± 30 days)

Subjects will be contacted at 36 months post hospital discharge via phone call for assessment of overall condition and medications. Alternatively, this contact can be performed in clinical visit with the referring physician.

Table 2. CVT-SFA Study Pre-Procedure, Procedural, Discharge and Follow Up Activities

PROCEDURE/TEST	Prior to Procedure (Within 14 days)	Pre-Procedure (Within 24 hours)	**PROCEDURE**	Pre-Discharge	30 days (±7 days) Phone call or Office\hospital Visit	180 days (±30 days) Office/hospital visit	365 days (±30 days) Office /hospital visit	24 and 36 months (±30 days)
Patient Medical/Clinical History	✓							
Chronic Concomitant Medications	✓			✓	✓	✓	✓	✓
Patient Informed Consent	✓							
General/Inclusion Exclusion	✓							
Angiographic/Anatomic Inclusion/Exclusion Criteria			✓					
Pregnancy Test (if applicable)	✓							
Serum Hematology	✓			✓*				
Blood Chemistry	✓			✓*				
Peripheral Angiogram with Runoff		✓	✓					
Duplex Ultrasonography Examination	✓#			✓		✓	✓	
Ankle Brachial Indices	✓			✓		✓	✓	
Rutherford-Becker Classification	✓			✓		✓	✓	
WIQ	✓					✓	✓	
Walking Test or Treadmill Test	✓					✓	✓	
Per-protocol Medications		✓	✓	✓				
Adverse Events			✓	✓	✓	✓	✓	✓

\# *optional*
* *If the subject presents with less than desired clinical outcome or symptoms of an adverse event*

5. ADVERSE EVENTS

5.1. Adverse Events

At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this protocol, an adverse event is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

In this study, subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF.

In addition, subjects will be instructed to contact the investigator, and/or study coordinator if any significant adverse events (e.g., MAE) occur between study evaluation visits.

Adverse event reporting begins when the index procedure is completed.

Adverse events should be followed to resolution or stabilization, and if an ongoing AE changes in severity, a new AE entry for this event should be recorded. If a mild adverse event changes to a moderate or severe adverse event, the end date for the mild event and the start date for the moderate or severe event should be the same. Additionally, the mild event is considered resolved with the initiation of the moderate or severe event.

Adverse events that are present at the end of a subject's participation in the study should be marked as on-going on the case report form and the subject should receive post-treatment follow-up as appropriate.

5.2. Anticipated Adverse Events

An anticipated adverse event is any untoward medical occurrence in a subject which is predefined in the protocol and/or Instruction for Use (IFU) and that is identified or worsens during a clinical study, regardless whether or not the event is considered related to the study device or drug regimen prescribed as part of the protocol.

The following is a list of adverse events that may result from the PTA procedure.

- Abrupt closure
- Acute MI
- Allergic reaction to contrast, concomitant medications (Allergic Reaction)
- Amputation
- Aneurysm
- Arrhythmias (bradycardia & tachycardia)
- Arterial dissection
- Arterial perforation or rupture
- Artery spasm
- AV fistula
- Bleeding

- Bypass graft surgery (emergent or non-emergent)
- Chest pain
- Death (cardiovascular or non-cardiovascular related)
- Discomfort during the procedure
- Embolism/PTA catheter embolism
- Endocarditis
- Fever
- Groin Bruising/Discomfort
- Hematoma
- Hemorrhage
- Hypertension
- Hypotension
- Injury to the groin blood vessel
- Infection or pain at insertion site
- Ischemia
- Nausea
- Pseudoaneurysm
- Renal failure
- Restenosis
- Sepsis /infection
- Stroke/CVA
- Wound complication or wound infection
- Thrombosis
- Total occlusion
- Vomiting / nausea

The oral formulation of everolimus has been evaluated in clinical trials and is approved worldwide for the prophylaxis of organ rejection in adult kidney transplant recipients at low-moderate immunologic risk and for the treatment of patients with advanced renal cell carcinoma. Oral dose of everolimus depending on the indication ranges between 1.5 and 20 mg/day. The following list includes the known risks of everolimus at these oral doses. *The following is a list of theoretical adverse events that may result from the addition of everolimus to a PTA catheter:*

- Abdominal pain
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation

- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dyspnea
- Dysgeusia
- Dyspepsia
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia
- Hyperlipidemia
- Hyperkalemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections
- Insomnia
- Interaction with strong inhibitors and inducers of CYP3A4 or PgP
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)
- Male infertility
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, and back
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis

- Thrombocytopenia
- Thrombotic microangiopathy
- Thrombotic thrombocytopenic purpura
- Tremor
- Urinary tract infection
- Upper respiratory tract infection
- Vomiting

5.3. Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae
Moderate	Interferes with the subject's usual activity and/or requires symptomatic treatment
Severe	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment

5.4. Relationship to Study Device

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study device:

Not Related	Relationship to the device or procedures can be excluded when: • The event has no temporal relationship with the use of the investigational device or the procedures related to the application of the investigational device. • The serious adverse event does not follow a known response pattern and is biologically impossible. • The discontinuation of medical device application or the reduction of the level or activation/exposure, when clinically feasible, and the re-introduction of its use do not impact on the serious adverse event. • The event involves a body-site or an organ that cannot be affected by the device or procedure. • The serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device/drug/treatment, or other risk factors). • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

Possible	The relationship with the use of the investigational device or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition, an effect of another device/drug/treatment). Cases where relatedness cannot be assessed, or no information has been obtained, should be also be classified as possible.
Probable	The relationship with the investigational device or the relationship with the procedures seems relevant and/or the event cannot be reasonably explained by another cause.
Highly Probable	The temporal sequence is relevant and the event abates upon device application completion/removal, or reappearance of the event on repeat device application (re-challenge). The serious adverse event is associated with the investigational device or with procedures beyond reasonable doubt when: • The event is a known side effect of the product category the device belongs to or of similar devices and procedures. • The event has a temporal relationship with the investigational device use/application or procedures. • The event involves a body-site or organ that a) the investigational device or procedures are applied to or b) the investigational device or procedures have an effect on. • The serious adverse event follows a known response pattern to the medical device. • The discontinuation of the medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase in the level of activation/exposure) impact on the serious adverse event (when clinically feasible). • Other possible causes (e.g. an underlying or concurrent illness/critical condition or/and an effect of another device, drug or treatment) have been adequately ruled out • Harm to the subject is due to error in use. • The event depends on a false result given by the investigational device used for diagnosis, when applicable.

5.5. Serious Adverse Events

An Adverse Event is considered serious if the event led to one of the following outcomes:

- Death of a subject
- Serious deterioration in the health of a subject that resulted in any of the following:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or body function
  - Hospitalization or prolongation of patient hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function
  - Chronic disease
- Foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Planned hospitalizations for pre-existing conditions or a procedure required by this protocol without serious deterioration in health is not considered a serious adverse event.

5.6. Procedures for Reporting Serious Adverse Event

Criteria for Reporting Serious Adverse Event

Serious adverse events are required to be reported for the following situations:

a. Any serious adverse event that has a causal relationship with the investigational device or the investigation procedure or where such as causal relationship is reasonably possible.

b. Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred or circumstances had been less fortunate.

c. Any new findings in relation to any event referred to in points (a) and (b) above.

Reporting by the Sponsor to National Competent Authorities

The Sponsor must report serious adverse events to the National Competent Authorities (NCAs) where the clinical investigation has commenced per the following timelines:

- For all reportable events which indicate an imminent risk of death, serious injury or serious illness and that requires prompt remedial action for other subjects, users or other persons or a new finding to the event: *Immediately but not later than two (2) calendar days after awareness by the Sponsor of a new reportable event or of new information in relation with an already reported event.*
- For other reportable events or a new finding/update: *Immediately but not later than seven (7) calendar days following the date of awareness by the sponsor of*

the new reportable event or of new information in relation with an already report event.

Reporting by the Clinical Trial Investigator to the Sponsor

The Clinical Trial Investigator will report to the Sponsor immediately but no later than three (3) calendar days after investigational site study personnel become aware of the event.

Risk Assessment

In conjunction with the Coordinating Clinical Investigator and/or, if need be, the Clinical Event Committee (section 10.4), the Sponsor shall decide whether, as a result of a serious adverse event, the safety of study participants is at risk or whether continuation of the trial is in jeopardy.

Corrective Measures

If any situation potentially jeopardizing the safety of subjects, users or third persons arise during a clinical trial or approved performance evaluation, the Sponsor and those persons carrying out the clinical trial or the performance evaluation shall immediately take all of the essential safety measures in order to protect subjects, users or third persons from direct or indirect danger. The Sponsor or his representative shall immediately inform the competent Authority and arrange for the competent Ethics Committee to be informed of the latest developments.

6. STATISTICAL DESIGN AND ANALYSIS

6.1. Statistical Overview of the Trial

The primary sample size calculation is based on the hypotheses that the primary safety and effectiveness endpoints meet pre-determined Objective Performance Criteria (OPC).

The OPCs for the primary safety and effectiveness endpoints have been determined using historical control data from published studies. Since this is a feasibility trial, the attainment of statistical significance is neither a necessary nor a sufficient condition for determining whether the device merits further study. For example, if the data exhibits a trend ($p \leq 0.15$) toward statistical significance when compared to historical control and raises no safety concerns, it may be deemed worthy of further investigation. In addition, there will be a focus on estimating the magnitude of observed rates at 180 days post-procedure and the associated 95% confidence intervals.

6.2. Analysis Populations

The primary endpoints will be analyzed on the entire safety population and on the evaluable subject population, as appropriate.

The safety population will consist of all subjects who enrolled into the study and for whom the procedure had been initiated.

All effectiveness endpoints will be analyzed using the evaluable population, which consists of subjects who had no bailout procedure and at least one valid follow-up visit.

6.3. Sample Size Justification

Approximately seventy-five (75) subjects at up to eight (8) active sites will be enrolled in the CVT-SFA Trial. All subjects will be scheduled for clinical examination and duplex ultrasonography assessment at six (6) months. The objective of the study is to assess the initial feasibility and performance of the CVT Everolimus-coated Catheter in the treatment of subjects with *de-novo* occluded/stenotic or re- occluded/restenotic superficial femoral (SFA) or popliteal arteries. The study is powered based on primary safety and effectiveness endpoints.

The primary safety endpoint for this analysis is freedom from Major Adverse Event (ffMAE, %) at six (6) months post-procedure. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $ffMAE_{\text{historical control}} \leq ffMAE_{\text{CVT treatment}}$
H_A: $ffMAE_{\text{historical control}} > ffMAE_{\text{CVT treatment}}$

The proposed sample size of N=75 is based on the primary safety endpoint of freedom from MAE at 6 months. The sample size calculation is based on the following assumptions:

- A single comparison of CVT Everolimus-coated PTA Catheter treatment group to a safety OPC.
    - The assumed difference between the OPC and the treatment group is **15%**. This assumption is made based on the results observed in the control arm of the IN.PACT, STELLAREX, LUTONIX, RANGER programs[3]
    - One-tailed α=0.025

The primary effectiveness endpoint for this analysis is patency (%) at six (6) months. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $Patency_{\text{historical control}} \leq Patency_{\text{CVT treatment}}$
H_A: $Patency_{\text{historical control}} > Patency_{\text{CVT treatment}}$

The sample size of N=75 is based on the primary effectiveness endpoint of patency (%) at six (6) months and the following assumptions:

- A single comparison of CVT Everolimus-coated PTA Catheter treatment group to a patency OPC.
    - The assumed difference between the OPC and the treatment group is **15%**. This assumption is made based on the results observed in the control arms of the IN.PACT, STELLAREX, LUTONIX, RANGER programs[3]
    - Approximately 10% rate of lost to follow-up or dropout.

[3] IN.PACT https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140010c.pdf STELLAREX https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160049B.pdf, LUTONIX https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130024S009B.pdf RANGER https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190019B.pdf

- One-tailed α=0.025

The primary safety endpoint for this analysis is the freedom from Major Adverse Events at six (6) months. The study is powered based on this primary safety endpoint and the goal is to compare the CVT Everolimus-coated PTA Catheter treated group to an OPC established using a database of historical studies[3]. Since this is a feasibility trial, hypothesis testing and the attainment of statistical significance when compared to historical control are neither necessary nor sufficient conditions to determine whether the device merits further study. Instead, the focus will be on estimating the frequency of Major Adverse Events at six (6) months post-procedure and the associated 95% confidence interval. The sample size for the study based on the primary safety endpoint of frequency of Major Adverse Events at six (6) months was calculated using the following assumptions:

- A single comparison of CVT Everolimus-coated PTA Catheter treatment group to an historical control group
- An OPC of 70%

Given the above assumptions, enrollment of 75 subjects (safety population) will be the recruitment goal.

If 11 of 75 (15%) subjects experience MAEs, the point estimate for ffMAE is 85% and the 95% CI is [75.3%, 92.4%], well above the OPC of 70%.

The primary effectiveness endpoint for this analysis is patency at six (6) months. The study is also powered on this endpoint and the goal is to compare the CVT Everolimus-coated PTA Catheter treated group to an OPC established using the same database of historical studies as was used above for safety. The sample size for the effectiveness endpoint of patency at six (6) months post-procedure and the associated 95% confidence interval is estimated under the following assumptions:

- A single comparison of CVT Treatment group to an historical control group
- A patency OPC of 65%

Given the above assumptions, enrollment of 75 subjects (yielding ~68 evaluable subjects) will be the recruitment goal.

If as few as 55 of 68 subjects remain patent at 6 months, the point estimate is 81% and the 95% CI is [71.5%, 90.2%], well above the OPC of 65%.

The power estimates from enrolling 75 subjects to detect 15%-point margins above the Safety and Effectiveness OPCs are 85% and 78%, respectively.

Sample size and power calculations were performed using PASS13.

6.4. Statistical Analyses

Detailed analyses of the primary endpoints will be performed when all of the subjects complete their primary follow-up visit at 180 days. No effort will be made to impute or extrapolate data to replace missing values. All calculations will be based on available data with missing data excluded. Any unused or spurious data will be noted as

appropriate in the final report.

Analysis of Primary Endpoints

The primary effectiveness endpoint of patency at six (6) months will be analyzed on a per-subject basis for the evaluable populations.

The primary safety endpoint of freedom from MAE at 6 months will be analyzed using the safety population.

For both primary endpoints (ffMAE and patency at 6 months), percentages and exact 95% confidence intervals using Clopper-Pearson's method will be calculated.

Analysis of Secondary Endpoints

All secondary endpoints will be analyzed for the per-treatment evaluable population descriptive statistics will be provided to gain better understanding of the data.

For binary variables such as MAE or technical success counts, percentages, and exact 95% confidence intervals using Clopper-Pearson's method will be calculated. For continuous variables, means, standard deviations, and 95% confidence intervals for the mean using the Gaussian approximation will be calculated. If the assumption of normality seems untenable, nonparametric summary statistics will be presented instead.

For time-to-event variables, such as time to target lesion revascularization, survival curves will be constructed using Kaplan-Meier estimates, and log rank test results will be displayed for descriptive purposes only.

Analysis of Other Data

The clinical laboratory values collected will be analyzed by tabulating the number and percentage of subjects with clinically significant changes from baseline for each parameter at each time point.

7. RISK ASSESSMENT

7.1. Potential Risks from Peripheral Catheterization, Stenting and PTA

It is expected that risks associated with this study will be not significantly different than those with standard interventional procedures for PAD disease in the superficial or popliteal (P1 segment) arteries. The list of adverse events that may result from peripheral intervention includes but is not limited to: abrupt closure, acute myocardial infarction, allergic reaction to contrast, amputation, aneurysm, arrhythmias, arterial dissection/perforation/rupture, artery spasm, AV fistula, bleeding, bypass graft surgery, chest pain, death, discomfort during procedure, embolism (air, tissue, thrombosis, device), endocarditis, fever, groin bruising/discomfort, hematoma, hemorrhage, hypertension, hypotension, injury to groin vessel, infection or pain at insertion site, ischemia, nausea, pseudoaneurysm, renal failure, restenosis, sepsis/infection, stroke/CVA, wound complication/infection, total occlusion, vomiting/nausea.

7.2. Potential Risks from Everolimus Coating

The oral formulation of everolimus has been evaluated in clinical investigations and has been approved in more than 90 countries. Everolimus has been approved for more than a decade and used as an immunosuppressant to prevent rejection of organ transplants and in the treatment of a number of cancers. Everolimus marketed under the trade names Zortress (USA), Certican (European Union and other countries) in transplantation medicine, and as Afinitor and Votubia in oncology[4],[5].

In animal studies, everolimus has shown a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test). In humans the toxicity data is limited; single doses of up to 70 mg have been administered with no difference in acute toxicity profile of what was observed for the 10 mg dose.

Everolimus is often used in combination with cyclosporine (microemulsion formulation) and corticosteroids.

Subjects treated with everolimus usually receive doses ranging up to 10mg/day over several months period and extending up to a year or more with achievement of state concentration within 4 to 7 days.

The following adverse events were noted in everolimus clinical investigations:

Abdominal pain, anemia, angioedema, anorexia, asthenia, constipation, cough, delayed wound healing/fluid accumulation, diarrhea, dyslipidemia, dyspnea, dysgeusia, dyspepsia, dysuria, dry skin, edema (peripheral), epistaxis, fatigue, headache, hematuria, hyperglycemia, hyperkalemia, hypertension, hypokalemia, hypomagnesaemia, hypophosphatemia, increased serum creatinine, infections, insomnia, interaction with strong inhibitors/inducers of CYP3A4 or PgP, leukopenia, male infertility, mucosal inflammation, nausea, neutropenia, non-infectious pneumonitis, pain, proteinuria, pruritus, pyrexia, rash, stomatitis, thrombocytopenia, thrombotic microangiography, thrombotic thrombocytopenic purpura, tremor, urinary tract infection, upper respiratory tract infection and vomiting[6].

Certain side effects and discomforts have been reported in subjects that have received everolimus in intravenous (IV) form as part of chemotherapy treatment. These subjects may have other comorbid conditions and/or have received concomitant medications that may also have contributed to the reported side effects. In the IV setting, the dose is delivered throughout the body and in doses hundreds of times higher than the total amount present on the CVT Everolimus-coated PTA Catheter used in this clinical study. The side effects reported by the chemotherapy subjects include allergic/immunologic reactions, alopecia, anemia, blood product transfusion, gastro-intestinal symptoms, hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia), hepatic enzyme changes, histologic changes in vessel wall, cellular damage or necrosis, myalgia/arthralgia and peripheral neuropathy.

[4] Trimukhe R, Vani P, Patel A, Salgotra V. Safety and performance of the EverProTM everolimus-eluting coronary stent system with biodegradable polymer in a real-world scenario. World J Cardiol. 2020;12(12):615-625. doi:10.4330/wjc.v12.i12.615

[5] Meng, M., Gao, B., Wang, X. et al. Long-term clinical outcomes of everolimus-eluting stent versus paclitaxel-eluting stent in patients undergoing percutaneous coronary interventions: a meta-analysis. BMC Cardiovasc Disord 16, 34 (2016).

[6] Certican® (Everolimus) Product Insert. Novartis, Mar 2013.

Based on current information available to date on everolimus as a drug entity and on the CVT Everolimus-coated PTA Catheter evaluated in preclinical studies, it is unlikely, with the total dosage on the CVT Everolimus-coated PTA Catheter and the targeted vessel delivery of the everolimus, that the side effects associated with high dose of everolimus would occur.

7.3. Risk Management Procedure

The CVT-SFA Trial will be conducted by skilled and trained investigators relative to interventional procedures and this protocol. The research team at each clinical site will undergo specific in-servicing and training prior to initiation of the study.

Subjects will be monitored closely throughout the study duration. Subjects will be evaluated clinically at pre-determined time points to assess their clinical condition. The subject's medication regimen will be in accordance with standard of care requirements for peripheral interventional procedures.

7.4. Potential Benefits

Given that paclitaxel, the drug used on most drug-coated balloons (DCBs) that have been a first-line treatment option of obstructive SFA disease since the mid-2010s, has a potentially increasing risk of late mortality at 2 years and beyond compared to patients treated with uncoated devices, [101] the replacement of paclitaxel with everolimus, a drug with a proven safety profile in drug-eluting stents (DES) and considered as the percutaneous treatment of choice for coronary artery disease (CAD), may be the alternative to reduce restenosis and late lumen loss in the superficial femoral and proximal popliteal arteries.

8. DATA HANDLING, RECORD KEEPING AND REPORTING

8.1. Case Report Form (CRF) Completion

All required study data will be accurately recorded by authorized personnel on CRFs which will be provided by CVT.

8.2. Source Documentation

Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the CRFs. Investigators will maintain all records pertaining to this study as mandated by the hospital requirements and national laws and regulations.

8.3. Reports

A report will be created after the primary endpoints have been analyzed and a final report on the study will be completed at the end of the study. Interim reports may be compiled, at the request of the sponsor, for regulatory purposes.

9. REGULATORY REQUIREMENTS

9.1. Investigator's Responsibility

Prior to enrolling subjects for this study, the investigator must read and understand the

protocol and must sign and complete an investigator agreement form. The investigator agreement form documents the investigator's agreement to all conditions of the protocol and an agreement to conduct the study accordingly.

This study will be conducted in accordance with Good Clinical Practice (GCP), ISO14155:2020 and the Declaration of Helsinki as well as any local or regional regulations.

Additional requirements must be met by the investigator and participating institutions.

9.2. Compliance with Protocol and Protocol Amendments

A protocol deviation is defined as any change, divergence or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB/EC. The investigator is responsible for promptly reporting protocol deviations to their IRB/EC per IRB/EC policy and to the sponsor. The sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety and determine if additional reports or actions are required. Additional action may include site re-training, removal of the devices, and/or site termination.

The investigator will not implement any changes to the protocol without first obtaining in written agreement from the sponsor and documented approval from the EC, except in the event of an immediate hazard to the subject. The investigator will report the deviation in accordance with the applicable regulations.

9.3. Investigator Requirements

All investigators must submit the following documentation to be considered approved investigators. The Sponsor will make final determination of approved investigators.

- Signed investigator's agreement
- Completed site specific in-servicing and training

Investigators must allow CVT or representatives of CVT to visit the site to periodically assess the data quality and study integrity. On site, CVT, or its representatives, will review study records in comparison with source documents, discuss the conduct of the study and verify that the facilities remain acceptable. In addition, the study may be evaluated by government inspectors who must be allowed access to CRFs, source documents and other study files.

The investigator must notify CVT promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to CVT.

The investigator should retain essential documents at least two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor

to inform the investigator/institution as to when these documents no longer need to be retained.

9.4. Institutional Requirements

The investigator and institution are required to submit the following documentation prior to shipment of first device and first treatment procedure:

- IRB/EC approved informed consent form
- IRB/EC approval of the final protocol

Any additional requirements imposed by the IRB/EC or regulatory authorities concerning the trial shall be followed.

9.5. Informed Subject Consent

If it is mandated by the respective country regulations, study subjects must provide written informed consent using an IRB/EC-approved informed consent form. The study must be explained to the study subjects in lay language. The investigator, or representative, must be available to answer all subjects' questions. Subjects will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

9.6. Device Accountability

This trial is a first-in-human study and devices may not be used for the treatment of subjects not qualified for inclusion into the study. The Investigator will maintain adequate records of the receipt and disposition of the investigational device, including lot numbers, device identification number, date used, subject ID number and treating physician. A device accountability log supplied by the Sponsor will be used.

Use of any investigational device outside of the protocol is strictly forbidden and may constitute grounds for removal of the investigator/site from the clinical trial/investigation.

9.7. Use of Information and Publication

All information and data generated in association with this study will be held in strict confidence until the study completion. The investigator agrees to use this information for the sole purpose of completing this study and for no other purpose without written consent from sponsor.

At the conclusion of each follow-up time point and the entire study, an abstract reporting the primary results may prepared and presented in an appropriate international forum. A manuscript may also be prepared for publication in a scientific journal. The data and results from the study are the sole property of CVT. CVT shall have the right to access and use all data and results generated during the study. CVT acknowledges that the Principal Investigator(s) might desire to publish a multi-center publication regarding the trial results. CVT must receive any proposed publication and/or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be

reviewed by CVT in compliance with CVT publication policy set forth in the Research Agreement or Investigator's Agreement.

9.8. Reporting Requirements

The investigator should notify the IRB/EC in writing within three months after completion, termination, or discontinuation of the study at the site. The same procedure will be applied to Competent Authority where required. A site reporting requirements summary is presented in **Table 3**.

Table 3. CVT-SFA Study Site Responsibilities for Submitting Data and Reports

Type of CRF/Report	Time Frame	Process
CRF (baseline, in-hospital summary, follow-up, non-compliance, reconciliation form, subject withdrawal)	Ongoing basis	CRF
Adverse Events	Ongoing Basis	CRF Details to be retrieved at monitoring visit
Serious Adverse Event Notification CRF (including death, device malfunction; failure, near incident, unanticipated adverse device effects)	Within 24 hours	Input within 24 hours of knowledge of event
Annual reports	Annually, as required by Ethic Committee	Material to be prepared by sponsor and copy to be provided to EC by investigator
Final report	Within 6 months of study completion or termination	Material to be prepared by sponsor and copy to be provided to EC by investigator

10. SPONSOR RESPONSIBILITIES COMPLIANCE/QUALITY ASSURANCE

10.1. Role of Sponsor

As the study sponsor, CVT has the overall responsibility for the conduct of the study, including assurance that the study satisfies international standards and the regulatory requirements of the relevant Competent Authorities.

General Duties

It is the sponsor's responsibility to ensure that the study is conducted according to Good Clinical Practice (GCP), ISO 14155:2020, the Declaration of Helsinki, and other applicable

regulatory requirements, the study protocol, or any conditions of approval imposed by the IRB/EC or regulatory authorities. Additionally, the sponsor will ensure proper clinical site monitoring is conducted.

Selection of Clinical Investigators and Sites

The sponsor will select qualified investigators and facilities which have adequate study subject population to meet the requirements of the investigation.

Training of Investigator/Site Personnel and Periodic Monitoring

The training of the investigator and appropriate clinical site personnel will be the responsibility of the sponsor and PI, or designee, and may be conducted during an investigator meeting, a site initiation visit or other appropriate training sessions.

Periodic monitoring visits will be conducted frequently enough to ensure that all clinical subject data are properly documented and that the study is properly conducted.

10.2. Investigator's Brochure

The sponsor will prepare, assemble and maintain all pre-clinical and available clinical data and documentation and will summarize this information in the clinical investigator's brochure.

10.3. Documentation

The sponsor will collect, store, guard and ensure completion by the relevant parties of the following documents:

- Records of any serious adverse events (SAEs) reported to the sponsor during the clinical investigation
- Any statistical analyses and underlying supporting data
- The final report of the clinical investigation

10.4. Committees

Clinical Events Committee

The Clinical Events Committee (CEC) is made up of angiologists/ radiologists/cardiologists or vascular surgeons who are not participants in the study. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on the protocol.

At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm to be followed in order to classify a clinical event. All members of the CEC will be blinded to the primary results of the trial.

The CEC will meet regularly to review and adjudicate all clinical events in which the required minimum data is not available. The committee will also review and rule on all deaths that occur throughout the trial.

Steering Committee

The steering committee (SC) is the main policy and decision-making committee of the study and has final responsibility for the scientific conduct. The specific tasks of the SC are to:

- Proper design and conduct of the trial
- Ethical and professional standards of the trial
- Ensuring that the results of the clinical trial and the scientific accomplishments are arrived at in the most efficient manner possible
- Periodical safety review
- Publication policy

The steering committee will be composed of the lead principal investigator, at least one investigator of a clinic participating in the trial and representatives from CVT.

11. TRIAL TERMINATION

The sponsor and Steering Committee will monitor the progression of the study. If warranted, the study may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the study population.

Notification of suspension or termination will occur no later than five (5) working days after the sponsor makes the determination. In the event of study suspension or termination, the sponsor will send a report outlining the circumstances to the IRB/EC and all investigators. A suspended or terminated study may not be reinitiated without approval of the reviewing IRB/EC (where applicable).

12. APPENDICES

- Appendix A Bibliographical References
- Appendix B Trial Abbreviations and Definitions
- Appendix C Informed Consent (LBL1116)
- Appendix D Declaration of Helsinki
- Appendix E Instructions for Use (LBL1117)
- Appendix F Schedule of Events
- Appendix G Research Agreement Template (FRM1118)
- Appendix H Investigators Responsibilities
- Appendix I Duplex Ultrasonography Core Lab Guidelines
- Appendix J Risk Analysis
- Appendix K General Safety and Performance Requirements Statement
- Appendix L Case Report Forms (FRM1119)
- Appendix M Angiography Core Lab Guidelines

APPENDIX A: BIBLIOGRAPHICAL REFERENCES

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APPENDIX B: TRIAL ABBREVIATIONS AND DEFINITIONS

Trial Abbreviations

ABI	Ankle-Brachial Index
ABR	Angiographic Binary Restenosis
AE	Adverse Event
aPTT	Partial Thromboplastin Time
AV	Arteriovenous
BMI	Body Mass Index
CBC	Complete Blood Count
CEC	Clinical Events Committee
CI	Clinically Indicated
CLI	Critical Limb Ischemia
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVT	Chansu Vascular Technologies
EC	Ethics Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	Identification
IFU	Instructions for Use
ISO	International Organization for Standardization
ITT	Intent-to-Treat
LLL	Late Lumen Loss
MAE	Major Adverse Event
MEC	Medical Ethics Committee
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
MR	Magnetic Resonance
PAD	Peripheral Artery Disease
PT	Prothrombin Time
PTA	Percutaneous Transluminal Angioplasty
QA	Quantitative Angiography
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SC	Steering Committee
SFA	Superficial Femoral Artery
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TER	Target Extremity Revascularization
TLR	Target Lesion Revascularization
WIQ	Walking Impairment Questionnaire

Trial Definitions

Abrupt or Acute Closure

Quantitative Angiography findings or obstruction of contrast flow in the dilated segment where there had previously been a patent segment and documented anterograde flow. For an initial subtotal lesion, acute closure describes a total obstruction to arterial flow, either sustained or transient at the site of the treated lesion. In a situation where the dilated segment was closed or occluded at the beginning of the procedure, acute closure should only be used to describe the outcome if there was a period of vessel patency during the procedure documented by normal anterograde contrast flow beyond the lesion site with the PTA catheter removed from the vessel followed by closure before the patient was discharged from the catheterization laboratory.

Acute Success

Acute success is classified according to the following definitions:

Clinical Success

Clinical success (per subject) is defined as technical success without the occurrence of major adverse events during procedure.

Lesion Success

Lesion success is defined as achievement of a final in-lesion residual diameter stenosis of <50% (by Quantitative Angiography), using any device after wire passage through the lesion. Pre and post-dilatation of the lesion with a non-study device is considered part of assigned device treatment.

Technical Success

Technical success is defined as achievement of a final in-lesion residual diameter stenosis of < 50% (by Quantitative Angiography), using the CVT Everolimus-coated Percutaneous Transluminal Angioplasty Balloon Catheter without a device malfunction after wire passage through the lesion. Pre and post-dilatation of the lesion are considered part of assigned device treatment.

Adverse Event (AE)

An adverse event 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.

Amputation

The removal of a body extremity by surgery. For this study, the definition of amputation will only apply to amputations of the limb that was treated.

A minor amputation will be defined as below the ankle; and a major amputation will be defined above the ankle.

Aneurysm

A localized abnormal expansion or protrusion of a blood vessel resulting from a disease or weakening of the vessel's wall (all 3 layers) that exceeds the reference vessel diameter (RVD) of the vessel by 1.5 times.

Angina Pectoris

Braunwald Classification of Unstable Angina:

New onset of severe or accelerated angina. Patients with new onset (< 2 months in duration) exertional angina pectoris that is severe or frequent (> 3 episodes/day) or patients with chronic stable angina who develop accelerated angina (that is, angina distinctly more frequent, severe, longer in duration, or precipitated by distinctly less exertion than previously) but who have not experienced pain at rest during the preceding 2 months.

Angina at rest, subacute. Patients with one or more episodes of angina at rest during the preceding month but not within the preceding 48 hours.

Angina at rest, acute. Patients with one or more episodes of angina at rest within the preceding 48 hours.

Canadian Cardiovascular Society (CCS) Classification of Stable Angina:

Ordinary physical activity does not cause angina; for example walking or climbing stairs, angina occurs with strenuous or rapid or prolonged exertion at work or recreation.

Slight limitation of ordinary activity; for example, angina occurs walking or stair climbing after meals, in cold, in wind, under emotional stress or only during the few hours after awakening, walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Marked limitation of ordinary activity; for example, angina occurs walking one or two blocks on the level or climbing one flight of stairs in normal conditions and at a normal pace.

Inability to carry on any physical activity without discomfort - angina syndrome may be present at rest.

Angiographic Binary Restenosis (ABR) Rate

Percent of patients with an in-lesion percent diameter stenosis of > 50%, by quantitative angiography (QA), at follow-up.

Ankle Brachial Index (ABI)

The ABI is the ratio of the ankle to arm pressure, and it is calculated by dividing the systolic blood pressure in the ankle of the one leg by the higher of the two systolic blood pressures in the arms.

An ABI of 0.9 – 1.3 is a normal range. A reduced ABI (less than 0.9) is consistent with peripheral artery occlusive disease, with values below 0.8 indicating moderate disease and below 0.5 indicates severe disease. A value greater than 1.3 is considered abnormal suggesting calcification of the walls of the arteries and non-compressible vessels, reflecting severe peripheral vascular disease. Patients with ABI values greater than 1.3 will be excluded from the analysis.

Calculation of the Ankle Brachial Index:

(Highest Ankle Systolic Pressure/Highest Brachial Systolic Pressure = ABI)

Improvement of Ankle Brachial Index:

Patients will be considered as having an improvement in ABI if their baseline value was less than 0.9 and either increased by more than 0.10, or the follow-up ABI value is in the normal range (0.9-1.3).

Worsening of Ankle Brachial Index:

Deterioration in the Ankle Brachial Index (ABI) by more than 0.15 from the maximum early post-procedural level.

Arterial Flow

During and following deployment, each vessel will be evaluated and graded, according to the following arterial flow parameters. These findings will be recorded and included in the study records.

Flow 0: No antegrade flow beyond the point of occlusion or target site.

Flow 1: Contrast passes the point of obstruction but "hangs up" and fails to opacify the entire distal vasculature during the duration of the cine-angiographic filming sequence.

Flow 2: Antegrade filling of contrast with complete filling of the artery and its major and minor branches, but with visually determined decreased rate of flow compared to flow rate observed during pretreatment angiogram. Alternatively, delayed contrast washout in the target site territory may occur.

Flow 3: Antegrade flow of contrast with complete filling of the artery and its major and minor branches with visually determined flow rate from equal to the flow rate observed during pretreatment angiogram.

Arterial Inflow

For a lesion in the superficial femoral artery (femoro-popliteal level) inflow refers to the aorto-iliac level. Good inflow implies that vessels proximal to a target treatment site are free of hemodynamically significant lesions (≥ 50%).

Arterial Outflow

For a lesion in the superficial femoral artery (femoro-popliteal level) outflow refers to combined levels distal to the lesion, including the following arteries: distal popliteal, tibioperoneal trunk, anterior tibial, posterior tibial, peroneal, dorsalis pedis, plantar and pedal. Good outflow implies that the distal popliteal, tibioperoneal trunk and at least one of the infrapopliteal arteries (anterior tibial, posterior tibial, peroneal) is free of hemodynamically significant lesions (≥ 50%) and that there is in-line flow into the foot.

Binary Restenosis

Defined as the presence of a hemodynamically significant restenosis (≥ 50%), as determined by quantitative angiography (QA).

Cerebrovascular Accident (CVA) or Stroke

Stroke or Cerebrovascular Accident is defined as sudden onset of focal neurological deficits due to vascular lesions of the brain that persists >24 hours. This may include cerebral infarction (ischemic stroke), intracerebral hemorrhage, and subarachnoid hemorrhage (hemorrhagic stroke).

Chronic Concomitant Medications

Medication that has been:

- Prescribed or over-the-counter (OTC) that has been taken or will continue to be taken regularly for at least a period of 6 months, or
- Is required to be taken indefinitely by the patient, or
- Prescribed or OTC that has been taken multiple times (each time for at least 6 months).

Death

When possible, death will be classified according to underlying cause. Death within 30 days of the study procedure will be classified as procedure related unless demonstrated otherwise.

Cardiovascular Death:

Any death due to proximate cardiac cause (eg, myocardial infarction (MI), low-output failure, fatal arrhythmia), unwitnessed death, or death of unknown cause.

Vascular Death:

Death caused by non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.

Non-cardiovascular Death:

Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Device Malfunction

A malfunction is a failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled

Dissection Grades

National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System: (0, A, B, C, D, E, F)

0: No dissection

A Minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff

B Luminal flap that is radiolucent and that runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff

C: Contrast appears outside of the vessel lumen as an "extra-luminal cap". The staining appears even after contrast clears the lumen

D: Spiral radiolucent luminal filling defects. Often persistent staining after contrast clears from the vessel.

E: New and persistent filling defects in the vessel lumen.

F: Lesions that progress to impaired flow or total occlusion.

Embolism

Formation of a thrombus within the target lesion with migration or atherosclerotic emboli migration to a distal artery.

Enrollment

The patient will be considered enrolled into the study upon the completion of all the following:

- A signed patient informed consent,
- General and angiographic criteria for enrollment has been met
- Successful treatment of the inflow (iliac) artery without complication, if applicable
- Target lesion is successfully crossed by the guidewire

- The study device has entered the patient's vasculature

Hematoma

A localized collection of blood in a space or tissue.

Intent-to-Treat (ITT) Population

The principle of including outcomes of all patients in the analysis who are enrolled into the clinical trial/investigation, regardless of the treatment actually received.

Late Lumen Loss (LLL)

Calculated as Minimum Lumen Diameter (MLD) post-procedure – MLD at follow-up

Mean in-lesion Late Loss will also be measured: (Mean In-lesion MLD, post-procedure) – (Mean In-lesion MLD at follow-up)

Lead Principal Investigator

A physician-specialist, related to the study, who is responsible for the overall conduct of the trial at all sites.

Major Adverse Event (MAE)

A composite rate of cardiovascular death, index limb amputation and ischemia-driven Target Lesion Revascularization (TLR).

Minimum Lumen Diameter (MLD)

The average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. MLD is visually estimated during angiography by the Investigator; it is measured during QA by the Angiographic Core Lab.

Multilevel Disease

Presence of obstructive lesions at more than one level in the same extremity as the treatment lesion.

Myocardial Infarction (MI)

Q-wave MI (QMI) - Development of new pathological Q-waves in 2 or more contiguous leads (according to the Minnesota code) with or without post-procedure creatine kinase (CK) or CK-MB levels elevated above normal.

Occlusion

Incomplete vessel opacification distal to the lesion or if the distal vessel fills via collateral circulation.

Chronic Occlusion:

An occlusion presumed to have been present for at least 1 month prior to the procedure.

Total Occlusion:

An occlusion with no ante grade filling of contrast to the distal segment.

Patency Rate

Patency rate defined as freedom from clinically-driven TLR and from Duplex ultrasound or angiographic stenosis >50% at 6, 12, and 24 months.

Percent Diameter Stenosis

The value calculated as 100 * (1 - MLD/RVD) using the mean values from two orthogonal views (when possible) by QA.

Popliteal Artery

Defined as the vessel located between Hunter's canal and the trifurcation of the anterior tibial, posterior tibial and peroneal arteries.

Primary Investigator

A physician responsible for conducting the clinical trial at each investigational site, which is responsible for the overall conduct of the trial at their site and compliance with protocol.

Reference Vessel Diameter (RVD)

An approximation of the diameter of the vessel at the location of the target lesion. RVD is visually estimated during angiography by the Investigator and it is measured during QA by the Angiographic Core Laboratory.

Restenosis

Re-narrowing of the artery following the reduction of a previous narrowing. It is defined as the presence of a hemodynamically significant restenosis (≥ 50%), as determined by angiography.

Rutherford/Becker Categories - Chronic Limb Ischemia

Category	Clinical Description	Objective Criteria
0	Asymptomatic, no hemodynamically significant occlusive disease	Normal results of treadmill*/stress test
1	Mild claudication	Treadmill* exercise complete, post exercise AP is greater than 50 mm Hg but more than 25 mm Hg less than normal
2	Moderate claudication	Symptoms between those of categories 1 and 3
3	Severe claudication	Treadmill* exercise cannot be completed post exercise AP is less than 50 mm Hg
4	Ischemic rest pain	Resting AP of 40 mm Hg or less, flat or barely pulsatile ankle or metatarsal plethysmographic tracing, toe pressure less than 30 mm Hg
5	Minor tissue loss, non-healing ulcer, or focal gangrene with diffuse pedal ischemia	Resting AP of 60 mm Hg or less, flat or barely pulsatile ankle metatarsal plethysmographic tracing flat or barely pulsatile, toe pressure less than 40 mm Hg
6	Major tissue loss, extending above transmetatarsal level, functional foot no longer salvageable	Same as category 5

*5 minutes at 3.2 km/h on a 12° incline

Worsening Rutherford Becker Clinical Category:

A deterioration (an increase) in the Rutherford Becker Clinical Category by more than 2 categories from the earliest post-procedural measurement or to a category 5 or 6.

Revascularization

Target Lesion Revascularization (TLR):

Target lesion revascularization (TLR) is defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.

Clinically Indicated (CI) Target Lesion Revascularization:

A revascularization of the target lesion is considered clinically-indicated if angiography shows a percent diameter stenosis ≥ 50% and there is worsening of the Rutherford Becker Clinical Category that is clearly referable to the target lesion. (worsening is defined as a deterioration (an increase) in the Rutherford Becker Clinical Category by more than 2 categories from the earliest post-procedural measurement or to a category 5 or 6.) An independent angiographic core laboratory should verify that the severity of percent diameter stenosis meets requirements for clinical indication and will overrule in cases where investigator reports are not in agreement.

Target Extremity Revascularization (TER)

Target extremity revascularization (TER) is defined as any percutaneous intervention or surgical bypass of any segment of the target extremity. The target extremity is defined as the ipsilateral limb arteries proximal and distal to the target lesion, which includes upstream and downstream branches and excludes the target lesion itself.

Serious Adverse Event (SAE)

An Adverse Event is considered serious if the event led, or might have led, to one of the following outcomes:

- Death of a subject
- Serious deterioration in the health of a subject that resulted in any of the following:
  - Life-threatening illness or injury
  - Permanent impairment of a body structure or body function
  - Hospitalization or prolongation of patient hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function
  - Chronic disease
- Foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Note: Planned hospitalizations for pre-existing conditions or a procedure required by this protocol without serious deterioration in health is not considered a serious adverse event.

Successful Pre-Dilatation

Pre-dilatation has been successfully completed without complications if all of the following apply:

- Diameter stenosis ≤ 70% (by visual estimate)
- Lesion length still within the requirements of the protocol/CIP
- No angiographic complications

Superficial Femoral Artery (SFA)

The SFA connects to the popliteal artery at the opening of adductor magnus or hunter's canal towards the end of the femur.

Thrombosis

Arterial thrombosis is defined as a total occlusion documented by duplex ultrasound and/or angiography at the site of the treated lesion with or without symptoms.

- Acute thrombosis: 0 - 24 hours post study procedure
- Subacute thrombosis: > 24 hours - 30 days post study procedure
- Late thrombosis/occlusion: 30 days - 1 year post study procedure

Thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the arterial sheath has been removed and the patient has left the interventional lab.

Target Lesion

The continuous diseased segment, between 3 cm and 15 cm in total length, in the superficial femoral or proximal (P1) popliteal arteries within 1 cm distal to the femoral bifurcation in the superficial femoral artery and 3 cm from the proximal margin of the intercondylar fossa and at least 2 cm from any stent if the vessel was previously stented.

Vascular Complications

Access Site Occlusion:

Access site occlusion is defined as total obstruction of the artery usually by thrombus (but may have other causes) usually at the site of access requiring surgical repair.

Arteriovenous Fistula

AV Fistula is defined as a connection between the access artery and the accompanying vein that is demonstrated by angiography or ultrasound and most often characterized by a continuous bruit. Indicate whether an arteriovenous (AV) Fistula occurred at the site of percutaneous entry during the procedure or after lab visit but before any subsequent lab visits.

Peripheral Embolization

Peripheral embolization is defined as a loss of distal pulse, pain and/or discoloration (especially the toes). This can include cholesterol emboli. Indicate whether a peripheral embolization occurred distal to the arterial access site during the procedure or after lab visit but before any subsequent lab visits, requiring therapy.

Pseudoaneurysm

Pseudoaneurysm is defined as the occurrence of a disruption and dilation of the arterial wall without identification of the arterial wall layers demonstrated by angiography or ultrasound. The location of the pseudoaneurysm should be indicated.

Walking Impairment Questionnaire (WIQ):

A disease-specific instrument utilized to characterize walking ability through a questionnaire as an alternative to treadmill testing. It is a measure of patient-perceived walking performance for patients with PAD and/or intermittent claudication.

APPENDIX C: PATIENT INFORMED CONSENT : LBL1116

(Note : the document included in this appendix is a controlled document ; the version in this appendix may not be the most current version. Contact the Sponsor or site coordinator for confirmation of the most current revision.)

APPENDIX D: DECLARATION OF HELSINKI

(4 pages)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by

the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research Involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people.

   The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not

benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

[1] *Note of clarification on paragraph 29 of the WMA Declaration of Helsinki*

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] *Note of clarification on paragraph 30 of the WMA Declaration of Helsinki*

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

APPENDIX E: INSTRUCTIONS FOR USE: LBL1117

(Note : the document included or referenced in this appendix is a controlled document ; the version in this appendix may not be the most current version. Contact the Sponsor or site coordinator for confirmation of the most current revision.)

APPENDIX F: SCHEDULE OF EVENTS

(1 page)

PROCEDURE/TEST	Prior to Procedure (Within 14 days)	Pre-Procedure (Within 24 hours)	**PROCEDURE**	Pre-Discharge	30 days (±7 days) Phone call or Office\hospital Visit	180 days (±30 days) Office/hospital visit	365 days (±30 days) Office /hospital visit	24 and 36 months (±30 days)
Patient Medical/Clinical History	✓							
Chronic Concomitant Medications	✓			✓	✓	✓	✓	✓
Patient Informed Consent	✓							
General/Inclusion Exclusion	✓							
Angiographic/Anatomic Inclusion/Exclusion Criteria			✓					
Pregnancy Test (if applicable)	✓							
Serum Hematology	✓			✓*				
Blood Chemistry	✓			✓*				
Peripheral Angiogram with Runoff		✓	✓					
Duplex Ultrasonography Examination	✓#			✓		✓	✓	
Ankle Brachial Indices	✓			✓		✓	✓	
Rutherford-Becker Classification	✓			✓		✓	✓	
WIQ	✓					✓	✓	
Walking Test or Treadmill Test	✓					✓	✓	
Per-protocol Medications		✓	✓	✓				
Adverse Events			✓	✓	✓	✓	✓	✓

\# *optional*
* *If the subject presents with less than desired clinical outcome or symptoms of an adverse event*

APPENDIX G: RESEARCH AGREEMENT TEMPLATE: FRM 1118

(Note : the document included or referenced in this appendix is a controlled document ; the version in this appendix may not be the most current version. Contact the Sponsor or site coordinator for confirmation of the most current revision.)

APPENDIX H: INVESTIGATOR'S RESPONSIBILITIES

(1 page)

Investigators Responsibilities

1. Have and maintain the resources necessary to conduct the clinical investigation properly.
2. Ensure that conducting the clinical investigation is not nor will not cause a conflict of interest.
3. Obtain from the sponsor information which the clinical investigator judges essential about the device and be familiar with this information.
4. Understanding of the Clinical Investigational Plan (CIP)/Protocol prior to signing it.
5. Compliance with the CIP and any amendments.
6. Support the monitor in their activities to verify compliance with the CIP, to perform source data verification, and to correct case report forms where inconsistencies or missing data is identified.
7. Discuss with the sponsor and monitor any question of modification of the clinical investigation plan and obtain written approval of the sponsor.
8. Ensure the clinical investigation plan is followed by all persons responsible for the conduct of the clinical investigation at the institution. Any deviation must be documented and reported to the sponsor.
9. Make the necessary arrangements to ensure the proper conduct and completion of the clinical investigation.
10. Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject.
11. Ensure that appropriate ethics committee approval has been received prior to the start of the clinical investigation at the center.
12. Provide the results from the ethics committee to the sponsor.
13. Inform the ethics committee and request opinion and/or approval for any significant change in the clinical investigation plan that has been approved by the sponsor.
14. Inform the ethics committee about any serious adverse device effect and/or serious adverse event.
15. Inform the sponsor about all adverse events, serious adverse ecents and adverse device effects in a timely manner.
16. Attempt to ensure an adequate recruitment of subjects.
17. Ensure that the subject has adequate information to give informed consent.
18. Ensure that informed consent is obtained and documented.
19. Ensure that clinical records are clearly marked to indicate the subject is enrolled in a particular clinical investigation. If appropriate, subjects enrolled in the clinical investigation must be provided with some means of showing their participation in the investigation, together with identification and compliance information for concurrent treatment measures. Contact addresses/telephone numbers must be provided. If appropriate, the subject's personal physician should, with the subject's agreement, be informed.
20. Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the clinical investigation plan will not require the prior approval of the sponsor or the ethics committee. Such deviations must not be considered as a breach of agreement but shall be documented and reported to the sponsor.

APPENDIX I: DUPLEX ULTRASONOGRAPHY CORE LAB GUIDELINES

(10 pages)

[redacted]

The CVT SFA Trial

Chansu Vascular Technologies LLC

[redacted]

Created: 20211207

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

To: Investigators of The CVT SFA Trial

Welcome to the [redacted]. We look forward to working with you on this clinical study. We have one responsibility: to ensure that all ultrasound images are of the highest quality, so that data collected will be reliable and accurate. We are here to help you. Please contact [redacted] so we may assist and provide support during the course of the trial.

Summary of [redacted] Responsibilities:

Develop Guidelines for the examiner, as well as the Duplex Ultrasound Protocol and Examiner Worksheet.

Review vascular cases for adherence to study protocol, technical quality, accuracy, and completeness.

Provide follow-up and feedback to research coordinators regarding deviations from imaging protocols and other related issues.

Analyze data and submit to sponsor or sponsor designee.

Site Responsibilities:

Sites may be required to submit a test case to [redacted] for review. *Please contact the Sponsor or your Study Monitor if you are uncertain as to whether you need to submit a test case.*

Follow study-specific [redacted] protocol instructions. The sonographic protocols for this study may differ from the standard testing protocols utilized in your clinical lab. However, the necessary changes must be implemented for standardization of all study subjects from all centers. We are not suggesting that your routine protocols are inadequate: clinical studies are different from clinical practice, and standardization of image acquisition is mandated by various regulatory agencies.

Complete documentation (i.e. Examiner Worksheet) when submitting cases.

Submit cases promptly for review.

Respond in a timely fashion to feedback and queries.

Please do not hesitate to contact [redacted] with any questions. We can be reached at [redacted]. When calling for technical support, please be sure to request to speak with our technical staff.

Thank you and we look forward to working with you.

[redacted]

[redacted]

The [redacted] provides services in compliance with Good Clinical Practice and [redacted] Standard Operating Procedures. The investigational protocols are by their nature research based. The content and procedural requirements are agreed upon by both the sponsor and research organization. As a result, the data collection required by the protocol may not provide adequate or complete information that would be necessary for use in the clinical evaluation or management of the subject.

[redacted]

[redacted]

CVT SFA DUS Protocol

Femoropopliteal Artery Duplex Ultrasound Scan

GOALS:

- Document patency of the total treated target lesion (TL).
- Determine the precise location of all stenoses within the TL and/or within the TV.
- Document abnormalities related to procedure and/or within the TL (dissections, aneurysmal dilatation, etc.).
- Use the TL measurements provided by the Angiographic Core Lab to measure the length and location of the TL.

TARGET LESION DEFINITION:

- The TL is defined as any segment of artery treated with CVT PTA catheter. The TL minimum length is 3cm with a maximum length of up to 15cm.
- Treated vessels may include:
    - Superficial femoral artery (SFA)
    - Proximal popliteal (P1)

EXAM PREP:

1. 2-D Ultrasound system (gray scale, color and pulsed wave Doppler)
2. Appropriate transducer frequency for depth of vessel being examined
3. Coupling gel
4. Image documentation and submission per sponsor instructions; image format determined by image vendor
5. Tape measure and skin markers

VESSELS EVALUATED:

- Distal common femoral artery (dCFA)
- Entire superficial femoral artery (SFA)
- Popliteal artery (PopA)

EXTERNAL MEASUREMENT PROCEDURE:

1. Prior to the scan, obtain the TL measurement form provided by the Angiographic Core Lab. The form provides the length and location of the TL/treated area of the artery. The measurements provided are from a referenced landmark – SFA/PFA bifurcation, or for distal lesions, a bony landmark. The zero marker of the ruler is always placed at the reference landmark used by the Angio Core Lab.
2. Obtain a B-mode image of the SFA/PFA bifurcation. Mark the location of the bifurcation on the skin (use any skin marker) – *See Figure 1.*
3. Place the zero marker of any tape measure at the CFA bifurcation skin marker. With the limb in the neutral position, place the tape measure along the medical aspect of the femur to the proximal edge of the treated segment as reported on the TL form. Place a skin marker to note the location of the proximal edge, then proceed to measure the distal edge of the treated segment. Mark the skin and measure the total length represented by the two skin markers. The total length should equal the total length reported on the TL measurement form. If discrepant,

[redacted]

repeat the procedure until the two total lengths are equivalent. Proceed with the scan, starting at the dCFA.

4. Record the TL measurements on the [redacted] Examiner Worksheet (EW). Label images by the anatomic location (proximal, mid, distal) and the location within the TL – *See Figure 2.*
5. To verify lesion length and location, cross-reference the EW at each visit.

Figure 1: Locate the SFA/PFA bifurcation. Mark the location on the skin and place the zero marker at the edge.

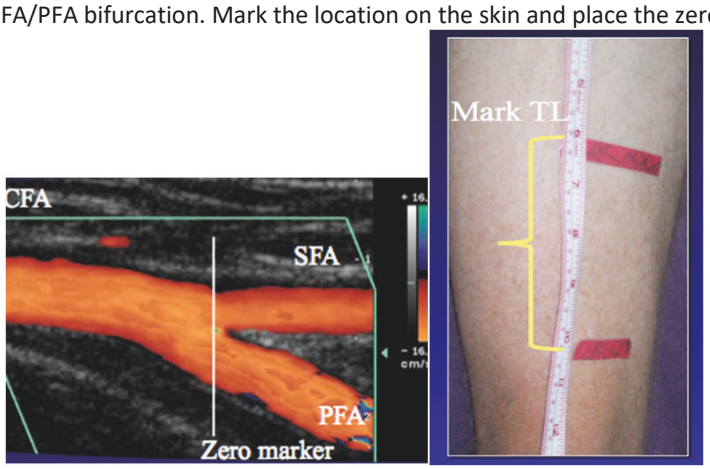


Figure 2: Image labeled correctly: Right leg 6cm in TL, clearly documents location of stenosis as TL

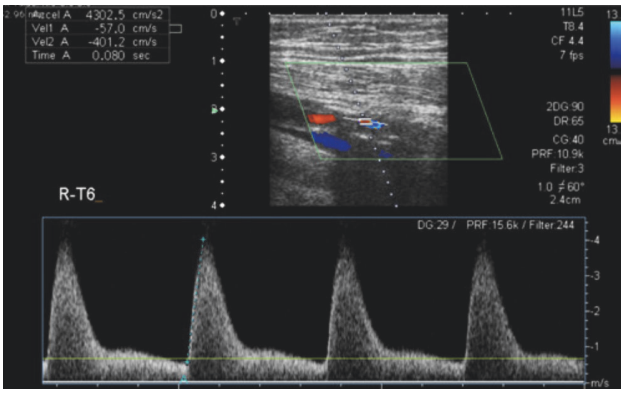


IMAGE ACQUISITION:

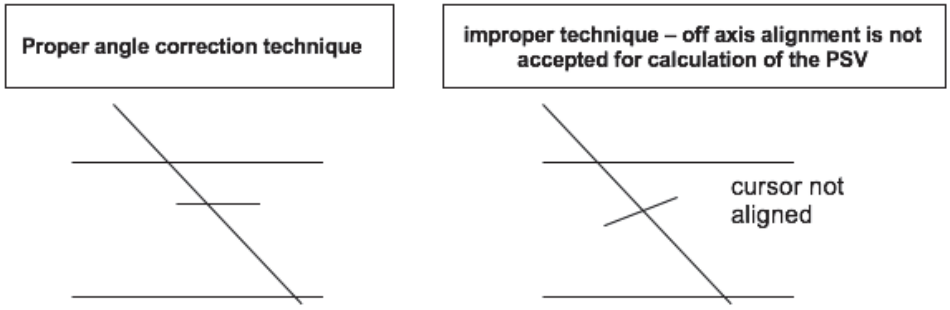
- Required images; dCFA, entire TV, every 2cm through the TL, representative outflow images through the distal popliteal artery. Document the maximum PSV from within each 2cm segment. If the highest PSV is at 3cm in TL, between 2-4cm, record the PSV from 3cm in TL.
- Long axis images are required. Optimize images to clearly display the arterial walls and the artery lumen. Any area that appears abnormal MUST include full-frame gray scale images from multiple views and planes (long and short axis).
- If the PSV is increased, capture a full-frame gray scale image to document the absence or presence of plaque and/or other abnormalities, dissections, pseudoaneurysms, etc.
- Color Doppler images – clear and concise images. Optimize color Doppler to avoid color overwrite, aliasing, and bleeding over intraluminal echoes. If color bleeds outside lumen, decrease color gain.

[redacted]

SPECTRAL DOPPLER EVALUATION:

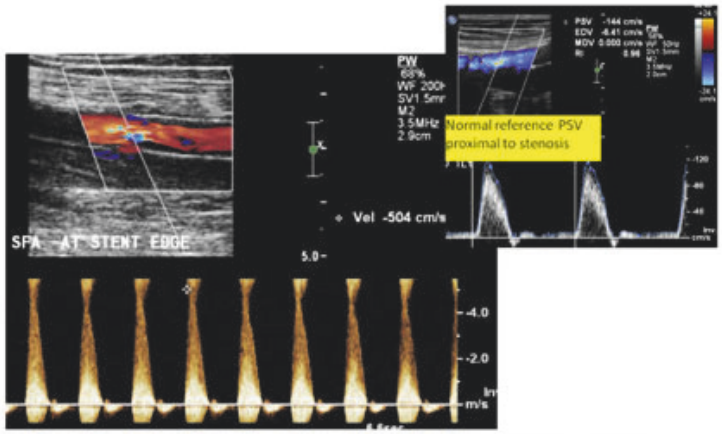
- Use a 60-degree angle or less with the cursor aligned parallel to the vessel wall – *See Figure 3.*
- Measure the PSV at all locations (refer to the EW). Automated trace is acceptable only when the waveforms are uniform and stable over time – not acceptable in the presence of cardiac arrhythmia.
- Obtain a waveform immediately distal to any area of increased PSV to assess for post stenotic turbulence (PST). Document an image and waveform from this area.

Figure 3: Proper angle correction technique



- Measure the PSV at all locations and complete the Examiner Worksheet.
- Calculate the peak systolic velocity ratio (PSVR) focal increase in the PSV present. Use a normal reference PSV from the nearest normal segment above the area of increase – *See Figure 4.*

Figure 4: Example of how to document stenosis and calculate the PSVR



Max PSV = 504 cm/sec

Reference PSV = 144 cm/sec

PSVR 504/144 = 3.5

[redacted]

CVT SFA
Examiner Worksheet

Completed worksheet must accompany all image submissions

Site #: _____ **Subject #:** _____ **Exam Date:** _____
DD MMM YYYY

Study Limb
◯ Right ◯ Left

Visit
◯ Pre-discharge ◯ 12 month
◯ 6 month ◯ Unscheduled, explain: _____

TL Revascularization ◯ Yes ◯ No **If yes, date:** _____ **Bailout Stent Placed** ◯ Yes ◯ No
DD MMM YYYY

Refer to the TL measurement form provided by the Angiographic Core Lab to complete this section

Anatomical Marker
◯ CFA bifurcation
◯ Superior edge of patella

TL Length: _____cm

TL Proximal Edge: _____cm

TL Distal Edge: _____cm

Peripheral Arterial Duplex Scan Findings

	PSV cm/sec		PSV cm/sec
Distal CFA	___ ___ ___	**8-10cm in TL**	___ ___ ___
Proximal to TL	___ ___ ___	**10-12cm in TL**	___ ___ ___
1-3cm above TL	___ ___ ___	**12-14cm in TL**	___ ___ ___
0-2cm in TL	___ ___ ___	**14-16cm in TL**	___ ___ ___
2-4cm in TL	___ ___ ___	**1-3cm Distal to TL**	___ ___ ___
4-6cm in TL	___ ___ ___	**Distal Popliteal**	___ ___ ___
6-8cm in TL	___ ___ ___		

Compare exam to previous visits - check for interval changes and confirm location and length of TL.

Comments (note any technical difficulties or unusual findings)

.....

.....

.....

Examiner Name (please print): _____ **Date:** _____
DD MMM YYYY

[redacted]

Case Submission Instructions

Electronic image upload: Please upload the duplex ultrasound image set and completed Examiner Worksheet to [redacted]

Please make sure the worksheet is filled out completely before submitting the exam for review.

Images uploaded without a worksheet will not be processed for review.

If you experience any upload issues, please reach out to your site monitor.

[redacted]

[redacted]

[redacted]

Please copy the following [redacted] staff members when emailing any staff member regarding trial related matters. As members of our team are intermittently out of the office, this practice will help ensure that messages are seen and responded to in a timely manner.

[redacted] – Technical Director

[redacted] – Administrative Manager

[redacted] Project Team Leader

[redacted] – Project Team Leader

[redacted] – Administrative Assistant

[redacted] – Administrative Assistant

[redacted] – Administrative Assistant

For technical support or administrative support, please call the [redacted] phone number: +[redacted].

[redacted]

APPENDIX J: RISK ANALYSIS

A full risk management file ([redacted]) is complete and available for the CVT Everolimus-coated PTA Catheter.

The summary of the risk analysis is presented in this appendix.

The local application of anti-proliferative drugs (e.g., sirolimus, zotarolimus, everolimus, and paclitaxel) for prevention of restenosis in coronary arteries via a stent delivery system has shown that these therapies successfully inhibit or reduce restenosis. This has reduced the need for patients with coronary artery disease to undergo repeat percutaneous and surgical revascularizations. The success of drug-eluting stents in the coronary arteries triggered an increased interest in using drug-eluting or drug-coated therapies in other vasculatures. Percutaneous transluminal balloon angioplasty (PTA) for revascularization of the superficial femoral artery (SFA) has an initial technical success rate of more than 95%. However, restenosis occurs in 50% to 60% of the treated segments after 6 to 12 months. Implantation of nitinol self-expanding stents in infra-inguinal arterial segments has improved intermediate and long-term patency compared with PTA, but the benefit has been limited by 30% to 40% restenosis and 5% to 15% stent fracture rates.

Neointimal hyperplasia remains one of the major stumbling blocks of all endoluminal therapies, particularly in the small caliber peripheral vessels and long diseased segments. To date, most trials involving drug-coated or drug-eluting stents have not shown reduced restenosis rates in the superficial femoral or proximal popliteal arteries.

Preliminary data suggest that drug-coated balloons using paclitaxel reduce restenosis and late lumen loss in the superficial femoral and proximal popliteal arteries when compared to PTA with standard balloon catheters. Therefore, the drug-coated balloons may have more advantages than angioplasty alone, especially in terms of controlling neointimal hyperplasia and lowering restenosis rates.

Overall Residual Risk Determination and Discussion

The risks associated with the use of the CVT Everolimus-coated PTA Balloon Catheter were evaluated for the intended use listed on page one of this risk management and for deliberate misuse of the device. The analysis yielded two overall residual risk hazardous situations and resulting harms that are categorized as “High”:

ID	Hazard	Event	Hazardous Situation(s)	Potential Harm	Rate of Occurence
2d	Cardiovascular complication	Post procedure complication	Thrombosis, persistent vessel occlusion	Myocardial Infarction (MI)	>0.1% and <1%
3f	Cardiac complication	Peri procedure, post procedure complication	Major thrombosis Acute MI	Death	>0.1% and <1%

These risks are inherent to the percutaneous interventional procedure and are not specific to the CVT-Everolimus coated balloon catheter. The use of the CVT-Everolimus coated catheter is not anticipated to increase the occurrence of the hazardous situations identified compared to current

percutaneous interventional techniques and, based on everolimus and everolimus-coated balloon studies conducted to date as well as currently marketed everolimus-coated balloon catheters, will provide a benefit to patients by reducing or eliminating the occurrence of restenosis.

Conclusion

The potential patient benefit of restoring blood flow to the occluded vessel and minimizing the restenosis currently observed with non-drug coated PTA catheters and stenting outweighs the incidence and severity of these risks.

APPENDIX K: GENERAL SAFETY AND PERFORMANCE REQUIREMENTS STATEMENT

Compliance with REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

1. The CVT device has been designed, manufactured and tested in such a way that, when used under the conditions and for the purposes intended, it should not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.
2. The solutions adopted by CVT for the design and construction of the device conform to safety principles, taking account of the generally acknowledged state of the art practices for the device's intended use.
3. The device has been pre-clinically tested to achieve the performances intended by CVT and it is packaged accordingly.
4. The characteristics and performances of the device have been tested to not adversely affect or compromise the clinical conditions and safety of the patients during its lifetime or when it is subjected to the stresses, which can occur during normal conditions of use.
5. The CVT device has been designed, manufactured and packaged in such a way that its characteristics and performances during its intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by CVT.
6. The CVT device is designed and manufactured with materials that guarantee its characteristics and performances while meeting all required standards regarding toxicity and biocompatibility.
7. The CVT device is designed and manufactured in such a way that it can be used safely with the materials, substances and gases with which it enter into contact during their normal use or during routine procedures.
8. The CVT device is delivered in a sterile state; it is designed, manufactured and packaged in a non-reusable package and remains sterile, under the storage and transport conditions identified, until the protective packaging is damaged or opened. It has been manufactured and sterilized by an appropriate, verified method.
9. The Information (Instructions for use and device labels) supplied by CVT with each device meet all the essential requirements.

APPENDIX L: CASE REPORT FORMS: FRM1119

(Note : the document included or referenced in this appendix is a controlled document ; the version in this appendix may not be the most current version. Contact the Sponsor or site coordinator for confirmation of the most current revision.)

APPENDIX M: ANGIOGRAPHIC CORE LAB GUIDELINES

(3 Pages)

[redacted]

CVT- SFA STUDY

INSTRUCTIONS TO THE SITE

All angiograms should be obtained paying strict attention to the following features:

1) Please acquire all angiograms in DICOM format, at the highest magnification which will still incorporate the entire segment of stenosis within the field of view.

2) A radio-opaque ruler must be used for calibration purposes, placed perpendicular to the imaging plane, flat on the patient. The ruler must be present in all film sequences to be analyzed. Once placed, the ruler should not be moved during the entire procedure.

3) The target lesion must be imaged when suitable in two views that are ≥30 degrees apart to determine study eligibility.

4) Please obtain an angiogram whenever suitable Subtracted and Unsubtracted, Cine Runs and Still Frames for each sequence and label them:

   - Baseline-cine run
   - Pre-dilatation balloon fully inflated
   - Post pre–dilatation -cine run
   - Study balloon fully inflated
   - Post Study balloon-cine run
   - Adjunctive treatment, Balloon and/or Stent after deployment (For bail-out only)
   - Final -cine-run
   - **Complete Distal Runoff image of the lower extremity* at Baseline, Post pre-dilatation, post Study Balloon, after any treatment of dissection, and Final procedure**

   **Lower extremity collection includes: target lesion, vessel distal to the target lesion, the popliteal, TP trunk, tibio-peroneal vessels, pedal arch and toes.*

5) Please film any complication that may occur during the procedure (e.g. dissection, perforation, abrupt closure, no reflow, thrombus, spasm, distal embolisation).

6) Please document thoroughly all steps of intervention and each device used on the technician's worksheet or procedure log.

7) For DUS analysis, please image in one field of view the entire study vessel from CFA bifurcation to the distal edge of treatment

8) Please label the CD with Site/Patient ID, Procedure date, Procedure Type (i.e. Index/Baseline, Clinical Event).

[redacted]

9) For any clinical event required angiography please use the same guidelines and same settings as used at baseline, including a complete Distal Runoff image

PLEASE AVOID:

- OBTAINING ANGIOGRAMS WITH ANY OF THE FOLLOWING:
  - VESSEL OVERLAP
  - FORESHORTENING
  - STREAMING ARTIFACTS DUE TO TOO LITTLE CONTRAST
- OVEREXPOSURE ("BURNOUT") BY USING WEDGE FILTERS
- FILMING THE CATHETER OR STENOSIS IN THE OUTER PORTIONS OF THE IMAGE
- SUPER VHS ARE NOT AN ACCEPTABLE FORMAT

All Images should be uploaded into [redacted], including

1. Cath Lab Procedure Log or Technician's Worksheet Form (Please keep a copy of the original)
2. Index/Baseline, Events Angiograms

If needed, please Ship Films to:

[redacted]

Please contact us anytime for questions.

[redacted]