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

A Clinical Evaluation in the Treatment of Subjects with In-Stent Restenosis of Previously-treated Coronary Artery Lesions

The CVT-ISR Trial

PROTOCOL

Protocol Number: TP1125

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Lead Principal Investigator: [redacted]

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The CVT-ISR Trial

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

A Clinical Evaluation in the Treatment of Subjects with In-Stent Restenosis of Previously-treated Coronary Artery Lesions

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

_____

Site Investigator Printed Name

_____ _____

Sponsor Signature Date

_____

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.
03	0074	24-Aug-2021	Updated principal investigators on page 1; clarified conduct physical exam versus physical questionnaire: when each occurs (Table 3, Appendix F) and what is included in each (Section 4.1 and Section 4.6). Updated Appendix L with risk analysis information from RMF1018. Revised angiographic core lab to "TBD".
A	0090	22-Sep-2021	Released document to alpha revision level; updated angiographic core lab information from TBD to Yale University. Clarified sheath size as 6Fr or larger. Rounded the drug content in Table 1 to whole numbers. Added angiographic core lab technician worksheet and collection instructions to Apnedix I. Removed Appendices J and K (IVUS and OCT Core Lab Guidelines); renumbered remaining appendices.

PROTOCOL SUMMARY

Investigational Device	CVT Everolimus-coated Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheter
Study Objective	To assess the safety and inhibition of restenosis of the CVT Everolimus-coated PTCA Catheter in the treatment of subjects presenting in-stent restenotic lesions in native coronary arteries.
Study Design	Prospective, multi-center, open, single arm study enrolling subjects with visually estimated nominal vessel diameter ≥2.0 mm and ≤3.5mm and lesion length ≤24 mm receiving up to two (2) CVT Everolimus CVT EVE-PTCA Catheters. Angiographic follow up, in combination with with either Intravascular Ultrasound (IVUS) or Optical Coherence Tomography (OCT), follow-up, will be carried out in a subset of 25 patients at 180 days following the index procedure.
Patient enrollment	A total of 50 subjects will be enrolled
Number of Sites	Up to fifteen (15) clinical sites in Europe
Primary Safety Endpoint	Freedom from target lesion failure (TLF) rate at 6 months post-index procedure, defined as a composite rate of cardiovascular death, target vessel myocardial infarction and clinically-driven target lesion revascularization (TLR).
Primary Effectiveness Endpoint	In-stent late lumen loss (LLL) at 180 days post-procedure.
Other Clinical Endpoints	• Target lesion failure (TLF) at 30 days, 1, 2 and 3 years post-procedure, defined as a composite rate of cardiovascular death, target vessel myocardial infarction and clinically-driven target lesion revascularization (TLR). • Target vessel failure (TVF) at 30 days, 180 days, and 1, 2 and 3 years post-procedure, defined as a composite rate of cardiovascular death, target vessel myocardial infarction, and target vessel revascularization (TVR). • Clinically-driven target lesion revascularization (TLR) at 1, 2 and 3 years post-procedure. • Clinically-driven target vessel revascularization (TVR) at 180 days and 1, 2 and 3 years post-procedure. • 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 <30% (by QCA), 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 <30% (by QCA), using the CVT Everolimus-coated PTCA 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 cardiac events during the procedure. • Procedural success (per subject) defined as lesion success without the occurrence of major adverse cardiac events during the procedure.
Angiographic, IVUS and OCT Endpoints	***Angiographic endpoints (subset of 25 subjects):*** • In-segment LLL at 180 days • In-stent and in-segment % diameter stenosis (%DS) at 180 days • In-stent and in-segment angiographic binary restenosis (ABR) rate at 180 days ***IVUS endpoint (subset of 15 subjects):*** • In-stent % volume obstruction (%VO) at 180 days ***OCT endpoints (subset of 10 subjects):*** • % of stent strut coverage at 180 days
Subject Population	Subjects with documented in-stent restenosis in native coronary arteries.
Treatment Strategy	• Treatment of a single in-stent restenosis coronary artery lesion with up to two (2) CVT Everolimus-coated PTCA Catheters. • Target lesion must be treated after confirmation that all inclusion criteria are met and in absence of any exclusion criteria. • Pre-dilation of the target lesion is mandatory. • Treatment of the target lesion measuring ≤24 mm in length by visual estimation in a vessel of visually estimated diameter ≥2.0mm and ≤3.5mm. • Recommendation is to select a CVT EVE- PTCA Catheter with balloon length that allows for coverage of the targeted lesion plus approximately 2 mm additional coverage, by visual estimate, on each side of the lesion while not allowing the balloon length extend beyond the edges of the stent. • All subjects will be maintained on their routine therapeutic anticoagulation treatment or, in the absence of pre-existing treatment, will receive a therapeutic daily dose of 75 mg of clopidogrel bisulfate (Plavix®) for a minimum of 6 months and aspirin ≥75 mg to be taken throughout the length of the clinical investigation following index procedure.

	• All subjects will undergo clinical examination at 6- and 12-months post-procedure and then will be contacted by phone at 24 and 36 months post-procedure to answer a health status questionnaire. • A subset of subjects will complete post-procedure angiography (n=25), with IVUS (n=15) or OCT (n=10) target vessel assessment, in order to compare with the angiographic, IVUS or OCT data obtained at the 6 month follow-up timepoint.
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, angiograms, IVUS/OCT and examinations. **Angiographic Inclusion Criteria** 1. Target lesion must be located within a stent (bare metal or drug eluting) placed in a native epicardial coronary vessel with visually estimated nominal vessel diameter of ≥2.0mm and ≤3.5mm. 2. Target lesion must measure ≤24 mm in length by visual estimation. 3. The target lesion must be with a visually estimated stenosis of ≥50% and < 100% with a TIMI flow of ≥1. 4. Non-clinical investigation, percutaneous intervention for lesions in a non-target vessel is allowed if done ≥90 days prior to or planned to be done 6 months after the index procedure. 5. Non-clinical investigation, percutaneous intervention for lesions in the target vessel is allowed if planned to be done 6 months after the index procedure.
Exclusion Criteria	Subject with **any** of the following should be excluded: 1. Subject with known diagnosis of acute myocardial infarction (AMI) within 30 days preceding the index procedure and CK-MB or troponin have not returned within normal limits at the time of procedure. 2. The subject is currently experiencing clinical symptoms consistent with AMI. 3. Subject has current unstable arrhythmia. 4. Subject has a known left ventricular ejection fraction (LVEF) <25%. 5. Subject has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, both clopidogrel and ticlopidine and structurally related compounds, everolimus, or contrast sensitivity that cannot be adequately pre-medicated. 6. Subject has known renal insufficiency (e.g., serum creatinine > 2.5 mg/dL, (i.e. 221 μmol/L) within 7 days prior to index procedure or creatinine clearance <30mL/min or subject is on dialysis. 7. Subject has a history of bleeding diathesis or coagulopathy or will

	refuse blood transfusions. 8. Subject has had a cerebrovascular accident (CVA) or transient ischemic neurological attack (TIA) within the past six months. 9. Subject has other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) that may cause non-compliance with the clinical investigation plan, confound the data interpretation or is associated with a limited life expectancy (i.e., less than one year). 10. Subject is already participating in another clinical investigation that has not yet reached its primary endpoint. 11. Subject is not, in the opinion of the investigator, an acceptable candidate to participate in the study. 12. In-stent lesions for stent are located within an arterial or saphenous vein graft or stent used to treat a previous ISR. 13. The target vessel contains visible thrombus. 14. Pregnant or lactating females.
Planned Schedule:	• First subject enrolled: 2021 • Last subject enrolled: 2022 • Last subject last contact: 2025

1. STUDY OVERVIEW AND RATIONALE

1.1 Study Overview

The CVT-ISR study is a prospective, multi-center, open, single arm study which will include fifty (50) subjects at up to fifteen (15) sites in Europe and will evaluate the clinical safety and efficacy of an everolimus-coated percutaneous transluminal coronary angioplasty (PTCA) catheter for the treatment of in-stent restenosis (ISR) in native coronary lesions previously treated with drug-eluting stent (DES) or bare-metal stent (BMS).

Study enrollment will be offered to all subjects who are suitable candidates for balloon PTCA to correct in-stent restenosis lesions in native coronary arteries. 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

Stenting has been shown to be a safe and effective treatment of de novo lesions in native coronary arteries through conduct of numerous studies, with first bare-metal stents (BMS) [1-9] supplanted by drug-eluting stents (DES).[10-18]

Notwithstanding a successful procedure, coronary stents can fail to conserve vessel patency due to either in-stent restenosis (ISR) or stent thrombosis (ST),[19] a relatively rare but serious complication that can cause a large non-fatal myocardial infarction (MI), or sudden death.[20] ISR, defined as the gradual re-narrowing of a stented coronary artery lesion due to arterial damage with subsequent neointimal tissue proliferation,[21] remains a serious concern as a late stent implant complication. It usually presents as acute coronary syndrome in approximately 70 percent of patients but also can present as acute MI in approximately 10 percent of patients.[22]

The incidence of ISR partly depends on type of stent originally implanted. BMS are becoming less commonly used in routine practice[23] and DES drastically reduce ISR observed with BMS. Overall, rates of ISR drop under 10 percent[23] with DES whereas rates range from 17 and 41 percent with BMS.[25] However, regardless of the lower ISR rate observed, in the field of interventional cardiology, ISR of DES remains a major clinical challenge.[26, 27]

Various therapies intended to reduce the rate of ISR have been tested in clinical investigations and in clinical practice. As a first line of treatment, medication (antiplatelet agents, oral sirolimus) did not provide any clinical benefit.[28, 29, 30]

Coronary surgery may be considered in patients with recalcitrant ISR, who are deemed to not be candidates for percutaneous intervention, particularly in those with a diffuse ISR pattern or associated or significant disease in other major vessels.[31]

Regarding medical devices, debulking techniques (including rotational atherectomy and laser) and cutting balloons have proved to be ineffective for the treatment of ISR.[32, 33]

Multiple studies comparing techniques of plain old balloon angioplasty (POBA), bare metal stenting, newer generation stenting and brachytherapy have established the

superiority of newer generation DES to other percutaneous coronary intervention (PCI) devices in treating ISR.[34-48]

In the last decade, paclitaxel drug-coated balloon catheters (DCBs) emerged as a competitive treatment option for ISR, as demonstrated in a large meta-analysis of 27 trials with a total of 5923 patients where paclitaxel DCB, among other ISR therapies (including POBA, debulking techniques, brachytherapy, BMS, DES), was the second most preferable approach to treating ISR but without a significant difference over limus therapies or paclitaxel-eluting stents.[49]

Despite the large volume of published data, the superiority of the everolimus-eluting stents (EES) compared with DCB remains controversial, particularly as the meta-analysis discussed above suggests but also because DCBs are currently not available for use in the United States[51] and no DCB coated with everolimus has been assessed to date to evaluated efficacy in treating ISR.

1.3 Study Rationale

Whereas the concerning long-term outcomes of paclitaxel-coated DCB catheters have led to controversy in the interventional vascular community[52-56], CVT has developed a possible catheter-based treatment alternative by combining a proven percutaneous transluminal coronary angioplasty (PTCA) catheter, designed to treat in-stent restenosis in coronary arteries, with a drug-coating using a proven drug, everolimus. Everolimus is an active pharmaceutical agent with a proven history of safety and efficacy for use in 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 widely used in drug-eluting stents (DESs) and is considered as the percutaneous treatment of choice for coronary artery disease (CAD). The safety profile of everolimus-eluting stents is well established and the efficacy profile is greater than paclitaxel-eluting stents in long-term clinical follow-up[2].

Use of everolimus, a drug with an excellent safety profile and a proven history for cardiovascular use, with a proven PTCA catheter was demonstrated in series of pre-clinical evaluations in swine animal models. Extensive bench and pre-clinical studies demonstrated that the CVT Everolimus-coated PTCA Catheter is safe for its intended use with no adverse reactions associated to the drug delivery for the stented segment up to 30

[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/s1

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, was associated with the possibility of prevention of restenostic reaction, characterized by signs of drug effects in the histopathology studies at that time point in the animal model.

The present trial will confirm the positive evaluations garnered to date of the CVT Everolimus- coated PTCA Catheter for its intended use of treating subjects with in-stent restenosis in native coronary arteries.

2. DESCRIPTION OF THE STUDY DEVICE

The Chansu Vascular Technologies (CVT) Everolimus-coated PTCA Catheter is a novel catheter designed to facilitate percutaneous treatment of subjects with in-stent restenosis in coronary arteries.

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

1) [redacted]

2) [redacted]

2.1 Basic Catheter Specifications

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

[redacted]

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

Balloon Diameter (mm)	Balloon Length (mm) and Total Drug Content (µg)		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Nominal dose of everolimus: [redacted]

2.2 Indication

The CVT Everolimus-coated PTCA Catheter is intended to be used for improving luminal diameter and myocardial perfusion in patients presenting in-stent stenotic lesions ≤24mm in length in native coronary arteries with reference vessel diameters of 2-3.5mm.

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

3. STUDY DESIGN

The CVT-ISR Trial investigates the inhibition of restenosis using the CVT Everolimus-coated PTCA Catheter in the treatment of in-stent stenotic lesions ≤24 mm in native coronary arteries with reference vessel diameters of 2 to 3.5mm. 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/clinical visit will occur at 6, 12, 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**.

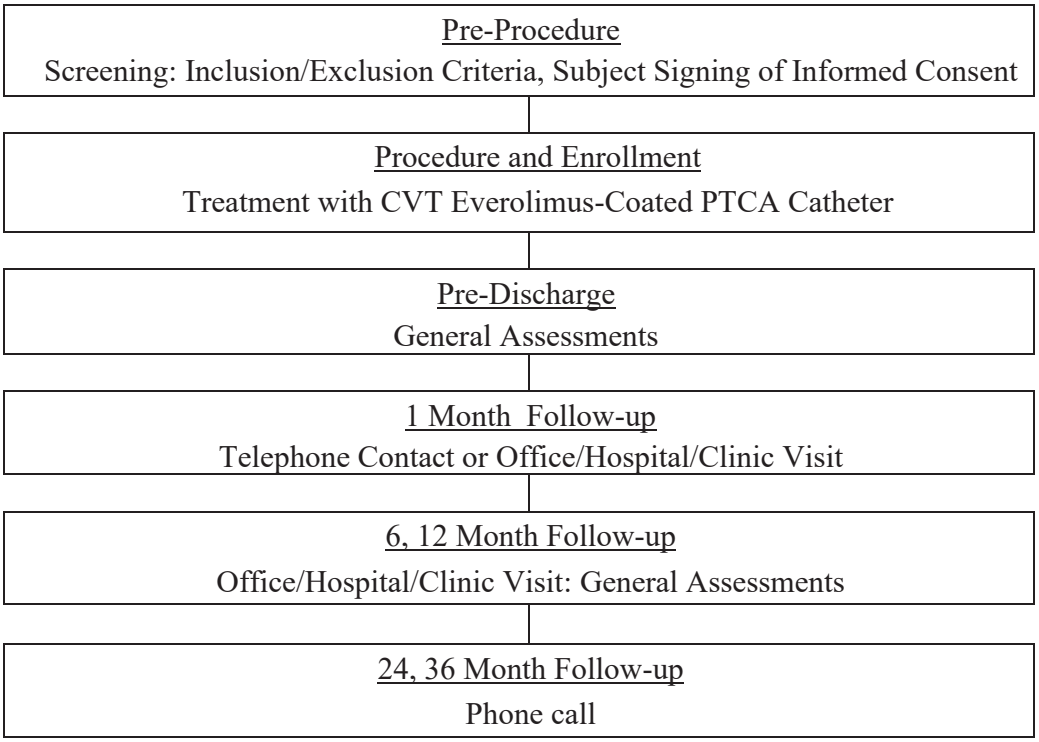


Figure 1. CVT-ISR Study Participation Flow Chart

3.1 Endpoints

The definitions for the endpoints of this study are taken from the Academic Research Consortium-2 Consensus Document, Standardized End Point Definitions for Coronary Intervention Trials.[3] Regarding the definition for Clinically Relevant Myocardial Infarction after Coronary Revascularization, this study adheres to the Expert Consensus Document from the Society for Cardiovascular Angiography and Interventions (SCAI)[4], Consideration of a New Definition of Clinically Relevant Myocardial Infarction after Coronary Revascularization.

3.2 Primary Safety Endpoint

The primary safety endpoint for the study is freedom from target lesion failure (TLF) rate at 6 months post-index procedure, defined as a composite rate of: all cardiac death, target vessel myocardial infarction and clinically-driven target lesion revascularization (TLR).

3.3 Primary Effectiveness Endpoint

The primary effectiveness endpoint for the study is late lumen loss (LLL) at 180 days post procedure.

3.4 Other Clinical Endpoints

[3] Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. Circulation. 2018;137(24):2635-2650. doi:10.1161/CIRCULATIONAHA.117.029289

[4] Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol. 2013;62(17):1563-1570. doi:10.1016/j.jacc.2013.08.720

- Target lesion failure (TLF) at 30 days, 1, 2 and 3 years, post-procedure, defined as a composite rate of cardiovascular death, target vessel myocardial infarction and clinically-driven target lesion revascularization (TLR).
- Target vessel failure (TVF) at 30 days, 180 days and 1, 2 and 3 years post-procedure, defined as a composite rate of cardiovascular death, target vessel myocardial infarction, and target vessel revascularization (TVR).
- Clinically-driven target lesion revascularization (TLR) at 1, 2 and 3 years post-procedure.
- Clinically-driven target vessel revascularization (TVR) at 180 days and 1, 2 and 3 years post-procedure.
- 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 <30% (by QCA), 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 <30% (by QCA), using the CVT Everolimus-coated PTCA 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 the procedure.

3.5 Angio-IVUS-OCT Endpoints

Angiographic endpoints:

- In-segment LLL at 180 days
- In-stent and in-segment % diameter stenosis (%DS) at 180 days
- In-stent and in-segment angiographic binary restenosis (ABR) rate at 180 days

IVUS endpoint:

- In-stent % volume obstruction (%VO) at 180 days

OCT endpoints:

- % of stent strut coverage at 180 days

3.6 Study Population

Subjects included in this study will be comprised of male and female subjects derived from the general interventional cardiology population. This study will include fifty (50) subjects with a with a single in-stent stenotic lesion in a native coronary artery, eligible to be treated by interventional therapy and who meet all the inclusion criteria and none of

the exclusion criteria of this study.

3.7 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.

3.8 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, angiograms, IVUS/OCT and examinations.

Angiographic Inclusion Criteria

1. Target lesion must be located within a stent placed in a native epicardial coronary vessel with visually estimated nominal vessel diameter of ≥2.0mm and ≤3.5mm. The previously implanted stent can be bare metal or a drug eluting stent.
2. Target lesion must measure ≤24 mm in length by visual estimation.
3. The target lesion must be with a visually estimated stenosis of ≥ 0% and <100% with a TIMI flow of ≥1.
4. Non-clinical investigation, percutaneous intervention for lesions in a non-target vessel is allowed if done ≥90 days prior to or if planned to be done 6 months after the index procedure.
5. Non-clinical investigation, percutaneous intervention for lesions in the target vessel is allowed if planned to be done 6 months after the index procedure.

3.9 Subject Exclusion Criteria

Subjects with any of the following criteria should be excluded:

1. Subject with known diagnosis of acute myocardial infarction (AMI) within 30 days preceding the index procedure and CK-MB and troponin have not returned within normal limits at the time of procedure.
2. The subject is currently experiencing clinical symptoms consistent with AMI.
3. Subject has current unstable arrhythmia.
4. Subject has a known left ventricular ejection fraction (LVEF) <25%.
5. Subject has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, both clopidogrel and ticlopidine and structurally related compounds, everolimus or contrast sensitivity that cannot be adequately pre-medicated.

6. Subject has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dL, (i.e. 221 μmol/L) within 7 days prior to index procedure or subject on dialysis.
7. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
8. Subject has had a cerebrovascular accident (CVA) or transient ischemic neurological attack (TIA) within the past six months.
9. Subject has other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) that may cause non-compliance with the clinical investigation plan, confound the data interpretation or is associated with a limited life expectancy (i.e., less than one year).
10. Subject is already participating in another clinical investigation that has not yet reached its primary endpoint.
11. Subject is not in the opinion of the investigator an acceptable candidate to participate in the study.
12. In stent lesions for stent are located within an arterial or saphenous vein graft.
13. The target vessel contains visible thrombus.
14. Pregnant or lactating females.

3.10 Subject Enrollment Point

All subjects who are candidates for treatment of in-stent restenosis in coronary arteries 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 has been met.
- Target lesion is successfully crossed by the guidewire.
- Successful pre-treatment of in-stent restenosis without complication, if applicable.
- CVT Everolimus-coated PTCA Catheter has entered the vasculature.

3.11 Subject Discontinuation

Every subject should remain in the trial 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 records. 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 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.

3.12 Early Termination of the Clinical Trial

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.

Notification of suspension or termination will occur no later than five (5) working days after 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 3** 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
A physical examination should be documented. The exam will include heart rate, blood pressure and body temperature.

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

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

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

The following laboratory tests should be obtained for all subjects within 72 hours of the index procedure.

- CK and/or CK-MB and cardiac troponin (cTn)
- 12 lead ECG.

4.2 Concomitant Medical Therapy

Antiplatelet medication should be administered according to hospital routine and in line with the applicable guidelines on Percutaneous Coronary Interventions and the Instructions for Use of the device.

All subjects will receive aspirin (a minimum of 75 mg daily, within 24 hours prior to the procedure) and a loading dose of any approved antiplatelet medication within 24 hours

prior to the procedure or immediately post procedure (within 30 minutes of last catheter removal). If the subject already has taken an appropriate dose of anti-platelet medication within 72 hours prior to the procedure, no loading dose is required.

During the index procedure, heparin or bivalirudin may be administered as per hospital standard of care to maintain adequate anticoagulation.

A GP IIb/IIIa receptor blocker may be administered at the Investigator's discretion.

Following the procedure, subjects will receive a minimum of 75 mg of aspirin daily indefinitely and an appropriate dose of any approved anti-platelet medication for a minimum of 6 months in all subjects or longer per the ACC/AHA/SCAI guidelines[5] and with the Investigator's discretion.

All antiplatelet/anticoagulant medications will be documented on the CRF from 24 hours pre-procedure through the 36-month follow-up assessment.

Table 2 summarizes the study required regimen for antiplatelet medication for subjects enrolled in the study prior and during procedure.

Table 2. CVT-ISR Study Required Antiplatelet Medication Regimen

Time Point	Medication	Regimen
Prior to Procedure	Heparin or bivalirudin	As needed
	Aspirin	A minimum of 75 mg daily (within 24 hours prior to procedure)
	Clopidogrel/Plavix, Prasugrel/Effient, Ticagrelor/Brilinta,or Ticlopidine/Ticlid or any market approved antiplatelet indicated.	Loading dose within 24 hours prior to procedure or immediately post procedure (within 30 minutes of last catheter removal) No loading dose is required if the subject has taken at least 3 maintenance doses within 72 hours prior to the procedure
During Procedure	Heparin or bivalirudin	To maintain adequate anticoagulation per hospital standard of care
	GP IIb/IIIa receptor blocker	Use at Investigator's discretion
Post-	Aspirin	A minimum of 75 mg daily indefinitely

[5] Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery [published correction appears in Circulation. 2016 Sep 6;134(10):e192-4]. Circulation. 2016;134(10):e123-e155.

Procedure	Clopidogrel/Plavix, Prasugrel/Effient, Ticagrelor/Brilintaor Ticlopidine/Ticlid or any market approved antiplatelet indicated	A minimum of 6 months in all subjects, or longer as according to appropriate guidelinesand upon Investigator's discretion

4.3 ISR PTCA Procedure

Procedural Medications

During the procedure, the 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.

Treatment Strategy

The treatment strategy for all subjects enrolled in the clinical investigation is as follows:

- Treatment of a single in-stent restenosis lesion in a native coronary artery with up to two (2) CVT Everolimus-coated PTCA Catheters.
- Target lesion must be treated after meeting all the general and angiographic inclusion and exclusion criteria.
- Pre-dilation of target lesion is mandatory.
- Treatment of target lesion measuring ≤24 mm in length by visual estimation in vessel of visually estimated diameter ≥2.0mm and ≤3.5mm.
- Recommendation is to select a CVT EVE-PTCA Catheter with a balloon length that allows for coverage of the targeted lesion plus approximately 2 mm additional coverage, by visual estimate, on each side of the lesion while not allowing the balloon length extend beyond the edges of the stent.

PTCA Procedure

Vascular access should be obtained as per site standard of care (depending on lesion location, subject factors or any other factors that would impact the choice of vascular access).

Angiography must be conducted according to the angiographic core laboratory guidelines.

As a next step, a compatible sheath should be inserted and anticoagulation should be administered as per the Investigator's discretion to obtain or maintain appropriate clotting time (reference section 4.2. Concomitant Medical Therapy). In order to identify the anatomical characteristics of the vasculature and to visualize and define the lesion, selective angiography will be performed. Following angiography, the appropriate catheter size(s) will be selected.

Pre-dilatation will be performed on all subjects per the following sequence: after crossing of the target lesion with a guidewire, pre-dilatation is performed with a non-study balloon catheter, making sure that the balloon length is shorter than previously placed stent

length. Note that the use of a non-drug coated standard semi-compliant balloon or cutting/scoring balloon is allowed.

Record an image of the target lesion after pre-dilatation is completed. Ensure to perform an angiography distal to the target lesion. Assess the subject for any angiographic complications after pre-dilatation and confirm the lesion to be treated meets the study angiographic inclusion and exclusion criteria.

Successful pre-dilatation of the target lesion is defined as:

- Residual stenosis of <30% after pre-dilatation (per visual estimate) AND
- No major (>Grade B) flow-limiting dissection.

In case of unsuccessful pre-dilatation of the target lesion planned to be treated with the investigational device, the subject should be considered a screen failure and all lesions should be treated as per standard of care.

Treatment with CVT Everolimus-coated Catheter

It is recommended to select a CVT EVE-PTCA Catheter with a balloon length that allows for coverage of the targeted lesion plus approximately 2 mm additional coverage, by visual estimate, on each side of the lesion while not allowing the balloon length extend beyond the edges of the stent.

The balloon should be inflated for 60 seconds in order to allow for an optimal drug delivery to the surrounding tissue.

Post-Procedure Angiography Subset

A subset of twenty-five (25) subjects will complete post-procedure angiography assessment of the target vessel, as per the angiographic core laboratory guidelines, at 6 months post-procedure.

The 25 subjects undergoing angiographic follow up will represent the first subjects enrolled into the study, with no more than 15 patients undergoing angiographic follow up from a single site.

Note: The end of the procedure is defined as the time after a complete final angiogram has been performed and the last guidewire and catheter have been removed. In case the subject needs to return to the procedure room and a guiding catheter is reinserted for dilatation, this is considered a reintervention. Removal of the sheath(s) may be done at the Investigators discretion.

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

Intravascular Ultrasound Examination (IVUS)

A subset of fifteen (15) subjects will complete an intravascular ultrasound (IVUS) examination at both the index procedure and at 6 months post-procedure, as per the IVUS core lab guidelines.

The 15 subjects undergoing IVUS examination will represent the first patients enrolled

into the study.

Note: The end of the procedure is defined as the time after a complete final angiogram has been performed and the last guidewire and catheter have been removed. In case the subject needs to return to the procedure room and a guiding catheter is reinserted for dilatation, this is considered a reintervention. Removal of the sheath(s) may be done at the Investigators discretion.

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

Optical Coherence Tomography (OCT)

A subset of ten (10) subjects will complete optical coherence tomography (OCT) imaging at both the index procedure and at 6 months post-procedure, as per the OCT core lab guidelines.

The 10 subjects undergoing OCT examination will represent the first subjects enrolled into the study undergoing angiographic follow up and not undergoing IVUS examination.

Note: The end of the procedure is defined as the time after a complete final angiogram has been performed and the last guidewire and catheter have been removed. In case the subject needs to return to the procedure room and a guiding catheter is reinserted for dilatation, this is considered a reintervention. Removal of the sheath(s) may be done at the Investigators discretion.

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

Criteria for Bail-Out or Alternative Procedures

Adjunctive therapies should be avoided if possible. In case of suboptimal procedure results (>50 % residual stenosis, perforation, occlusive complication (recoil) or flow limiting dissection) prolonged balloon inflation should be attempted. If a subject in this study experiences a major dissection or an occlusive complication (as evidenced by decreased target vessel flow, chest pain, or ischemic electrocardiogram (ECG) changes which do not respond to standard rescue techniques), bailout stenting procedures may be performed. All other adjunctive therapies (including but not limited to: laser, atherectomy, cryoplasty or brachytherapy) are not allowed.

If bailout procedures are performed, justification should be documented on the CRF. Subjects undergoing bailout procedures will continue in the study and their data will remain part of the statistical analyses.

4.4 Post-Procedure Subject Management

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

Sheath Removal and Ambulation

Use of approved vascular closure devices are allowed, provided the device is used according to the manufacturer's IFU 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

All subjects will be maintained on their routine therapeutic anticoagulation treatment or, in the absence of pre-existing treatment, subjects will receive a therapeutic daily dose of 75 mg of clopidogrel bisulfate (Plavix®) for a minimum of 6 months and aspirin ≥75 mg to be taken throughout the length of the clinical investigation following index 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.

Laboratory Tests

- Complete Blood Count
- Absolute Platelet Count
- Coagulation tests as per standard of care of the hospital (e.g., Prothrombin Time (PT) and activated Prothrombin Time (aPTT).

Cardiac Tests

- CK and/or CK-MB and cardiac troponin (cTn)
- 12 lead ECG

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, medications, physical questionnaire and adverse events. Alternatively, this contact can be performed in a site visit and include a physical examination. The physical questionnaire will include the following: arterial access site status, heart rate abnormalities, presence of elevated temperature, clinical events that

required a doctor's visit or hospital admission.

Subject Clinical Visit at 6 months (180 ±30 days) according to the following sequence

- Physical examination
- 12 lead ECG
- Concomitant medication (name, dose, duration)
- Adverse event assessment
- Data regarding any emergent treatment and or serious adverse events and/or need for repeat angiography or interventions, and results of such if applicable
- Angiographic, IVUS or OCT follow-up per core laboratory guidelines for the subset of 25 subjects that has undergone these imaging procedures at index procedure.

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

- Physical examination
- 12 lead ECG
- Concomitant medication (name, dose, duration)
- Adverse event assessment
- Data regarding any emergent treatment and or serious adverse events and/or need for repeat angiography or interventions, and results of such if applicable.

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, physical questionnaire 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, physical questionnaire and medications. Alternatively, this contact can be performed in clinical visit with the referring physician.

Table 3. CVT-ISR Study Pre-Procedure, Procedural, Discharge and Follow Up Activities

PROCEDURE/TEST	Prior to Procedure	Pre-Procedure	Procedure	Pre-Discharge	30 days (± 7 days)	180 days (± 30 days)	1 year (± 30 days)	2 years (± 28 days)	3 years (± 30 days)
Patient Medical History	X								
Review Inclusion/Exclusion Criteria[5]	X								
Patient Informed Consent	X								
Chronic Concomitant Medications/History	X	X	X	X	X	X	X	X	X
Creatinine	X								
CBC, Platelet Count	X			X					
Coagulation Tests	X			X					
Pregnancy Test (if applicable)	X								
CK-Mb		X		X					
Cardiac Troponin (cTn)		X		X					
12 Lead ECG[3]		X		X		X	X		
Coronary angiogram			X[1]			X[2]			
IVUS			X[6]			X[6]			
OCT			X[7]			X[7]			
Physical Examination	X				X[8]	X	X		
Per-protocol medications		X	X	X	X	X	X	X	X
Physical status q'naire					X[8]			X	X
Adverse events[4]			X	X	X	X	X	X	X

1 Prior to and immediately post in-stent treatment with CVT Everolimus-coated PTCA Catheter.
2 In a subset of 25 patients at both index procedure and 180 day follow up
3 A 12 lead ECG will be performed within 24 hours post-procedure. Relevant copies of ECGs will be collected for death or any (suspected) myocardial infarction or (suspected) stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Events Committee (CEC). This includes copies of the baseline ECG (screening and discharge) and event ECG (most abnormal ECG and last ECG recorded) if available.
4 AE collection will start when CVT Everolimus-coated PTCA Catheter has entered the vasculature.
5 A log of patients presenting to sites with in-stent restenosis be maintained and provide reasons for not including subjects in the study.
6. In a subset of 15 subjects at both index procedure and 180 day follow up
7. In a subset of 10 subjects at both index procedure and 180 day follow up
8. Depending on if the 30 day follow up is an office visit (exam) or phone call (questionnaire)

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 person, 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., MACE) occur between study evaluation visits.

AE collection will start when CVT Everolimus-coated PTCA Catheter has entered the vasculature.

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 that 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 PTCA procedure.

- Acute myocardial Infarction (Cardiac)
- Aneurysm
- Arrhythmias, including ventricular fibrillation (bradycardia & tachycardia)
- Arterial Dissection
- Arteriovenous fistula
- Bleeding
- Coronary artery spasm
- Coronary artery thrombosis
- Death (Cardiovascular or non-cardiovascular related)
- Discomfort during procedure

- Drug reactions or allergic reactions to contrast medium
- Distal Embolism (air, thrombus, plaque)/Device Embolism
- Endocarditis
- Fever
- Groin bruising/discomfort
- Hematoma
- Hemorrhage
- Hypotension/hypertension
- Injury at blood vessel access site requiring surgical or medical treatment
- Ischemia
- Pseudoaneurysm
- Renal failure
- Restenosis of the dilated vessel
- Sepsis, infection
- Stroke or cerebrovascular event
- Total occlusion of the coronary artery or bypass graft
- Unstable angina
- Vessel dissection, perforation, rupture or injury
- Thrombosis
- 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 PTCA 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

The following is a list of adverse events that may result from the follow-up angiography

procedures:

- Acute myocardial Infarction
- Arrhythmias, including ventricular fibrillation (bradycardia & tachycardia)
- Arteriovenous fistula
- Coronary artery spasm
- Death (Cardiovascular or non-cardiovascular related)
- Drug reactions or allergic reactions to contrast medium
- Hematoma (Access Site Complication or Bleeding)
- Hypotension/hypertension
- Infection (Access Site Complication)
- Pain and tenderness
- Pseudoaneurysm
- Restenosis of the dilated vessel
- Stroke, air embolism, and embolization or fragmentation of thrombotic or atherosclerotic material (Neurologic)
- Total occlusion of the coronary artery or bypass graft
- Unstable angina
- Vessel dissection, perforation, rupture or injury

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 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, 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

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 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 10.2) 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, then 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 *a priori* specified Objective Performance Criteria (OPC).

The OPCs for the primary safety endpoint and effectiveness endpoints have been set using historical control data from thirty-two (32) published studies that evaluate treatments for ISR, analyzed in meta-analysis and also reviewed in a consensus document[6]. Since this is a feasibility trial, the attainment of statistical significance is neither a necessary nor a sufficient condition for determine whether the device merits further study. If the data exhibit a trend ($p \leq 0.10$) toward statistical significance when compared to historical control and raise no safety concerns, it may be deemed worthy of further investigation. In addition, there will be a focus on estimating the magnitude of observed values at 180 days post-procedure and their associated 90% confidence

[6] Jeger et al. Third International DCB Consensus Group Report JACC: Cardiovascular Interventions, 2020June;1 3(12):1391-402
Ae-Young Her et al. Current Management of In-Stent Restenosis, Korean Circ J. 2018 May;48(5):337-349
Leos Pleva et al. Treatment of coronary in-stent restenosis: a systematic review *J Geriatr Cardiol* 2018; 15: 173-184

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 trial 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 and at least one valid follow-up visit.

6.3 Sample Size Justification

Approximately 50 subjects at up to 15 active sites will be enrolled in the CVT-ISR Trial. All subjects will be scheduled for clinical examination at six (6) months. The objective of the study is to assess the initial feasibility and performance of the CVT Everolimus-Coated PTCA Catheter in the treatment of subjects presenting in-stent restenosis in coronary arteries. The study is powered (per PASS13) based on the primary safety and effectiveness endpoints.

The primary safety endpoint for this analysis is freedom from target lesion failure (TLF) rate at 6 months post-index procedure, defined as a composite rate of all cardiac death, target vessel myocardial infarction and clinically-driven target lesion revascularization (TLR). The null (H0) and alternative (HA) hypotheses are:

H_0: $ffTLF_{\text{historical control}} \leq ffTLF_{\text{CVT treatment}}$

H_A: $ffTLF_{\text{historical control}} > ffTLF_{\text{CVT treatment}}$

The proposed sample size of N=50 is based on the primary safety endpoint of freedom from TLF rate at 6 months post-index procedure. The sample size calculation is based on the following assumptions:

- A single comparison of CVT Treatment group to a safety OPC of 65%.
  - A positive safety endpoint result would be where the lower limit of the 90% CI exceeded the OPC=65%
  - One-tailed α=0.05

The safety focus will be to estimate the frequency of TLF at six (6) months post-procedure and the associated 90% confidence interval.

If 8 of 50 (16%) subjects experience TLF, the point estimate for ffTLF is 84% and corresponding the 90% CI is [73%, 92%], well above the OPC of 65%.

By enrolling 50 subjects there is 95% power to detect a 19%-point margin over the Safety OPC, with a one-tailed α=0.05.

The primary effectiveness endpoint is late lumen loss at six (6) months. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $\text{Late Loss}_{\text{historical control}} \leq \text{Mean Late Loss}_{\text{CVT treatment}}$

H_A: $\text{Late Loss}_{\text{historical control}} > \text{Mean Late Loss}_{\text{CVT treatment}}$

The power calculation is based on the following assumptions:

- A single comparison of CVT Treatment group to an historical control group.
- A true mean difference between the historical control group and the treatment group of 0.50 mm. This assumption is made based on the results of historical studies. Assuming the true mean late loss for the CVT treatment group is 0.30 mm, the difference between the control group and treatment group is calculated as: 0.80 mm – 0.30 mm = 0.50 mm.
    - Standard deviation is assumed to be 0.5 mm in the treatment group.
- Two-tailed α=0.10

Given the above assumptions, enrolling 25 subjects (analysis of 25 evaluable subjects) will provide 87% power for demonstrating CVT treatment's superiority over historical controls in LLL.

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.

Analysis of Primary Endpoints

The primary safety endpoint of freedom from target lesion failure (TLF) rate at 6 months post-index procedure will be analyzed using the safety population.

The analysis of the primary effectiveness endpoint of LLL at 6 months will utilize the evaluable populations.

Analysis of Secondary Endpoints

All secondary endpoints will be analyzed using descriptive statistics.

For binary variables, such as 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 methods will be employed instead.

For time-to-event variables, such as time to target lesion revascularization, survival curves will be constructed using Kaplan-Meier estimates.

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 Percutaneous Coronary Diagnostic and Treatment Procedures

It is expected that risks associated with using CVT Everolimus-coated PTCA Catheter are those associated with treatment procedures and percutaneous coronary diagnostic

including angiography, intravascular ultrasound (IVUS) and optical coherence tomography (OCT). These risks may include but are not limited to the following: acute myocardial infarction, aneurysm, arrhythmias, including ventricular fibrillation, arterial dissection, arteriovenous fistula, bleeding, coronary artery spasm, coronary artery thrombosis, death, discomfort during procedure, drug reactions or allergic reactions to contrast medium, distal embolism (air, thrombus, plaque) or device embolism, endocarditis, fever, groin bruising/discomfort, hematoma, hemorrhage, hypotension/hypertension, injury at blood vessel access site, ischemia, pseudoaneurysm, renal failure, restenosis of the dilated vessel, sepsis/infection, stroke or cerebrovascular event, total occlusion of the coronary artery or bypass graft, unstable angina, vessel dissection, perforation, rupture or injury, thrombosis and vomiting/nausea.

The fluoroscopy time of the angiographic follow up assessment is expected to be very limited and expected to be no longer than any routine diagnostic angiography. The Sponsor considers that this assessment does not pose additional risks to the subject or laboratory personnel.

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[7].

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,

[7] 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
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).

pruritus, pyrexia, rash, stomatitis, thrombocytopenia, thrombotic microangiography, thrombotic thrombocytopenic purpura, tremor, urinary tract infection, upper respiratory tract infection and vomiting[8].

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 PTCA 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.

Based on all current information available to date on everolimus as a drug entity and on the CVT Everolimus-coated PTCA Catheter as a device, it is unlikely, with the total dosage on the CVT Everolimus-coated PTCA 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-ISR Trial will be conducted by skilled and trained investigators relative to interventional procedures. 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 line with standard of care requirements for coronary interventional procedures.

7.4 Potential Benefits

The potential benefits of the CVT Everolimus-coated PTCA Catheter have not been documented; nevertheless, subjects who undergo Percutaneous Transluminal Coronary Angioplasty (PTCA) of the coronary arteries may benefit by the use of the everolimus-coated coronary balloon because everolimus is a drug with a proven safety profile with long-term, worldwide use in drug-eluting stents (DES) considered as the percutaneous treatment of choice for coronary artery disease (CAD). Also, the use of CVT Everolimus-coated PTCA Catheter may eliminate, decrease and/or delay the chance of restenosis and re-occlusion in the treated artery, with an expected subsequent clinical benefit in terms of symptom relief.

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

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 registering 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 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 invetigator'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. Sponsor will make final determination of approved investigators.

- Signed investigator's agreement
- Completed device 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 implant.

- 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 of study subject's questions. Subjects will be assured that they may withdraw 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 4. CVT-ISR 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.

10.2 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.

10.3 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.

10.4 Training of Investigator and Site Personnel and 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.

10.5 Investigator's Brochure

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

10.6 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

10.7 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 clinical events committee 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 clinical events committee 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 clinical events committee will be blinded to the primary results of the trial.

The clinical events committee 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 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 (LBL1120)
- Appendix D: Helsinki Declaration
- Appendix E: Instructions for Use (LBL1121)
- Appendix F: Schedule of Events
- Appendix G: Research Agreement Template (FRM1122)
- Appendix H: Investigators Responsibilities
- Appendix I: Angiographic Core Lab Guidelines and Worksheet
- Appendix J: Risk Analysis

- Appendix K: General Safety and Performance Requirements Statement
- Appendix L: Case Report Forms (FRM1123)

APPENDIX A: BIBLIOGRAPHICAL REFERENCES

1. Holmes DR Jr, Hirshfeld J Jr, Faxon D, Vlietstra RE, Jacobs A, King SB III. ACC Expert Consensus document on coronary artery stents: document of the American College of Cardiology. J Am Coll Cardiol 1998;32:1471–1482
2. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331(8):489-495. doi:10.1056/NEJM199408253310801
3. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331(8):496-501. doi:10.1056/NEJM199408253310802
4. Savage MP, Fischman DL, Rake R, Leon MB, Schatz RA, Penn I, Nobuyoshi M, Moses J, Hirshfeld J, Heuser R, Baim D, Cleman M, Brinker J, Gebhardt S, Goldberg S. Efficacy of coronary stenting versus balloon angioplasty in small coronary arteries. Stent Restenosis Study (STRESS) Investigators. J Am Coll Cardiol. 1998 Feb;31(2):307-11. doi: 10.1016/s0735-1097(97)00511-1. PMID: 9462572
5. Wong P, Lau KW, Lim YL, Oesterle SN. Stent placement for non-STRESS/BENESTENT lesions: a critical review. Catheter Cardiovasc Interv 2000;51:223–233.
6. Koning R, Eltchaninoff H, Commeau P, et al. Stent placement compared with balloon angioplasty for small coronary arteries: in-hospital and 6-month clinical and angiographic results. Circulation. 2001;104(14):1604-1608. doi:10.1161/hc3901.096695
7. Muramatsu T, Iwasaki K, Inou N, Horita Y, Tanaka T, Fujita N. Efficacy of coronary stenting versus balloon angioplasty in vessels of diameters less than 3.0 mm and less than 2.5 mm: CHIVAS investigators (abstract). Am J Cardiol 2002;90:96H.
8. Moreno R, Fernández C, Alfonso F, et al. Coronary stenting versus balloon angioplasty in small vessels: a meta-analysis from 11 randomized studies. J Am Coll Cardiol. 2004;43(11):1964-1972. doi:10.1016/j.jacc.2004.01.039
9. Agostoni P, Biondi-Zoccai GG, Gasparini GL, et al. Is bare-metal stenting superior to balloon angioplasty for small vessel coronary artery disease? Evidence from a meta-analysis of randomized trials. Eur Heart J. 2005;26(9):881-889. doi:10.1093/eurheartj/ehi116
10. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346(23):1773-1780. doi:10.1056/NEJMoa012843
11. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349(14):1315-1323. doi:10.1056/NEJMoa035071
12. Schofer J, Schlüter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet. 2003;362(9390):1093-1099. doi:10.1016/S0140-6736(03)14462-5

13. Schampaert E, Cohen EA, Schlüter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). J Am Coll Cardiol. 2004;43(6):1110-1115. doi:10.1016/j.jacc.2004.01.024

14. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. Circulation. 2003;107(1):38-42. doi:10.1161/01.cir.0000047700.58683.a1

15. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation. 2003;108(7):788-794. doi:10.1161/01.CIR.0000086926.62288.A6

16. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350(3):221-231. doi:10.1056/NEJMoa032441

17. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA. 2005;294(10):1215-1223. doi:10.1001/jama.294.10.1215

18. Dawkins KD, Grube E, Guagliumi G, et al. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. Circulation. 2005;112(21):3306-3313. doi:10.1161/CIRCULATIONAHA.105.552190

19. Torrado J, Buckley L, Durán A, et al. Restenosis, Stent Thrombosis, and Bleeding Complications: Navigating Between Scylla and Charybdis. J Am Coll Cardiol. 2018;71(15):1676-1695. doi:10.1016/j.jacc.2018.02.023

20. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation. 2001;103(15):1967-1971. doi:10.1161/01.cir.103.15.1967

21. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol. 2010;56(23):1897-1907. doi:10.1016/j.jacc.2010.07.028

22. Magalhaes MA, Minha S, Chen F, et al. Clinical presentation and outcomes of coronary in-stent restenosis across 3-stent generations. Circ Cardiovasc Interv. 2014;7(6):768-776. doi:10.1161/CIRCINTERVENTIONS.114.001341

23. García Del Blanco B, Rumoroso Cuevas JR, Hernández Hernández F, Trillo Nouche R. Spanish cardiac catheterization and coronary intervention registry. 22nd official report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2012). Rev Esp Cardiol (Engl Ed). 2013;66(11):894-904. doi:10.1016/j.rec.2013.08.001

24. Pleva L, Kukla P, Hlinomaz O. Treatment of coronary in-stent restenosis: a systematic review. J Geriatr Cardiol. 2018;15(2):173-184. doi:10.11909/j.issn.1671-5411.2018.02.007

25. Buccheri D, Piraino D, Andolina G, Cortese B. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis. 2016 Oct;8(10):E1150-E1162

26. Alraies MC, Darmoch F, Tummala R, Waksman R. Diagnosis and management challenges of in-stent restenosis in coronary arteries. World J Cardiol. 2017;9(8):640-651. doi:10.4330/wjc.v9.i8.640

27. Shlofmitz E, Iantorno M, Waksman R. Restenosis of Drug-Eluting Stents: A New Classification System Based on Disease Mechanism to Guide Treatment and State-of-the-Art Review [published correction appears in Circ Cardiovasc Interv. 2019 Oct;12(10):e000044]. Circ Cardiovasc Interv. 2019;12(8):e007023. doi:10.1161/CIRCINTERVENTIONS.118.007023

28. Moustapha A, Assali AR, Sdringola S, et al. Abciximab administration and clinical outcomes after percutaneous intervention for in-stent restenosis. Catheter Cardiovasc Interv. 2002;56(2):184-187. doi:10.1002/ccd.10166

29. Hausleiter J, Kastrati A, Mehilli J, et al. Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. Circulation. 2004;110(7):790-795. doi:10.1161/01.CIR.0000138935.17503.35

30. Kufner S, Hausleiter J, Ndrepepa G, et al. Long-term risk of adverse outcomes and new malignancies in patients treated with oral sirolimus for prevention of restenosis. JACC Cardiovasc Interv. 2009;2(11):1142-1148. doi:10.1016/j.jcin.2009.08.015

31. Alfonso F, Pérez-Vizcayno MJ, Cruz A, et al. Treatment of patients with in-stent restenosis. EuroIntervention. 2009;5 Suppl D:D70-D78.

32. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-2619. doi:10.1093/eurheartj/ehu278

33. Albiero R, Silber S, Di Mario C, et al. Cutting balloon versus conventional balloon angioplasty for the treatment of in-stent restenosis: results of the restenosis cutting balloon evaluation trial (RESCUT). J Am Coll Cardiol. 2004;43(6):943-949. doi:10.1016/j.jacc.2003.09.054

34. Lemos PA, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. Circulation 2004; 109:1366.

35. Alfonso F, Zueco J, Cequier A, et al. A randomized comparison of repeat stenting with balloon angioplasty in patients with in-stent restenosis. J Am Coll Cardiol 2003; 42:796.

36. Alfonso F, Augé JM, Zueco J, et al. Long-term results (three to five years) of the Restenosis Intrastent: Balloon angioplasty versus elective Stenting (RIBS) randomized study. J Am Coll Cardiol 2005; 46:756.

37. Mehran R, Dangas G, Abizaid A, et al. Treatment of focal in-stent restenosis with balloon angioplasty alone versus stenting: Short- and long-term results. Am Heart J 2001; 141:610.

38. Sousa JE, Costa MA, Abizaid A, et al. Sirolimus-eluting stent for the treatment of in-stent restenosis: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2003; 107:24.

39. Degertekin M, Regar E, Tanabe K, et al. Sirolimus-eluting stent for treatment of complex in-stent restenosis: the first clinical experience. J Am Coll Cardiol 2003; 41:184.

40. Neumann FJ, Desmet W, Grube E, et al. Effectiveness and safety of sirolimus-eluting stents in the treatment of restenosis after coronary stent placement. Circulation 2005; 111:2107.

41. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005; 293:165.

42. Alfonso F, Pérez-Vizcayno MJ, Hernandez R, et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. J Am Coll Cardiol 2006; 47:2152.

43. Alfonso F, Pérez-Vizcayno MJ, Hernández R, et al. Long-term clinical benefit of sirolimus-eluting stents in patients with in-stent restenosis results of the RIBS-II (Restenosis Intra-stent: Balloon angioplasty vs. elective sirolimus-eluting Stenting) study. J Am Coll Cardiol 2008; 52:1621.

44. Garg S, Smith K, Torguson R, et al. Treatment of drug-eluting stent restenosis with the same versus different drug-eluting stent. Catheter Cardiovasc Interv 2007; 70:9.

45. Abe M, Kimura T, Morimoto T, et al. Sirolimus-eluting stent versus balloon angioplasty for sirolimus-eluting stent restenosis: Insights from the j-Cypher Registry. Circulation 2010; 122:42.

46. Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. JAMA 2006; 295:1253.

47. Holmes DR Jr, Teirstein P, Satler L, et al. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. JAMA 2006; 295:1264.

48. Ellis SG, O'Shaughnessy CD, Martin SL, et al. Two-year clinical outcomes after paclitaxel-eluting stent or brachytherapy treatment for bare metal stent restenosis: the TAXUS V ISR trial. Eur Heart J 2008; 29:1625.

49. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet. 2015;386(9994):655-664. doi:10.1016/S0140-6736(15)60657-2

50. Giacoppo D, Colleran R, Cassese S, et al. Percutaneous Coronary Intervention vs Coronary Artery Bypass Grafting in Patients With Left Main Coronary Artery Stenosis: A Systematic Review and Meta-analysis. JAMA Cardiol. 2017;2(10):1079-1088. doi:10.1001/jamacardio.2017.2895

51. Alraies MC, Darmoch F, Tummala R, Waksman R. Diagnosis and management challenges of in-stent restenosis in coronary arteries. World J Cardiol. 2017;9(8):640-651. doi:10.4330/wjc.v9.i8.640

52. The Food and Drug Administration Update: Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality. August 7, 2019. https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel. Accessed December 15, 2020.

53. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2018;7:e011245.
54. Agence Nationale de Sécurité du Medicament et des Produits de Santé, Paclitaxel-coated balloons and paclitaxel-eluting stents. June 18, 2020. Safety information. https://ansm.sante.fr/S-informer/Informations-de-securite-Autres-mesures-de-securite/Ballons-recouverts-de-paclitaxel-et-stents-a-elution-de-paclitaxel-Information-de-securite. Accessed December 15, 2020
55. Bundesinstitut für Arzneimittel und Medizinprodukte, Field Safety Notice June 2020. https://www.bfarm.de/SharedDocs/Kundeninfos/EN/07/2020/08550-20_kundeninfo_en.pdf?__blob=publicationFile&v=1. Accessed December 15, 2020
56. Medicines & Healthcare products-Regulatory Agency, Paclitaxel drug-coated balloons (DCBs) or drug-eluting stents (DESs): Reconfirmed position on use in patients with intermittent claudication and critical limb ischaemia. 18 February 2021. https://www.gov.uk/drug-device-alerts/paclitaxel-drug-coated-balloons-dcbs-or-drug-eluting-stents-dess-reconfirmed-position-on-use-in-patients-with-intermittent-claudication-and-critical-limb-ischaemia. Accessed March 01, 2021

APPENDIX B: TRIAL ABBREVIATIONS AND DEFINITIONS

ABR	Angiographic Binary Restenosis
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
AMI	Acute Myocardial Infarction
AV	Arteriovenous
BMI	Body Mass Index
BMS	Bare-Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CEC	Clinical Events Committee
CI	Clinically Indicated
CK	Creatine Kinase
CK-MB	Creatine Kinase - Myocardial-Band isoenzyme
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
cTn	Cardiac Troponin
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVT	Chansu Vascular Technologies
DCB	Drug Coated Balloon
DES	Drug-Eluting Stent
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	Identification
IFU	Instructions for Use
ISO	International Organization for Standardization
ISR	In-Stent Restenosis
ITT	Intent-to-Treat
IVUS	IntraVascular UltraSound
LLL	Late Lumen Loss
MACE	Major Adverse Cardiac Event
MEC	Medical Ethics Committee
MI	Myocardial Infarction
MLD	Minimum Lumen Diameter
µg	Microgram
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
QA	Quantitative Angiography
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SC	Steering Committee
TLF	Target lesion failure

TLR	Target Lesion Revascularization
TnT	Troponin T
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization

Acute Closure

The occurrence of new (during the procedure) severely reduced flow (TIMI grade 0-1) within the target vessel that persisted and required rescue by stenting or other treatment, or resulted in myocardial infarction or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not mean "no reflow" (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not mean transient closure with reduced flow in which the index treatment application does reverse the closure.

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.

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.

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).

Clinically Relevant Myocardial Infarction after Coronary Revascularization:

1) In subjects with normal baseline values:

   Elevation of CK-MB values ≥10xURL (Upper Reference Limit) or TnT values ≥70xURL within 48 hours of the procedure

   Or

   Elevation of CK-MB values ≥5xURL or TnT values ≥35xURL with new pathological Q-waves in 2 contiguous leads or new persistent left bundle branch block (LBBB) in ECG,

2) In subjects without CK-MB measurements and a normal baseline cardiac troponin (cTn I or T) level measured within 48 hours of the PCI rises to ≥70xURL, or ≥35xURL with new pathological Q-waves in 2 contiguous leads, or new persistent LBBB.

3) In subjects with elevated baseline values, but stable or falling, Increment rise of CK-MB ≥10xURL or TnT values ≥70xURL.

4) In subjects with elevated baseline values, but not stable or falling, Increment rise of CKMB≥10xURL or TnT values ≥70xURL with new pathological Q-waves in 2 contiguous leads or new persistent LBBB in ECG.

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.It is defined as death resulting from cardiovascular causes. The following categories may be collected: 1. Death caused by acute MI 2. Death caused by sudden cardiac, including unwitnessed, death, 3. Death resulting from heart failure, 4. Death caused by stroke, 5. Death caused by cardiovascular procedures, 6. Death resulting from cardiovascular hemorrhage, 7. Death resulting from other cardiovascular cause.

Noncardiovasculardeath. It i*s defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be collected: 1. Death resulting from malignancy, 2. Death resulting from pulmonary causes, 3. Death caused by infection (includes sepsis), 4. Death resulting from gastrointestinal causes, 5. Death resulting from accident/trauma, 6. Death caused by other noncardiovascular organ failure, 7. Death resulting from other, noncardiovascular cause*

Undetermined. It *is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination.*

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.

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, which is responsible for the overall conduct of the trial at all sites.

Major Adverse Cardiac Event (MACE)

Death, myocardial infarction (Q wave and non-Q wave), emergent coronary bypass surgery, or clinically driven repeat target lesion revascularization by percutaneous or surgical methods.

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.

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.

Percent Diameter Stenosis

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

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.

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.

Target Lesion Revascularization (TLR)

Target lesion revascularization is defined as any repeat PCI of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.

Target vessel revascularization (TVR)

Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.

Target Lesion

Stent placed in a native epicardial coronary vessel with visually estimated nominal vessel diameter of ≥ 2.0mm and ≤ 3.5mm

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.

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.

APPENDIX C: INFORMED CONSENT: FRM1120

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

Chansu Vascular Technologies Everolimus Drug Coated Percutaneous Transluminal Coronary Angioplasty Catheter First in Human Clinical Investigation:

A Clinical Evaluation of the Everolimus CVT-PTCA-DCB in the Treatment of Patients with In-Stent Restenosis of previously treated Coronary Artery Lesions:
The CVT-ISR Trial

INFORMED CONSENT

INTRODUCTION

In this consent form, "you" always means the study participant. If you are a legally authorized representative, please remember that "you" means the study participant.

WHY AM I BEING ASKED TO BE IN THIS STUDY?

You are being asked to be in a study that involves clinical research. Being in this study is voluntary. Before you decide if you would like to be in the study, it is important you understand why the study is being conducted and what it will involve. Please read this form carefully and ask your doctor if you have any questions. Upon reading this form and asking any questions you have; you will sign and date the last page of this form if you decide to be in this study.

You are being asked to be in this study because your doctor recommends that you get a Drug-Coated Balloon angioplasty treatment, to open an in-stent restenosis in one of your coronary arteries which already has been treated previously without the desired results.

The heart muscle, like every other organ or tissue in your body, needs oxygen-rich blood to survive. Blood is supplied to the heart by its own vascular system, called coronary circulation. The aorta (the main blood supplier to the body) branches off into two main coronary blood vessels (also called arteries). These coronary arteries branch off into smaller arteries, which supply oxygen-rich blood to the entire heart muscle. Narrowing of these arteries by atherosclerosis or other diseases is called stenosis of the coronary arteries. Restenosis is the recurrence of a narrowing in an artery, which has been treated earlier. When a stent is used and restenosis occurs, this is called in-stent restenosis or ISR.

To open the narrowed or blocked coronary arteries, a long, thin tube called a catheter will be used that has a small balloon on its tip, which is coated with an anti-proliferative medication. The medication aims to prevent the formation of scar tissue in the coronary artery thereby minimizing the risk for a new stenosis. The catheter will be inserted into a blood vessel in the groin or wrist until it reaches the narrowed or blocked portion of the artery. The balloon will be inflated at the blockage site in the artery to flatten or compress the plaque against the artery wall and to deliver the medication on the balloon surface to the artery wall and surrounding tissue. This procedure is called angioplasty or percutaneous transluminal coronary angioplasty (PTCA).

The Chansu Vascular Technologies (CVT) Everolimus-coated PTCA Catheter being used in this study is investigational because the safety and efficacy of the device are not sufficiently known yet to allow commercial certification. The device is a combination of technologies that are already commercially available separately (the catheter and the medication).

STUDY PURPOSE:

The purpose of this study is to evaluate the clinical safety and efficacy of the CVT Everolimus-coated PTCA Catheter in the treatment of in-stent restenosis (ISR) previously treated with a drug-eluting or bare metal stent in one of your coronary arteries.

SYSTEM DESCRIPTION:

The CVT Everolimus-coated PTCA Catheter is a PTCA system that contains an anti-proliferative medication. The product consists of a catheter with a drug-coated balloon at the tip. The medication will reduce the occurrence of restenosis. The CVT Everolimus-coated PTCA Catheter, is considered an investigational device and is not market-released in Europe or anywhere else. This means that the effectiveness and safety of the investigational device needs to be evaluated before the device will be commercially released. The CVT Everolimus-coated PTCA Catheter leverages two existing technologies which both are already commercially released. Thereby the new CVT Everolimus-coated PTCA Catheter combines the advantages of both technologies into a new Coronary Drug-Coated Balloon Catheter system.

This study with the CVT Everolimus-coated PTCA Catheter is approved by the Medical Ethics Committee of *insert name of committee*. It is being performed in accordance with the national and international legal requirements.

HOW LONG WILL I BE IN THE STUDY? HOW MANY PEOPLE WILL BE IN THE STUDY?

About 50 subjects will be enrolled in this study in Europe. Your participation in the study may last about 36 months. The study will be conducted for a minimum of 36 months from treatment of the final subject, and it is expected that 50 patients can be enrolled in the study in approximately 9 months. This means that the overall study duration is expected to last a total of 45 months.

WHAT ARE MY RESPONSIBILITIES DURING THE STUDY?

Being in this study, it is important that you:

- Tell the study doctor about your medical and medication history.
- Attend all visits scheduled with the study doctor.
- Call the study doctor's office to reschedule a missed visit as soon as possible.
- Report any injuries, hospitalizations, emergency room visits, symptoms or complaints to the study doctor or nurse as soon as possible.
- Keep your contact information up to date (address, telephone number, etc.).
- Are compliant with the study procedures and the medications that your doctor prescribes.

WHAT WILL HAPPEN IF I AM IN THIS STUDY?

If you decide to be in this study, the study doctor and study nurse will collect information about you and your medical history. This includes any medication you currently take and any other information in your medical records related to your condition or treatment that may be relevant to you being in the study.

To determine if the CVT Everolimus-coated PTCA Catheter is a good treatment choice for you, a screening will take place.

The screening will be performed by a qualified member of the research team and the hospital. During the screening it will be determined if you meet the eligibility criteria to be included in this study. Your medical and cardiac history will be checked and an existing angiogram (X-ray imaging of your heart's blood vessels) will be analyzed as well to determine if an angioplasty can be performed successfully.

If your study doctor decides you are suitable for the study, you will receive the angioplasty with the CVT Everolimus-coated PTCA Catheter. However, after the screening your study doctor may decide that you are not suitable for the study or it is not possible to receive the angioplasty with the CVT Everolimus-coated PTCA Catheter. In that case you may receive another treatment which is best to treat your condition and you will not participate in the study.

STUDY PROCEDURES:

For this study, your study doctor will schedule 2 follow-up visits with you after the procedure has taken place and you will also receive 3 phone calls. You must make sure that you can come to each visit as scheduled or respond to emails or be available for a phone call follow-up.

BASELINE: PRIOR TO THE BALLOON ANGIOPLASTY PROCEDURE

Prior to your procedure the following will be collected/performed:

- You will be asked questions about your medical history; including your cardiac history.
- You will be asked questions to check your medical status.
- You will have routine laboratory tests done within 7 days before your planned Balloon Angioplasty Procedure. About 10-20 ml (about 2-4 teaspoons) of blood will be drawn within 72 hours before your Balloon Angioplasty Procedure. This is done to measure your blood count for any blood clotting problems, for possible infection and to look at your cardiac biomarkers (a substance released from the heart muscle). Tests will check to see that no damage has been done to your heart muscle. Tests will also check the function of your kidneys. These tests are routine when having a PTCA procedure. The blood draws can cause some pain from the needle stick and bruising at the site of the blood draw.
- An Electrocardiogram (ECG) will be done to record the electrical activity of your heart.
- If you are female and of child-bearing potential, a pregnancy test may be done within 14 days before your procedure to confirm you are not pregnant. If you are pregnant you will be exited from this study. You must be willing to use a reliable method of contraception for the entire duration of study participation.
- Antiplatelet Medications will be given within 24 hours before your procedure. It is routine to take medication before your procedure. Antiplatelet medicines help prevent blood clots from forming. This includes aspirin and medicine, such as clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®), or ticagrelor (Brilinta®).

BALLOON ANGIOPLASTY PROCEDURE VISIT

Your balloon angioplasty procedure will be done following standard procedures at the study site.

The study doctor will perform an angiogram. It is a procedure that uses contrast dye and x-ray to allow the study doctor to see inside the arteries. The angiogram requires catheters to be placed into your arteries to allow injection of a special contrast dye which can be seen on x-ray. The x-ray machine then takes pictures of the arteries (angiography) that show your study doctor where the blockage is and how severe the blockage is. He uses angiography to decide whether the narrowed artery is usable for the study. If you will be treated with the study device, the procedure will be recorded by x-ray filming of the artery and a copy will be used for analysis.

At the time of the angiogram, the study doctor may perform an Intravascular Ultrasound (IVUS = device using sound waves to see inside blood vessels) or an optical coherence tomography (OCT = device using infrared light to see inside blood vessels) if the hospital has one or the other device. These devices provide more precise information regarding the coronary artery which has been treated.

If you do not meet the requirements for this study, you may receive treatment with a different market approved coronary balloon or other treatment. If that happens, you will not be considered to be participating in the study and will not be followed in the study. Your doctor will follow up with you as part of your standard care.

DISCHARGE (BEFORE YOU LEAVE THE HOSPITAL AFTER THE ANGIOPLASTY PROCEDURE)

After the **balloon angioplasty** procedure, the following will be collected/performed:

- Lab tests will be done within the 24 hours after your procedure. About 10-20 ml of blood (about 2-4 teaspoons) will be drawn to look at your health status and cardiac biomarkers. Other blood may be drawn if more monitoring is needed.
- An ECG will be done within 24 hours after your procedure to record the electrical activity of your heart.
- Antiplatelet Medications – It is routine to take medicine after the procedure. Antiplatelet medicines help prevent blood clots in your coronary arteries. Antiplatelet medicine will be prescribed to you, at an amount that is best for you, after the procedure for at least six months. Your study doctor will ask you to take aspirin indefinitely.

It is very important you take all of the medicine as you are told by the study doctor and that you do not stop taking any medicine without first talking to the study doctor or study staff. It is also important to understand how missing any doses or not taking these medicines may affect you. Stopping the prescribed antiplatelet medication earlier than instructed by the study doctor could result in a higher risk of blood clots, heart attack or death.

FOLLOW-UP AT 6 MONTHS:

At this follow-up the following will be collected/performed:

- Physical examination
- ECG
- You will be asked if you have had any problems or symptoms since your last visit
- Antiplatelet medications will be evaluated

You may be selected for an angiographic follow up and angiogram of your coronary arteries. You will be informed about this at the time of the procedure. These angiographic images will be reviewed to check the efficacy of the procedure.

At the time of the angiogram, the study doctor may perform an IVUS or an OCT if the hospital has one or the other device. The images obtained from these devices will be reviewed to check the efficacy of the procedure as well.

FOLLOW-UP AT 12 MONTHS:

At this follow-up, the following will be collected/performed:

- Physical examination
- ECG
- You will be asked if you have had any problems or symptoms since your last visit.
- Antiplatelet Medications will be evaluated

FOLLOW-UP AT 30 DAYS, 24 MONTHS, AND AT 36 MONTHS:

At these follow-up times, you will be contacted by phone and you will have to answer a series of questions about your medical status, the antiplatelet medication you are taking and you will be asked if you have had any problems or symptoms since your last visit or phone call.

SUMMARY TABLE OF EXAMINATIONS AND PROCEDURES BASED ON VISIT DATES

VISIT WINDOW/PERIOD *(The day of the ablation procedure is Day 0, so all of the follow-up visit windows are determined from this date)*	DESCRIPTION OF THE SUBJECT VISIT
Screening and enrollment visit(s) in the 14 days prior to the ablation procedure	Signature of the consent form, physical examination, laboratory tests, ECG, chronic concomitant medications, antiplatelet/anticoagulant medications.
Day of discharge from the hospital	Physical examination, laboratory tests, ECG, chronic concomitant medications, antiplatelet/anticoagulant medications, occurrence of problems or symptoms since the procedure.
Follow-up visit at 30 days ± 7 days	Phone contact or site visit / assessment of your medical status, antiplatelet medications / occurrence of problems or symptoms since the last visit.
Follow-up visit at 180 (6 months) ± 30 days	Physical examination / ECG / coronary angiogram / chronic concomitant medications, antiplatelet/anticoagulant medications / occurrence of problems or symptoms since the last phone call.
Follow-up visit at 365 (12 months) ± 30 days	Physical examination / ECG / chronic concomitant medications, antiplatelet/anticoagulant medications / occurrence of problems or symptoms since the last visit.
Follow-up visit at 24 months (± 30 days)	Phone contact / assessment of your medical status, antiplatelet medications / occurrence of problems or symptoms since the last visit.
Follow-up visit at 36 months (± 30 days)	Phone contact / assessment of your medical status, antiplatelet medications / occurrence of problems or symptoms since the last phone call.

It is very important that the study staff is able to contact you at each of the time points to collect the required study data. If the study staff is not able to reach you at one of these time points, they may contact a relative, a person whom you have provided contact details for or your regular doctor.

By signing the Consent Form for this study, you agree to allow the people listed above to be contacted if you cannot be reached.

You will be exited from the study after completing your 36 month visit and you will continue to receive standard care from your doctor.

WHAT ARE THE POSSIBLE RISKS, SIDE-EFFECTS AND INCONVENIENCES?

Since the CVT Everolimus-coated PTCA Catheter is an investigational device, the risks are not entirely known but are believed to be similar to those that are associated with the standard, customary angioplasty with a commercially available drug-coated balloon of a stenosed coronary artery. The risks associated with using this device are related to the drug, and risks associated with standard percutaneous coronary diagnostic and treatment procedures.

All efforts will be made to minimize the risks in this study by selecting doctors who are experienced and skilled in interventional procedures including stenting, by clearly defining inclusion/exclusion criteria to ensure only appropriate patients are enrolled, and by ensuring that treatment and follow-up of the patient are consistent with current medical practices.

EVEROLIMUS AND BALLOON COATING

The balloons are coated with a drug called Everolimus. Potential side-effects unique to the Everolimus drug coating may include:

- Abdominal pain
- Anemia (the body does not get enough oxygen rich blood)
- Angioedema (rapid swelling of the skin and mucous membranes, sometimes affecting the face and throat)
- Anorexia (loss of appetite)
- Asthenia (physical weakness or lack of energy)
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dry Skin
- Dyslipidemia (abnormal level of fats in the blood) including hyperlipidemia (abnormally elevated level of fats in the blood) and hypercholesterolemia (abnormally elevated level of cholesterol in the blood)
- Dyspnea (shortness of breath)
- Dysgeusia (condition where perception of taste is altered)
- Dyspepsia (indigestion)
- Dysuria (painful or difficult urination)
- Edema (excess fluid in the tissues)

- Epistaxis (nosebleeds)
- Fatigue
- Headache
- Hematuria (blood in the urine)
- Hyperglycemia (abnormally high blood sugar)
- Hyperkalemia (abnormally high level of potassium in the blood)
- Hyperlipidemia (abnormally high concentration of fats or lipids in the blood)
- Hypertension (abnormally high blood pressure)
- Hypokalemia (abnormally low level of potassium in the blood)
- Hypomagnesemia (abnormally low level of magnesium in the blood)
- Hypophosphatemia (abnormally low level of phosphate in the blood)
- Increased serum creatinine (sign of poor kidney function)
- Infections and Serious Infections: bacterial, viral, fungal, and protozoal infections (infectious disease caused or transmitted by a parasite)
- Insomnia
- Interaction with strong inhibitors and inducers of CYP3A4 or PgP (interaction of everolimus with specific substances of the organism could reduce the efficacy of some pharmaceutical drugs)
- Leukopenia (decrease in the number of leucocytes [colorless cell that circulates in the blood and body fluids and involved in counteracting foreign substances and disease])
- Lymphoma (cancer of the lymphatic system, which is part of the body's germ-fighting network) and other malignancies (including skin cancer)
- Male infertility
- Mucosal inflammation including oral ulceration and oral mucositis (inflammation and/or ulceration of the oral mucosal membranes)
- Nausea
- Neutropenia (decrease in the number of neutrophils [a type of white blood cell that helps heal damaged tissues and resolve infections])
- Non-Infectious pneumonitis (noninfectious general inflammation of lung tissue)
- Pain: extremity, incision site and procedural, and back
- Proteinuria (elevated levels of protein in urine)
- Pruritus (itch)
- Pyrexia (fever)

- Rash (abnormal changes in skin color or texture)
- Stomatitis (inflammation of the mouth and lips)
- Thrombocytopenia (abnormally low number of thrombocytes [platelets] in the blood, which increases the risk of bleeding)
- Thrombotic microangiopathy (destruction of red blood cells and organ damage due to the formation of microscopic blood clots in capillaries and small arteries)
- Thrombotic thrombocytopenic purpura (blood disorder that results in blood clots forming in small blood vessels throughout the body)
- Tremor
- Urinary tract infection
- Upper respiratory tract infection
- Vomiting

PERCUTANEOUS CORONARY DIAGNOSTIC AND TREATMENT PROCEDURES

Other risks associated with using this device are those associated with the treatment procedures. These risks may include the following:

- Acute myocardial infarction also known as heart attack (a blood clot in the vessels that supply blood to your heart that causes part of the heart muscle to die)
- Aneurysm (enlarged part of a blood vessel caused by a weakening of the artery wall)
- Arrhythmias (irregular heartbeat) including ventricular fibrillation (situation when the ventricles merely quiver and do not contract in a coordinated way), Bradycardia (slower than normal heart rate) and Tachycardia (faster than normal heart rate)
- Arterial dissection (a tear within the wall of a blood vessel, which allows blood to separate the wall layers)
- Arteriovenous fistula (an abnormal connection between an artery and a vein)
- Bleeding
- Coronary artery spasm (a brief, sudden narrowing of one of the blood vessels supplying blood and oxygen to the heart)
- Coronary artery thrombosis (formation of a blood clot inside a blood vessel of the heart)
- Death (Cardiovascular or non-cardiovascular related)
- Discomfort during the procedure
- Drug reactions or allergic reactions to contrast medium (a substance used to enhance the visibility of blood vessels)
- Distal Embolism of air (migration of one or more bubbles of air downstream of the blood vessel), thrombus (migration of blood clot downstream of the blood vessel), plaque (fatty deposits downstream of the blood vessel) / Device Embolism (migration of device or parts of

device used during the treatment procedure in the blood vessel)

- Endocarditis (inflammation of the inner lining of your heart's chambers and valves)
- Fever
- Groin Bruising/Discomfort
- Hematoma (bruising)
- Hemorrhage (bleeding)
- Hypertension (abnormally high blood pressure)
- Hypotension (abnormally low blood pressure)
- Injury at blood vessel access site requiring surgical or medical treatment
- Ischemia (vascular disease involving an interruption in the arterial blood supply to a tissue, organ, or extremity that, if untreated, can lead to tissue death)
- Pseudoaneurysm (false aneurysm; a collection of blood that forms between the inner and outer layer of a blood vessel, usually caused by an injury to the vessel)
- Renal failure (condition in which the kidneys are no longer able to filter and clean blood)
- Restenosis of the dilated vessel (re-narrowing of the blood vessel that received treatment to clear the blockage)
- Sepsis (blood infection)
- Stroke or cerebrovascular event (sudden death of brain cells in a localized area due to not enough blood flow)
- Total occlusion (no more blood flow possible in the blood vessel) of the coronary artery or bypass graft (blood vessel removed from another area of the body to bypass narrowed heart arteries)
- Unstable angina (pain in the chest)
- Vessel dissection (a tear within the wall of a blood vessel, which allows blood to separate the wall layers), perforation (a leak in the wall of a blood vessel), rupture (broken blood vessel) or injury
- Thrombosis (formation of blood clots in blood vessels)
- Vomiting/Nausea

FOLLOW-UP ANGIOGRAPHY PROCEDURES:

The risks associated with the follow-up angiography procedures may include the following:

- Acute myocardial infarction also known as heart attack (a blood clot in the vessels that supply blood to your heart that causes part of the heart muscle to die)
- Arrhythmias (irregular heartbeat) including ventricular fibrillation (situation when the ventricles merely quiver and do not contract in a coordinated way), Bradycardia (slower than

normal heart rate) and Tachycardia (faster than normal heart rate)

- Arteriovenous fistula (an abnormal connection between an artery and a vein)
- Coronary artery spasm (a brief, sudden narrowing of one of the blood vessels supplying blood and oxygen to the heart)
- Death (Cardiovascular or non-cardiovascular related)
- Drug reactions or allergic reactions to contrast medium (a substance used to enhance the visibility of blood vessels)
- Hematoma (bruising)
- Hypertension (abnormally high blood pressure)
- Hypotension (abnormally low blood pressure)
- Infection at access site
- Pain and tenderness
- Pseudoaneurysm (false aneurysm; a collection of blood that forms between the inner and outer layer of a blood vessel, usually caused by an injury to the vessel)
- Restenosis of the dilated vessel (re-narrowing of the blood vessel that received treatment to clear the blockage)
- Stroke (sudden death of brain cells in a localized area due to not enough blood flow), air embolism (migration of one or more bubbles of air in the circulatory system), and embolization or fragmentation of thrombotic or artherosclerotic material (a blood clot or plaque dislodged from the blood vessel and becomes free-floating in the circulatory system with the risk of blocking a blood vessel supplying the brain)
- Total occlusion (no more blood flow possible in the blood vessel) of the coronary artery or bypass graft (blood vessel removed from another area of the body to bypass narrowed heart arteries)
- Unstable angina (pain in the chest)
- Vessel dissection (a tear within the wall of a blood vessel, which allows blood to separate the wall layers), perforation (a leak in the wall of a blood vessel), rupture (broken blood vessel) or injury

RADIATION RISKS:

As a result of your participation in this study, you will be exposed to radiation from x-ray procedures. In addition to the routine procedures you will undergo, the x-ray exams used for this study include a required angiographic evaluation of the CVT Everolimus-coated PTCA Catheter at 6 months follow-up. These x-ray exams deliver up to a total radiation dose of approximately 5 milliSievert (mSv). A milliSievert is a unit of radiation dose. For comparison, the average person in Europe receives 1.8 mSv each year from natural sources of radiation. A slight increase in cancer risk may exist for people exposed to radiation. The dose from this procedure is comparable to that received from many diagnostic medical x-ray and nuclear medicine

procedures. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure.

Following the fluoroscopic procedure, the skin area exposed to the x-rays could react to produce an effect similar to a sun burn. A skin reaction, if it occurs at all, could show up from a few hours to a few weeks after the procedure, and usually goes away on its own. If you have a skin reaction, you should promptly report this to your study doctor.

If you are or you become pregnant, there may be risks to you or your unborn child that are not yet known.

There may be additional risks related to this study that are not yet known.

WHAT ARE THE POSSIBLE BENEFITS OF THE STUDY?

If you agree to be in this study, it is possible that you may not have any direct medical benefits. The information from this study may benefit other subjects with similar conditions in the future.

WHAT HAPPENS WHEN I END BEING IN THE STUDY?

When you end being in this study, you will continue to receive standard care from your doctor.

WHAT OTHER TREATMENT CHOICES DO I HAVE IF I AM NOT IN THE STUDY?

You do not have to be in this study to be treated for coronary artery disease.

If you decide not to be in this study, there is other care available to you. You will be treated in other ways, for example, treatment with another commercially available coronary drug-coated balloon or a stent. You may choose no treatment at all. You should discuss other treatments and their possible risks and benefits with your doctor.

WHO IS PAYING FOR THIS STUDY?

The site will receive payment from CVT for work involved in collecting study data and managing the study at the site. Being in this study may contribute to the development of commercial products from which CVT may receive economic benefit.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will not receive any compensation for your participation in this study.

WHAT WILL I HAVE TO PAY FOR IF I AM IN THIS STUDY?

Testing and services done only for the study will be provided at no cost to you. All costs that are part of your usual medical care that would have been provided if you were not in the study will be covered by your medical insurance.

In the event of physical injury or physical illness resulting from your participation in this study, any immediate medical treatment you need will be provided.

Your *name of national healthcare coverage* should cover the costs of medical care and treatment.

WHAT HAPPENS IF I AM INJURED OR HURT DURING THIS STUDY?

In the event of physical injury or physical illness resulting from your participation in this study, any immediate medical treatment you need will be provided. The study sponsor, CVT has agreed to pay back the site for the costs of medical or surgical care it provides for any illness or injury related to your participation in the study, if the treatment is not already covered by your medical insurance.

By agreeing to this, you do not give up any of your legal rights. You do not release CVT, study doctors, or the hospital from responsibility for their negligence.

DO I HAVE THE RIGHT TO REFUSE TO BE IN THIS STUDY OR TO LEAVE THIS STUDY?

Being in this study is voluntary. You may choose not to be in the study or to leave the study at any time for any reason. If you choose not to be in the study or to leave the study, this will not result in any penalty and you will not lose any benefits to which you are entitled. Your regular care and your relationship with the hospital or clinic and your doctors will not be affected.

You will be told about any new information that may make you change your mind about staying in the study. You may be asked to sign a new consent form if this occurs.

You may leave the study simply by telling the study doctor. There are no specific tests that are required prior to leaving the study. You may be asked to come in for a final product check or visit.

The study doctor may take you out of the study without your permission if:

- It is in your best medical interest
- You do not follow your study doctor's instructions
- The study sponsor or regulatory authority stops the study

If this happens you will be notified about being removed from the study and you will be provided with an explanation about such decision.

All of your health data already collected for the study can still be used by the study sponsor unless you object and ask for deletion of the data.

WHAT IS THE ROLE OF THE STUDY SPONSOR'S REPRESENTATIVE?

Trained CVT personnel may be present at the intervention and at study follow-up visits. The role of the CVT person is to give technical support. All of these actions will be done under the careful direction of your study doctor.

HOW WILL THE STUDY SPONSOR USE THE STUDY INFORMATION?

Your participation in this study is entirely confidential to the extent allowed by law. If you are in this study, the following data will be collected by the study team:

- Identifying data (name, age, address).
- Medical and health data from your medical records.
- Data on your living habits.
- Identifying biological samples taken from you. (hereinafter called "personal data")

Your personal data will be processed at all times in accordance with applicable legal requirements.

In general only the study doctor and/or nurse as well as the study monitor who acts on behalf of CVT have direct access to your personal data in your subject file. Furthermore it may happen that members of the Ethics Committee and representatives of national, European or other international public authorities are granted direct access to your personal data in order to comply with legal requirements.

For conducting the study your personal data will be transferred to and processed by CVT or a third party designated by CVT - **but solely in a key coded form**. This means that your data will be transferred to CVT or a third party designated by CVT which is located in your country, in a member state of the European Economic Area but maybe also in the United States or another country where the European Directive on Data Protection does not apply.

CVT may also use your personal data for additional purposes such as overseeing and improving the performance of its product, new medical research, developing new medical products or procedures, and other business purposes.

You are entitled to access the personal data collected about you and to have inaccuracies corrected.

Any published information including reports and articles about the study will not include your name or any information that could personally identify you. Information received during the study will not be used to market to you; your name will not be placed on any mailing lists or sold to anyone for marketing purposes.

You may change your mind and take back this permission to continue collecting your personal data at any time. To take back this permission, you will need to write to *insert name and contact information*. However, if you take back this permission, you will no longer be a participant in the study. All of your personal data that was already collected will still be used unless you object and ask for deletion of data.

WHERE CAN I FIND OUT ABOUT THE STUDY RESULTS?

A description of this study will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can consult the general outcome and results of this study after they have been made publicly available by consulting this website.

WHO CAN I CALL WITH QUESTIONS, COMPLAINTS OR IF I'M CONCERNED ABOUT MY RIGHTS AS A PARTICIPANT?

If you have any questions about the research or being in this study, you should contact *insert name* at *insert telephone number.*

If you think you have a research-related injury, you should contact *insert name* at *insert telephone number.*

If you have any questions about your rights as a participant you should contact *insert name* at *insert telephone number.*

WHO HAS REVIEWED THE STUDY?

This study was reviewed and approved by the *insert name of committee* Research Ethics Committee.

INFORMED CONSENT FOR THE CVT ISR CLINICAL STUDY

SUBJECT INFORMED CONSENT FORM SIGNATURE SHEET

- I have read the subject information for this study and my study doctor has answered all my questions regarding the study.
- I had sufficient time to consider my participation in this study, I am aware that participation in this study is completely voluntary, and I agree to follow the instructions from the study doctor.
- I realize that I may decide to refuse participation or stop participation at any time without penalty and without affecting the quality of my health care or the relationship with my study doctor.
- I understand and agree that personal information about me will be collected from my medical records, used and processed (manually and by computer) by the manufacturer of a product used in my treatment or any other designated party that is involved in the study (e.g., hospital, study doctor, regulatory authorities, ethics committees).
- I understand and agree that representatives from CVT, regulatory authorities and the Ethics Committee will be granted direct access to my medical records.
- I understand and agree that the study doctor(s)/hospital will release the relevant personal information about me for the purpose of the study.
- I understand that I am entitled to access the personal information collected about me and to have inaccuracies corrected.
- I agree to voluntarily be in and comply with this study.
- I understand that I will receive a dated and signed copy of the subject informed consent form.

It is your choice if you would like your personal physician to be informed of your participation in this study. Please check one of the boxes below to show your choice:

I agree to inform my personal doctor about my participation in this study.

I do not agree to inform my personal physician about my participation in the study.

Signature of the subject

I agree to be in this study, and I have consented before the initiation of any study specific procedures.

Name: _____

Signature: _____

Date: (DD/MM/YYYY) _____

Study doctor or designated person by study doctor:

I have conducted the informed consent discussion.

Name: _____

Signature: _____

Date: (DD/MM/YYYY) _____

If subject is unable to read:

I have attended the entire informed consent discussion. I attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. Informed consent was freely given by the subject.

Impartial Witness Name: _____

Signature: _____

Date: (DD/MM/YYYY)_____

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: LBL1121

(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.)

CVT EVEROLIMUS-COATED PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA) CATHETER

INSTRUCTIONS FOR USE

ALL INSTRUCTIONS, PRECAUTIONS AND WARNINGS SHOULD BE CAREFULLY READ AND UNDERSTOOD BEFORE USE. FAILURE TO DO SO MAY RESULT IN COMPLICATIONS.

EXCLUSIVELY FOR CLINICAL INVESTIGATIONS

CONTENTS

1. DEVICE NAME

Everolimus-coated Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheter manufactured by Chansu Vascular Technologies (CVT).

2. INTRODUCTION

The CVT Everolimus-coated PTCA Catheter consists of an Rx PTCA catheter with an Everolimus-coated balloon.

Caution: Only physicians experienced in percutaneous coronary interventional procedures should use the CVT Everolimus-coated PTCA Balloon Catheter. Before using the catheter, the operators should be familiar with the contents of the instructions for use. Special attention should be made to the indications, contraindications, restrictions, warnings and precaution statements as noted in this manual.

3. DEVICE DESCRIPTION

3.1. Description of the Device

Figure 1. CVT Everolimus-coated PTCA Catheter

Basic Catheter Specifications

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

The investigational device will be provided sterile, with the sterile device packaged in a foil pouch and contained within a single unit box.

3.2. CVT Everolimus Coating Description

[redacted]

4. INDICATIONS FOR USE

The CVT Everolimus-coated PTCA Catheter is intended to be used for improving luminal diameter and myocardial perfusion in patients presenting in-stent stenotic lesions ≤24 mm in length in native coronary arteries with reference vessel diameters of 2-3.5mm.

5. CONTRAINDICATIONS

5.1. Contraindications

Refer to the Clinical Investigational Plan for study exclusion criteria.

5.2. Restrictions

The CVT Everolimus-coated PTCA Catheter is an investigational device and may only be used if the subject has provided study informed consent. Use is restricted to investigator physicians who are experienced in the clinical and technical aspects of angioplasty.

6. WARNINGS

- The CVT Everolimus-coated PTCA Catheter is supplied STERILE for single use only. Do not use if the sterile barrier (inner Tyvek pouch) is compromised.
- Do not reprocess or re-sterilize the CVT Everolimus-coated PTCA Catheter. Re-processing and/or re-sterilizing could increase the risk of patient infection and the risk of compromised device performance.
- This device is not recommended for stent delivery.

- Do not use after the labeled “Use by” date.
- Do not exceed the Rated Burst Pressure (RBP) for the device. Refer to product label for device specific inflation information. At least 99.9% of the balloons (with a 95% confidence) will not burst at or below the RBP. Balloon rupture may occur if the RBP is exceeded.
- Use of a pressure-monitoring device is recommended to prevent over pressurization.
- Use only the recommended balloon inflation medium. Never use air or any gaseous medium to inflate the balloon.
- Since the use of this device carries the associated risk of subacute thrombosis, vascular complications and/or bleeding events, judicious selection of subjects is necessary.
- After use, dispose of the catheters and accessories according to safety requirements related to products contaminated by blood.
- Do not expose the catheter to ionizing radiation, ultraviolet light or organic solvents, e.g. alcohol.
- To reduce the potential for vessel damage, the inflated diameter of the balloon should approximate the diameter of the vessel just proximal and distal to the stenosis.
- When the CVT Everolimus-coated PTCA Catheter is exposed to the vascular system, it should be manipulated under high-quality fluoroscopic observation.
- If resistance is encountered at any time during the insertion procedure, determine the cause before proceeding.
- Do not attempt to straighten the CVT Everolimus-coated PTCA Catheter if the shaft has become bent or kinked as this may result in the shaft breaking. Instead, retract the device and prepare a new device for use.

7. PRECAUTIONS

- A thorough understanding of the principles, clinical applications and risks associated with Percutaneous Transluminal Coronary Angioplasty (PTCA) is necessary before using this product.
- Any use of the CVT Everolimus-Coated PTCA Catheter for procedures other than those indicated in these instructions is not recommended.

- This CVT Everolimus-Coated PTCA Catheter is not recommended for use in lesions that may require inflation higher than those recommended for the device.
- Do not use if the package is open or damaged.
- Prior to angioplasty, the CVT Everolimus-Coated PTCA Catheter should be examined to verify functionality and ensure that its size and shape are suitable for the specific procedure for which it is to be used.
- Proper functioning of the CVT Everolimus-Coated PTCA Catheter is dependent on its integrity. Care should be used when handling the catheter. Damage may result from kinking, stretching or manipulation of the catheter.
- Before removing CVT Everolimus-Coated PTCA Catheter from the sheath/guiding catheter it is very important that the balloon is completely deflated.
- Precautions to prevent or reduce clotting should be taken when any catheter is used. Flush or rinse all products entering the vascular system with sterile isotonic saline or a similar solution via the guidewire access port prior to use. Consider the use of systemic heparinization.
- Never attempt to move the guidewire when the balloon is inflated.
- Never advance the catheter without the guidewire extending from the tip.
- If resistance is felt upon the removal of the device, the CVT Everolimus-coated PTCA Catheter, guidewire and sheath/guiding catheter should be removed together as a unit, particularly if balloon rupture or leakage is suspected. This may be accomplished by firmly grasping the CVT Everolimus-coated PTCA Catheter, guidewire and sheath/guiding catheter as a unit and withdrawing all together from the vasculature, using a twisting motion combined with retraction.
- During the procedure, appropriate anti-coagulant therapy must be provided to the subject as needed. Anti-coagulant therapy should be continued for a period of time to be determined by the physician after the procedure.

8. DRUG INFORMATION

8.1. Mechanism of Action

[redacted]

8.2. Drug Interactions

Formal drug interaction studies have not been conducted for the CVT Everolimus-coated PTCA Catheter. The respective instructions for use for all drugs used in conjunction with the CVT Everolimus-coated PTCA Catheter should be consulted for interactions with Everolimus. Consideration should be given to the potential for systemic and local drug interactions in the vessel wall in a patient who is taking a drug with known interactions to Everolimus or when deciding to initiate drug therapy in a patient who has been treated with the CVT Everolimus-coated PTCA Catheter. In the absence of formal drug interaction studies, caution should be exercised when administering Everolimus.

8.3. Carcinogenicity, Genotoxicity and Reproductive Toxicology

No long-term studies have been performed to evaluate the carcinogenic potential of the CVT Everolimus-coated PTCA Catheter. Do not use the CVT Everolimus-coated PTCA Catheter in women who are pregnant or intending to become pregnant.

9. POTENTIAL ADVERSE EVENTS

9.1. Adverse Events

Potential complications which may be associated with *a coronary balloon dilation procedure* include, but may not be limited to, the following:

Acute myocardial Infarction (Cardiac) • Aneurysm • Arrhythmias, including ventricular fibrillation (bradycardia & tachycardia) • Arterial dissection • Arteriovenous fistula • Bleeding • Coronary artery spasm • Coronary artery thrombosis • Death (cardiovascular or non-cardiovascular related) • Discomfort during procedure • Drug reactions or allergic reactions to contrast medium • Distal embolism (air, thrombus, plaque)/Device embolism • Endocarditis • Fever • Groin bruising/discomfort • Hematoma • Hemorrhage • Hypotension/hypertension • Injury at blood vessel access site requiring surgical or medical treatment • Ischemia • Pseudoaneurysm • Renal failure • Restenosis of the dilated vessel • Sepsis, infection • Stroke or cerebrovascular event • Total occlusion of the coronary artery or bypass graft • Unstable angina • Vessel dissection, perforation, rupture or injury • Thrombosis • 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 PTCA catheter*:

Abdominal pain • Anemia • Angioedema • Anorexia • Asthenia • Constipation • Cough • Delayed wound healing/fluid accumulation • Diarrhea • Dyslipidemia (including hyperlipidemia and hypercholesterolemia) • Dysgeusia • Dyspepsia • Dyspnea • Dysuria • Dry Skin • Edema (peripheral) • Epistaxis • Fatigue • Headache • Hematuria • Hyperglycemia • Hyperkalemia • Hyperlipidemia • 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 • Nausea • Neutropenia • Non-infectious pneumonitis • Pain: extremity, incision site and procedural, back • Proteinuria • Pruritus • Pyrexia • Rash • Stomatitis • Thrombocytopenia • Thrombotic microangiopathy • Thrombotic thrombocytopenic purpura •Tremor • Upper respiratory tract infection • Urinary tract infection • Vomiting

10. HOW SUPPLIED

10.1. Sterile, For Single Use only

The CVT Everolimus-coated PTCA Catheter is supplied sterile (ethylene oxide sterilization). The device is for single patient use only. Do not re-sterilize, re-use or re-process the device. Do not use if the Tyvek sterile barrier is damaged.

10.2. Storage

The CVT Everolimus-coated PTCA Catheter should be stored at ambient temperature in a dry location in its original packaging. The device should be used prior to the labeled "Use by" date on the device packaging.

11. INSTRUCTIONS FOR USE

11.1. Materials Required

- 20 cc syringe
- Heparinized saline solution
- Three-way stopcock
- Contrast Media-the standard inflation medium is a 1:1 mixture of contrast medium and normal saline. ***Do not use contrast media that is contraindicated for intravascular use.***
- Appropriately sized exchange guidewire (refer to product labeling)
- Appropriately sized hemostatic introducer sheath (refer to product labeling)
- Inflation device with manometer

11.2. Inspection Procedures

Inspect the CVT Everolimus-coated PTCA Catheter and packaging. Do not use if packaging or product damage is evident. This product may be a potential biohazard; handle and dispose of it in accordance with accepted medical practice and applicable local, state and federal laws and regulations.

Inspect the CVT Everolimus-coated PTCA Catheter "Use By" date. Use before the labeled "Use By" date.

11.3. Preparation of Catheter for Use

1. Carefully remove the CVT Everolimus-coated PTCA Catheter from the package.

2. Slide the protective sheath off the balloon. Remove any mandrel that might be present in the guidewire lumen.
3. Flush the guidewire lumen with heparinized saline solution.
4. Prepare an inflation device with the recommended contrast medium (50% contrast and 50% saline as per normal procedure).
5. To evacuate air from balloon segment:
    a. Fill a 20 cc syringe or inflation device with approximately 4 cc of the recommended contrast medium.
    b. After attaching syringe or the inflation device to the balloon inflation lumen, orient the CVT Everolimus-coated PTCA Catheter with the distal tip and the balloon pointing in a downward vertical position.
    c. Apply negative pressure and aspirate for 15 seconds. Slowly release pressure to neutral, allowing contrast to fill the shaft of the catheter.
    d. Disconnect the syringe or inflation device from the inflation port of the CVT Everolimus-coated PTCA Catheter.
    e. Remove all air from the syringe or inflation device barrel. Reconnect the syringe or inflation device to the inflation port of the CVT Everolimus-coated PTCA Catheter. Maintain negative pressure until air no longer returns to the device.
    f. Slowly release the device pressure to neutral.
6. Disconnect the 20cc syringe (if used) and connect the inflation device to the inflation port of the catheter without introducing air into the system. *Note: All air must be removed from the balloon and displaced with contrast prior to inserting in the body otherwise, complications may occur.*
7. Replace the syringe with an inflation device with manometer, taking care not to introduce air into the catheter.

11.4. Catheter Introduction and Dilatation

1. The CVT Everolimus-coated PTCA Catheter can be introduced percutaneously through an appropriately sized introducer sheath. ***Do not attempt to use a smaller sized introducer sheath than indicated on the product label.***
2. Apply negative pressure to the balloon.

3. Place the prepared CVT Everolimus-coated PTCA Catheter over a pre-positioned guidewire, which has been placed through the lesion, and introduce the catheter percutaneously. Negative pressure should be maintained during advancement over the guidewire. Advance the catheter tip to the treatment location. A suitable length guidewire should be used at all times to maintain control and position of the guidewire.

4. ***Use fluoroscopic guidance for all further catheter manipulations during the procedure. If resistance is encountered at any time during the insertion procedure, do not force passage. Resistance may cause damage to the device or lumen. If resistance is encountered carefully withdraw the CVT Everolimus-coated PTCA Catheter. It may be necessary to remove the device, guidewire and guiding catheter/sheath as one unit.***

5. Position the CVT Everolimus-coated PTCA Catheter at the treatment location. The radiopaque marker bands indicate the working length of the balloon. ***The position of the balloon may only be modified with the guidewire in place.***

6. Inflate the balloon to dilate the desired target diameter according to the compliance chart printed on the device packaging. Inflation should be maintained for sixty (60) seconds. ***Inflation should not be in excess of the rated burst pressure***.

7. Deflate the balloon and apply negative pressure.

8. With the guidewire in place and with negative pressure in the balloon, withdraw the CVT Everolimus-coated PTCA Catheter. ***Do not retract the device unless the balloon is free and fully deflated.***

9. If more than one CVT Everolimus-coated PTCA Catheter is required to treat a single lesion, the balloon portion of each device must overlap by at least one (1) centimeter. A new, unused balloon must be used for each deployment. ***No more than 2 devices can be used to treat a single lesion.***

10. Results should be verified by angiography.

11. The CVT Everolimus-coated PTCA Catheter is a single use device. Do not re-use or re-sterilize.

12. If the CVT Everolimus-coated PTCA Catheter has entered the vasculature and cannot be deployed, the device CANNOT be re-inserted for deployment.

11.5. Post-Treatment Dilatation or Stenting

1. If post-treatment dilatation is required, a standard PTCA catheter should be used.
2. If provisional (bail out) stenting is required a bare metal stent indicated for treatment of coronary arteries should be used.

11.6. Instructions on Related, Additional Devices

If required, a bare metal stent indicated for use in the native coronary arteries can be used after treatment with the CVT Everolimus-coated PTCA Catheter.

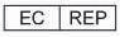
12. INSTRUCTIONS ON HOW TO SAFELY DISPOSE OF THE CVT EVEROLIMUS-COATED PTCA CATHETER

After use, the CVT Everolimus-coated PTCA Catheter may be considered a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.

13. WARRANTY

Although the CVT Everolimus-coated PTCA Catheter has been manufactured under carefully controlled conditions, CVT has no control over the conditions under which this product is used. CVT therefore disclaims all warranties, both express and implied, with respect to the product including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. CVT shall not be liable to any person or entity for any medical expenses, or any direct, incidental or consequential damages caused by any use, defect, failure or malfunction of the product, whether a claim for such damages is based upon warranty, contract, tort or otherwise. No person has any authority to bind CVT to any representation or warranty with respect to the product. The exclusions and limitations set out above are not intended to, and should not be construed so as to, contravene mandatory provisions of applicable law. If any part or term of this Disclaimer of Warranty is held to be illegal, unenforceable or in conflict with applicable law by a court competent jurisdiction, the validity of the remaining portions of this Disclaimer of Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Disclaimer of Warranty did not contain the particular part or term held to be invalid.

14. SYMBOLS

Symbol	Meaning
	Manufacturer
	Available by Prescription only
	Authorized European Community Representative
	Do Not Use if Damaged
NP	Nominal Pressure
RBP	Rated Burst Pressure
	Balloon Diameter
	Balloon Length
	Guide Wire
Content	Quantity of Contents
	Catalog Number
	Manufacturing Date
	Use By (Expiry Date)
	Lot Number
	For Single Use only
	Protect from Sunlight
	Sterile by Ethylene Oxide Process
	Caution, Consult Accompanying Documents
	Keep Dry
	Single Sterile Barrier System with Protective Packaging Outside
	Do Not Resterilize

Chansu Vascular Technologies, LLC
[redacted]

EC REP
[redacted]

APPENDIX F: SCHEDULE OF EVENTS

(1 page)

PROCEDURE/TEST	Prior to Procedure	Pre-Procedure	Procedure	Pre-Discharge	30 days (± 7 days)	180 days (± 30 days)	1 year (± 30 days)	2 years (± 28 days)	3 years (± 30 days)
Patient Medical History	X								
Review Inclusion/Exclusion Criteria[5]	X								
Patient Informed Consent	X								
Chronic Concomitant Medications/History	X	X	X	X	X	X	X	X	X
Creatinine	X								
CBC, Platelet Count	X			X					
Coagulation Tests	X			X					
Pregnancy Test (if applicable)	X								
CK-Mb		X		X					
Cardiac Troponin (cTn)		X		X					
12 Lead ECG[3]		X		X		X	X		
Coronary angiogram			X[1]			X[2]			
IVUS			X[6]			X[6]			
OCT			X[7]			X[7]			
Physical Examination	X				X[8]	X	X		
Per-protocol medications		X	X	X	X	X	X	X	X
Physical status q'naire					X[8]			X	X
Adverse events[4]			X	X	X	X	X	X	X

1 Prior to and immediately post in-stent treatment with CVT Everolimus-coated PTCA Catheter.
2 In a subset of 25 patients at both index procedure and 180 day follow up
3 A 12 lead ECG will be performed within 24 hours post-procedure. Relevant copies of ECGs will be collected for death or any (suspected) myocardial infarction or (suspected) stent thrombosis that occurs after the index procedure for adjudication purposes by a Clinical Events Committee (CEC). This includes copies of the baseline ECG (screening and discharge) and event ECG (most abnormal ECG and last ECG recorded) if available.
4 AE collection will start when CVT Everolimus-coated PTCA Catheter has entered the vasculature.
5 A log of patients presenting to sites with in-stent restenosis be maintained and provide reasons for not including subjects in the study.
6. In a subset of 15 subjects at both index procedure and 180 day follow up
7. In a subset of 10 subjects at both index procedure and 180 day follow up
8. Depending on if the 30 day follow up is an office visit (exam) or phone call (questionnaire)

APPENDIX G: RESEARCH AGEEMENT TEMPLATE: FRM1122

(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.)

CLINICAL STUDY RESEARCH INSTITUTION AGREEMENT

[redacted]

CVT-ISR FIH CLINICAL TRIAL	ETUDE CVT-ISR FIH
Sponsor: Chansu Vascular Technologies LLC (CVT) **Contact Person:** [redacted] **Research Institution:** [redacted] **Research Institution/Contact Person:** [redacted] **THIS CLINICAL STUDY AGREEMENT** [redacted] **Chansu Vascular Technologies LLC (CVT),** [redacted] ("Sponsor"), **and** **INSTITUTION XXXXXX** [redacted]	**Promoteur : Chansu Vascular Technologies LLC** [redacted] **Etablissement :** **Institut de recherche/Contact:** **LE PRESENT CONTRAT RELATIF A UNE ETUDE CLINIQUE** [redacted] **Chansu Vascular Technologies LLC (CVT),** [redacted] (le « Promoteur »), **et** **INSTITUTION XXXXXX** [redacted]

1. SCOPE Of WORK

[redacted]

1.2 **Research Institution**

[redacted]

1.3 **Study Device**

[redacted]

1. ETENDUE DE LA CHARGE DE TRAVAIL

[redacted]

1.2 **Institut de recherche**

[redacted]

1.3 **Dispositif expérimental.**

[redacted].

[redacted]

1.3.2 **Billing**: [redacted]

1.4 **Adverse Events**

[redacted].

1.5 **Deviations.** [redacted]

1.6 **Public Registry**. [redacted]

2. **COSTS: PAYMENT**

2.1 **Consideration**. [redacted]

[redacted]

1.3.2 **Facturation**. [redacted]

1.4 **Evènements indésirables**.

[redacted]

1.5 **Déviations.** [redacted]

1.6 **Registre public.** [redacted]

2. **COUTS: PAIEMENTS**

2.1 **Rémunération.** [redacted]

[redacted]

2.2 **Fair Market Value**. [redacted]

2.3 **Disclosure of Payments to Health Care Professionals**. [redacted]

[redacted]

2.2 **Juste valeur marchande**. [redacted]

2.3 **Divulgation de paiement aux professionnels de santé**. [redacted]

[redacted]

3. **REPORTS: ACCESS**

3.1 **Documentation Provided by Investigator**

[redacted]

3.2 **Subject Privacy**

[redacted]

[redacted]

3. **RAPPORTS: ACCES**

3.1 **Documentation fournie par l'investigateur**.

[redacted]

3.2 **Protection de la vie privée des Patients**

[redacted]

[redacted]

3.3 **Access.** [redacted]

[redacted]

[redacted]s en matière de protection de la vie privée.

3.3 **Accès.** [redacted]

[redacted]

3.4 **Inspections**.

3.5 **Records and Reports. Research.**

3.4 **Inspections**.

e

3.5 **Registres et rapports**.

[redacted]

4. **SPONSOR MATERIALS**

[redacted]

4. **MATERIELS DU PROMOTEUR**

[redacted]

5. **CONFIDENTIAL INFORMATION**

[redacted]

6. **REPORTS, RESULTS AND INVENTIONS**

6.1 **Reports and Results**. [redacted]

5. **INFORMATIONS CONFIDENTIELLES**

[redacted]

[redacted]

6.2 **Inventions.** [redacted]

7. **INDEMNITY AND INSURANCE**

7.1 **By Sponsor**. [redacted]

6. **RAPPORTS, RESULTATS ET INVENTIONS**

6.1 **Rapports et résultats.** [redacted]

6.2 **Inventions.** [redacted]

7. **INDEMNISATION ET ASSURANCE**

7.1 **Par le Promoteur**. [redacted]

7.2 **By Research Institution.** [redacted]

7.3 **Conditions of Indemnity**

[redacted]

7.4 **Insurance**

7.4.1 **Sponsor.** [redacted]

7.2 **Par l'institut de recherche.** [redacted]

7.3 **Conditions d'indemnisation.**

[redacted]

7.4.2 **Research Institution.**

7.4.3

8. **TERM AND TERMINATION**

8.1 **Term.**

8.2 **Early Termination.**

8.3 **Duties upon Termination.**

7.4 **Assurance.**

7.4.1 **Promoteur.**

7.4.2 **L'institut de recherche.**

7.4.3 **Par ailleurs,**

8. **DUREE DE VALIDITE ET RESILIATION**

8.1 **Durée de validité.**

8.2 **Résiliation anticipée.**

9. **COVENANTS AND WARRANTIES**

9.1 **Absence of Restrictions**.

9.2 **Conduct of Study**.

9.3 **Prior and Future Conduct**.

8.3 **Obligations en cas de résiliation**.

9. **ENGAGEMENTS ET GARANTIES**

9.1 **Absence de restrictions**.

9.2 **Déroulement de l'Etude**.

9.3 **Conduite antérieure et ultérieure**.

[redacted]

9.4 **Compliance with Applicable Laws.** [redacted]

[redacted]

9.4 **Conformité au Droit applicable.** [redacted]

[redacted]

10. **MISCELLANEOUS**

10.1 **Entirety**. [redacted]

11.2 **Governing Law**. [redacted]

10.3 **Severability**. [redacted].

10.4 **Assignment.** [redacted]

10.5 **Notices**. [redacted]

If to Research Institution:
XXXXXX

If to Sponsor:
Chansu Vascular Technologies LLC.
[redacted]

10.6 **Independent Contractors**. [redacted]

[redacted]

10. **DISPOSTIONS DIVERSES**

10.1 **Intégralité du Contrat**. [redacted]

10.2 **Droit applicable**. [redacted]

10.3 **Autonomie des dispositions**. [redacted]

10.4 **Cession**. [redacted]

10.5 **Avis**. [redacted]

10.7 **Modification.**

10.8 **Waiver.**

10.9 **Counterparts.**

10.10 **Headings**.

10.11 **Interpretation**.

10.12 **Publicity.**

Pour l'institut de recherche :
XXXX

Pour le Promoteur :
Chansu Vascular Technologies LLC.

10.6 **Entrepreneurs indépendants.**

10.7 **Modification.**

10.8 **Renonciation.**

10.9 **Exemplaires.**

[redacted]	[redacted] 10.10 **Titres**. [redacted] 10.11 **Interprétation.** [redacted] 10.12 **Publicité**. [redacted]
The parties have caused this Agreement to be executed as of the Effective Date.	Les parties ont fait signer le présent Contrat à la Date d'entrée en vigueur.

Sponsor/Promoteur
Chansu Vascular Technologies LLC

By / Par : _____
[redacted]

Date: _____

Research Institution /Coordinateur de la recherche

By / Par : _____
Name title
Date: _____

EXHIBIT A /ANNEXE A

EXHIBIT A	**XXXXXX A**
STUDY BUDGET – FEE SCHEDULE	
Sponsor: Chansu Vascular Technologies LLC **Institution:** **Investigator:**	**Promoteur:** **Institution:** **Investigator:**
1. Scope of Work [redacted] *(Remainder of page intentionally left blank.)*	**1. XXXXXX**

2. Payee Information All payments associated with the Study shall be made by Sponsor. Complete table	**2. XXX**

Payee/Company Information

Company Name:	
Address:	
City, State and Zip:	
Contact Name:	Telephone Number: Email:
Tax ID Number (if applicable):	

COMPLETE THIS SECTION IF ELECTING TO RECEIVE ELECTRONIC PAYMENTS

Bank Name:	Bank Address:
SWIFT Code:	Bank Code:
Account Number:	IBAN:
Account Name:	

xxxxxxxx / xxxxxxxxxx

xxxxxxxx:	
xxxxxx:	
xxxxxxx:	
xxxxxxx:	tel.: e-mail:
xxxx (xxxxxxxx):	

XXXXX
XXXXXX

xxxxx:	xxxxx:
SWIFT:	xxxx:
xxxxx:	IBAN xxxx:
xxxxxxxx:	

3. Study Device and Equipment [redacted]	**3. xxxxxxxxx**

4. Institution Fees

Ethics Committee (EC) Fees	Amount
1. [redacted] 2. [redacted] 3. [redacted]	[redacted]

Study Start-up Fee	Amount
[redacted]	[redacted]

4. xxxxxx

xxxxx (EC)	xxxxxx
1. xxxx 2. xxxxx 3. xxxxx	

poplatek za zahájení studie	částka

5. Baseline Administration Support Research Services

[redacted]

5. xxxxxxx

[redacted] **Milestone Schedule.** [redacted]	**xxxxxxxxxxxxx.**

Milestone	Amount
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
TOTAL	[redacted]

xxxxx	xxxxx
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
TOTAL	[redacted]

6. Expedited Data Collection	**6. xxxxxxxxx**

7. Medical Procedures or Services	**7. xxxxxxxxx**
a) Preauthorization/Precertification for Standard of Care Medical Procedures or Services.	**a) xxxxxxxxxxxxxx**
b) Study Devices.	**b) xxxxxxxxxxxxxx.**
8. Qualifications for Payments.	**8. xxxxxx.**

9. Payment. [redacted] Please send all the invoices with specified wire transfer instructions to: Chansu Vascular Technologies LLC; [redacted]	**9. xxxxxx**.

Please send all the invoices with specified wire transfer instructions to:
Chansu Vascular Technologies LLC; [redacted]

THIS EXHIBIT A SETS FORTH ALL PAYMENTS TO BE MADE BY SPONSOR TO RESEARCH INSTITUTION AND INVESTIGATORS IN CONNECTION WITH THIS AGREEMENT AND, IF THE PARTIES HAVE ENTERED INTO A CLINCAL TRIAL AGREEMENT FOR THE CVT-ISR-FIH TRIAL, IN CONNECTION WITH EXPEDITED DATA COLLECTION PURSUANT TO SUCH OTHER AGREEMENT, IF APPLICABLE. NO OTHER ADDITIONAL PAYMENT REQUESTS WILL BE CONSIDERED WITHOUT THE PRIOR WRITTEN CONSENT OF SPONSOR.

AGREED TO BY:

Name Printed: _____

Signature _____

Title: _____

Date: _____

SPONSOR

Name Printed: _____

Signature _____

Title: _____

Date: _____

APPENDIX H: INVESTIGATOR'S RESONSIBILITIES

(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: ANGIOGRAPHIC CORE LAB GUIDELINES AND WORKSHEET

(4 pages)

[redacted]

[redacted]

Technician's Worksheet
CVT-ISR Study

Instructions for use:

[redacted]

For each sequence, please document the lesion undergoing treatment using the following abbreviations:
Lesion treated: Left Anterior Descending Artery(LAD), Diagonal Branch(Diag), Diag, Left Circumflex Artery(LCX), Obtuse Marginal Branch(OM), Right Coronary Artery(RCA), Posterior Descending Artery(PDA), Posterolateral Branches(PL**).**

Please note whether catheter was a diagnostic (D) catheter or a guiding (G) catheter.
The size of all devices used must recorded.

Site ID _____
Patient ID _____
Patient Initials _____ Cath date: ___ ___ _____

MM DD YYYY

Sequences	Lesion Treated	Device Name with Size information	Catheter French size	IC NTG(Yes/No)

[redacted]

Angiographic Core Laboratory

[redacted]

CVT-ISR TRIAL

INSTRUCTIONS TO THE SITE

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

[redacted]

Angiographic Core Laboratory

ANGIOGRAPHIC Do's and Don'ts

Do's

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

Don't

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

IMAGE TRANSFER/SHIPPING REQUIREMENTS

Please send the angiograms as instructed by sponsor.

If instructed to send images along with TWS to ACL, please ship to:

[redacted]

[redacted]

Angiographic Core Laboratory

Contact Sheet

APPENDIX J: RISK ANALYSIS

A full risk management file (RMF1018) is complete and available for the CVT Everolimus-coated PTCA 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 PTCA Balloon Catheter were evaluated for the intended use listed on page one of this risk management and for deliberate mis-use of the device. The analysis yielded three overall residual risk hazardous situations and resulting harms that are categorized as “High”:

ID	Hazard	Event	Hazardous Situation(s)	Potential Harm	Rate of Occurence
2c	Cardiovascular complication	Catheter deployment or post lesion treatment	Dissection	Ischemia/ Myocardial Infarction (MI)	>1% and <10%
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 (PTCA and stenting) 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 PTCA 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: FRM1123

(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.)

Inclusion Criteria Form

Inclusion Criteria: All items must be answered YES for subject to be eligible.

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, angiograms, IVUS/OCT and examination.
4.	Target Lesion must be located within a stent (bare metal or drug eluting) placed in a native epicardial coronary vessel with visually estimated nominal vessel diameter of ≥2.00mm and ≤3.5mm.
5.	Target lesion must measure ≤ 24mm in length by visual estimation
6.	Target lesion(s) must be with a visually estimated stenosis of ≥50% and <100% with a TIMI flow of ≥1
7.	Non-Clinical Investigation, percutaneous intervention for lesions in a non-target vessel is allowed if done ≥ 90 days prior to or if planned to be done 6 months after the index procedure.
8.	Non-Clinical Investigation, percutaneous intervention for lesions in the target vessel is allowed if planned to be done 6 months after the index procedure.

Were all of the inclusion criteria met? ☐ YES ☐ NO

If no, which criteria were violated (indicate all that apply): _____

Exclusion Criteria Form

Exclusion Criteria: All items must be answered NO for subject to be eligible.

1.	Subject has had a known diagnosis of acute myocardial infarction (AMI) within 30 days preceding the index procedure and CK and CK-MB have not returned within normal limits at the time of procedure.
2.	The subject is currently experiencing clinical symptoms consistent with AMI
3.	Subject has current unstable arrhythmia
4.	Subject has a known left ventricular ejection fraction (LVEF) < 25%.
5.	Subject has a known hypersensitivity or contraindication to aspirin, both heparin and bivalirudin, both clopidogrel and ticlopidine, and structurally related compounds, everolimus or contrast sensitivity that cannot be adequately pre-medicated.
6.	Subject has known renal insufficiency (e.g., serum creatinine level of more than 2.5 mg/dL, (i.e. 221 µmol/L) within 7 days prior to index procedure or subject on dialysis)..
7.	Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
8.	Subject has had a cerebrovascular accident (CVA) or transient ischemic neurological attack (TIA) within the past six months.
9.	Subject has other medical illness (e.g., cancer or congestive heart failure) or known history of substance abuse (alcohol, cocaine, heroin etc.) that may cause non-compliance with the clinical investigation plan, confound the data interpretation or is associated with a limited life expectancy (i.e., less than one year).
10.	Subject is already participating in another clinical investigation that has not yet reached its primary endpoint
11.	Subject is not in the opinion of the investigator an acceptable candidate to participate in the study.
12.	In stent lesions for stent located within an arterial or saphenous vein graft.
13.	The target vessel contains visible thrombus.
14.	Pregnant or lactating females.

Were any of the exclusion criteria met? □ YES □ NO

If yes, which criteria were violated (indicate all that apply): _____

Pre-Screening & Enrollment Form

Date Subject Signed Informed Consent: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

Date of Subject Visit (when the following data was collected): |___|___| |___|___||___|___|___|___|
DD MM YYYY

Demographics

1. Year of Birth: |___|___|___|___| YYYY

2. Sex: □ Male □ Female
3. Ethnicity: □ Hispanic or Latino □ Not Hispanic or Latino
4. Subject's self-determination of geographic ancestry:
   □African □European
   □Asian □Pacific Islander
   □Americas □Unknown

Baseline Measurements

1. Weight: _____ kg □ Not Done
2. Height: _____ cm □ Not Done
3. Blood Pressure: _____ / _____ mmHg □ Not Done
   (Systolic) (Diastolic)

Lead Electrocardiogram Report

ECG Performed	□ YES □ NO	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	□ YES □ NO
	Abnormal ST segment changes	□ YES □ NO
	Abnormal T wave inversion	□ YES □ NO

Medical History Form

Note: Peripheral Vascular History is collected on a separate form.

1. Has the subject ever smoked? ☐ YES ☐ NO
2. Does the subject currently smoke? ☐ YES ☐ NO

	Check if History	Check if No History	Diagnosis or Abnormality
1.	☐	☐	Peripheral Vascular Disease
2.	☐	☐	Hypertension
3.	☐	☐	Hyperlipidemia
4.	☐	☐	Angina Pectoris
5.	☐	☐	Previous Percutaneous or Surgical Coronary Revascularization (If History When: _____)
6.	☐	☐	Congestive Heart Failure
7.	☐	☐	Renal Insufficiency
8.	☐	☐	Liver Disease
9.	☐	☐	Cerebrovascular disease (known carotid artery disease, history of minor or major stroke or transient ischemic attack)
10.	☐	☐	Chronic Obstructive Pulmonary Disease (COPD)
11.	☐	☐	Obesity
12.	☐	☐	Deep Vein Thrombosis

Medical History (Continued)

13. Previous Q wave or non-Q wave MI? □ Yes (if yes when) □ No □ Unknown
    13.1. Most recent MI date: _____/_____/_____ (dd/mmm/yyyy)
14. History of prior percutaneous coronary revascularization? □ Yes □ No □ Unknown
    14.1. Was the target vessel revascularized? □ Yes □ No □ Unknown
    14.1.1. Method of revascularization: □ PTCA □ Stenting
15. History of prior CABG? □ Yes □ No
16. Diabetes mellitus? □ Yes □ No □ Unknown
    4.1. Most recent pre-hospital treatment**:** □ Insulin □ Oral antidiabetic agents □ Diet
17. Is there premature CAD in a first-degree relative? □ Yes □ No □ Unknown
18. Number of diseased major coronary arteries that have received catheter treatment:
    □ 0 □ 1 □ 2 □ 3

Assessment of Anginal Status

19. □ Stable angina □ Unstable angina □ MI
20. Worst Canadian Cardiovascular Society Class leading to this revascularization:
    □ CCS 0 □ CCS1 □ CCS2 □ CCS3 □ CCS 4 □UNK
21. Did the patient have a positive stress test? □ YES □ NO □ UNK

Pre-Procedure Laboratory Blood Values

1. Is the subject female and of childbearing potential? ☐ YES ☐ NO ☐ NA (if Male)

   1.1. If yes, sample date of pregnancy test: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

   1.2. Result of pregnancy test: ☐ Postive ☐ Negative ☐ Not Done

Blood Test Sample Date: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

Parameter	Result	Unit	Range			Clinically Significant (if out of range)		Comment or Not Done
			IN	OUT High	OUT Low	Yes	No	
WBC			☐	☐	☐	☐	☐	☐ Not Done
Differential WBC								
Eosinophils			☐	☐	☐	☐	☐	☐ Not Done
Basophils			☐	☐	☐	☐	☐	☐ Not Done
Neutrophils			☐	☐	☐	☐	☐	☐ Not Done
Monocytes			☐	☐	☐	☐	☐	☐ Not Done
Lymphocytes			☐	☐	☐	☐	☐	☐ Not Done
Hemoglobin			☐	☐	☐	☐	☐	☐ Not Done
Hematocrit			☐	☐	☐	☐	☐	☐ Not Done
Absolute Platelet Count			☐	☐	☐	☐	☐	☐ Not Done
Serum Creatinine			☐	☐	☐	☐	☐	☐ Not Done
Prothrombin Time			☐	☐	☐	☐	☐	☐ Not Done
Activated Prothrombin Time			☐	☐	☐	☐	☐	☐ Not Done

CK and/or CK-MB cardiac Troponin
□ Not done.

Cardiac Enzymes	Date of Test: (dd/mm/yyyy)	Time (24 hour clock)	Value (U/L)	Upper Normal Limit (U/L)
CK	__ __/__ __/__ __ __ __	__ __ : __ __		
CK-MB	__ __/__ __/__ __ __ __	__ __ : __ __		
Troponin	__ __/__ __/__ __ __ __	__ __ : __ __		

Antiplatelet and Anticoagulant Medication

1. Was Aspirin Administered ☐ YES ☐ NO
2. Was an Antiplatelet Administered ☐ YES ☐ NO

3. What anticoagulant was administered: _____

4. Was a glycoprotein (GP) IIb/IIIa receptor blocker used: ☐ YES ☐ NO

Procedural Form

Target Lesion Treatment DCB # 1 □ DCB # 2 □

1. What was the location of vascular access
   □ Femoral □ Radial □ Brachial
2. Arterial sheath size □ 5F □ 6F □ 7F □ 8F

3. ISR Stent Location

□ Right Coronary Artery	□ Left Anterior Descending	□ Circumflex.
□ Proximal □ Mid □Distal	□ Proximal □ Mid □ Distal	□ Proximal □ Mid □ Distal
□ Right Post. Descending	□ Diagonal branch	□ Obtuse Marginal

4. Type of stent with ISR: □ BMS □ DES Sirolimus □ DES Everolimus □ DES Paclitaxel
   □ DES Zotarolimus □ DES other drug Specify _____
5. Angiographic Assessment □ Visual □ QCA
   - 5.1 Reference Vessel Diameter _____mm
   - 5.2 Minimum Luminal Diameter in Lesion_____mm
   - 5.3 Lesion Length _____mm
   - 5.4 % Diameter stenosis _____mm
6. CVT DCB Lot #_____ and serial number _____ (if applicable)
7. CVT DCB Size:

□ [redacted]	□ [redacted]	□ [redacted]	□ [redacted]
□ [redacted]	□ [redacted]	□ [redacted]	□ [redacted]
□ [redacted]	□ [redacted]	□ [redacted]	□ [redacted]

8. Maximum pressure used with: _____ (atm)
9. a. Time device entered the vasculature (HH:MM): __ __: __ __
   b. Time the device was inflated (HH:MM): __ __: __ __
   c. Was the balloon inflated against the vessel wall for 1 minute or more? □ YES □ NO
   d. Duration the balloon was inflated (minutes: seconds) __ __: __ __
10. Percent stenosis after the CVT DCB Deployment: _____ %
11. Dissection after this catheter treatment (Grade): □ 0/Not Applicable □ A □ B □ C
    □ D □ E □ F

Procedural Form (Continued)

12. Treatment required to treat dissection: □ YES □ NO □ N/A

13.1. If yes specify device used _____

13.2. If stent used, what type of stent □BMS □ DES Specify _____

13. Was the target lesion post-dilated following the use of DCB # 1?
□ YES □ If NO, go to question 2.

13.1. If yes:

Balloon diameter : _____mm

Balloon length : _____mm

13.2. Maximum pressure used:_____ (atm)

13.3. Percent stenosis after post-dilatation (visual estimate): _____ %

13.4. Dissection after post-dilatation (grade):□ 0/Not Applicable □ A □ B
□ C □ D □ E □ F

14. Treatment required to treat dissection: □ YES □ NO □ N/A

14.1. If yes specify device used _____

14.2. If stent used, what type of stent □BMS □ DES Specify _____

15. Indicate the final percent stenosis of target lesion after all treatment (pre-dilatation, treatment catheter, post-dilatation and, if applicable, stenting): _____ %

Procedural Form (Continued)

□ Check if the subject had a second balloon used and complete a second procedural form.

Post-Index Procedure Angiography

16.Was an angiogram of the study lesion captured during the procedure per angiographic core lab instructions ? □ YES □ NO

a. If yes, was the angiogram sent or uploaded to the core lab? □ YES □ NO

Pre-Hospital Discharge Form

Date of Subject Discharge: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

Blood Assessment

1. Were blood labs taken post-procedure and pre-discharge? □ YES □ NO
   If yes, complete the **Laboratory Blood Values** Form.

CK and/or CK-MB cardiac Troponin

Cardiac Enzymes	Date of Test: (dd/mm/yyyy)	Time (24 hour clock)	Value (U/L)	Upper Normal Limit (U/L)
CK	__ __/__ __/__ __ __ __	__ __ : __ __		
CK-MB	__ __/__ __/__ __ __ __	__ __ : __ __		
Troponin	__ __/__ __/__ __ __ __	__ __ : __ __		

12-Lead Electrocardiogram Report

ECG Performed	□ YES □ NO	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	□ YES □ NO
	Abnormal ST segment changes	□ YES □ NO
	Abnormal T wave inversion	□ YES □ NO

Reminder: Record all medications including study medications on the **Concomitant Medications Log**. Record all adverse events unresolved as of the end of the index procedure through discharge on the **Adverse Events Log.**

Medications

Time point: □ Pre-discharge □ 1 month follow up □ 6 Month follow up
□ 12 Month follow up □ 24 Month follow up □ 36 Month follow up

Medications	**Pre-Procedure**	**During Procedure**	**Post-Procedure**
ASA	□ YES □ NO □ UNK		□ YES □ NO □ UNK
Clopidogrel	□ YES □ NO □ UNK	□ YES □ NO □ UNK	□ YES □ NO □ UNK
Ticlopidine	□ YES □ NO □ UNK	□ YES □ NO □ UNK	□ YES □ NO □ UNK
Other Anti coagulants	□ YES □ NO □ UNK	□ YES □ NO □ UNK	□ YES □ NO □ UNK
IIb/IIIa Inhibitors			

1 Month Follow-up Visit

Date of Subject Visit: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

☐ Check if the visit was not performed

General Assessment

1. Did the subject visit the clinic?
   - ☐ YES
   - ☐ If NO, was the visit conducted via telephone?
     - ☐ YES
     - ☐ NO
2. Were current medications discussed?
   - ☐ If YES, update the **Concomitant Medications Log** as appropriate
   - ☐ NO
3. Was the subject asked if any adverse events occurred from the last study visit
   - ☐ If YES, update the **Adverse Event Log** as appropriate
   - ☐ NO
4. Did the subject have any coronary reinterventions since the last study visit?
   - ☐ If YES, complete the **Intervention/Revascularization Form** and record the precluding adverse event on the **Adverse Event Log**
   - ☐ NO

12-Lead Electrocardiogram Report

ECG Performed	☐ YES ☐ NO ☐ NA	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	☐ YES ☐ NO
	Abnormal ST segment changes	☐ YES ☐ NO
	Abnormal T wave inversion	☐ YES ☐ NO

6 Month Follow-up visit

Date of Subject Visit: |___|___| |___|___| |___|___|___|___| ☐ Not Done
DD MM YYYY

Clinical Follow up

1. Were current medications discussed?

   ☐ If YES, update the **Concomitant Medications Log** as appropriate

   ☐ NO

2. Was the subject asked if any adverse events occurred from the last study visit?

   ☐ If YES, update the **Adverse Event Log** as appropriate

   ☐ NO

3. Did the subject have any reinterventions since the last study visit?

   ☐ If YES, complete the **Intervention/Revascularization Form** and record the precluding adverse event on the **Adverse Event Log**

   ☐ NO

12-Lead Electrocardiogram Report

ECG Performed	☐ YES ☐ NO	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	☐ YES ☐ NO
	Abnormal ST segment changes	☐ YES ☐ NO
	Abnormal T wave inversion	☐ YES ☐ NO

Angiographic Follow up

1. Was angiographic follow-up performed? ☐ YES ☐ NO

2. Was IVUS performed per laboratory guidelines? ☐ YES ☐ NO

3. Was OCT performed per core laboratory guidelines? ☐ YES ☐ NO

4. Were results sent to the core laboratory? ☐ YES ☐ NO

12 Month Follow-up Visit

Date of Subject Visit/Contact: |___|___| |___|___| |___|___|___|___| ☐ Not Done
DD MM YYYY

☐ Check if Follow-up (12 months) was not performed and leave the rest of the page blank.

General Assessment

1. Did the subject visit the clinic?
   ☐(1) YES
   ☐(2) If NO, was the visit conducted via telephone?
      ☐(1) YES
      ☐(2) NO
2. Were current medications discussed?
   ☐ If YES, update the **Concomitant Medications Log** as appropriate
   ☐ NO
3. Did any adverse events occur since last study visit?
   ☐ If YES, update the **Adverse Event Log**
   ☐ NO
   ☐ Did not discuss
4. Did the subject have any reinterventions since the last study visit?
   ☐ If YES, complete the **Intervention/Revascularization Form** and record the precluding adverse event on the **Adverse Event Log**
   ☐ NO

12-Lead Electrocardiogram Report

ECG Performed	☐ YES ☐ NO ☐ NA	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	☐ YES ☐ NO
	Abnormal ST segment changes	☐ YES ☐ NO
	Abnormal T wave inversion	☐ YES ☐ NO

24 Month Follow-up Visit

Date of Subject Visit: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

□ Check if the visit was not performed

General Assessment

1. Did the subject visit the clinic?
   - □YES
   - □ If NO, was the visit conducted via telephone?
     - □ YES
     - □ NO
2. Were current medications discussed?
   - □ If YES, update the **Concomitant Medications Log** as appropriate
   - □ NO
3. Was the subject asked if any adverse events occurred from the last study visit?
   - □ If YES, update the **Adverse Event Log** as appropriate
   - □ NO
4. Did the subject have any reinterventions since the last study visit?
   - □ If YES, complete the **Intervention/Revascularization Form** and record the precluding adverse event on the **Adverse Event Log**
   - □ NO

12-Lead Electrocardiogram Report

ECG Performed	□ YES □ NO □ NA	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	□ YES □ NO
	Abnormal ST segment changes	□ YES □ NO
	Abnormal T wave inversion	□ YES □ NO

36 Month Follow-up Visit

Date of Subject Visit: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

☐ Check if the visit was not performed

General Assessment

1. Did the subject visit the clinic?
   - ☐ YES
   - ☐ If NO, was the visit conducted via telephone?
     - ☐ YES
     - ☐ NO
2. Were current medications discussed?
   - ☐ If YES, update the **Concomitant Medications Log** as appropriate
   - ☐ NO
3. Was the subject asked if any adverse events occurred from the last study visit?
   - ☐ If YES, update the **Adverse Event Log** as appropriate
   - ☐ NO
4. Did the subject have any reinterventions since the last study visit?
   - ☐ If YES, complete the **Intervention/Revascularization Form** and record the precluding adverse event on the **Adverse Event Log**
   - ☐ NO

12-Lead Electrocardiogram Report

ECG Performed	☐ YES ☐ NO ☐ NA	
DATE	__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)	
	Abnormal Q-waves	☐ YES ☐ NO
	Abnormal ST segment changes	☐ YES ☐ NO
	Abnormal T wave inversion	☐ YES ☐ NO

Study Completion/Termination Form

1. Did the subject complete the entire course of the study? ☐ YES ☐ NO

   1.1. If yes, date of subject completion: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

   1.2. If no, date of subject termination: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

   1.2.1. Reason for termination (mark only one)

   ☐ Withdrawal of Consent by the Subject

   ☐ Lost-to-follow-up

   Date of last contact: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

   ☐ Other-Specify: _____

   ☐ Death

   Date of Death: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

   ☐ Primary Cause of death: _____

   ☐ Underlying cause(s) of death: _____

   Was death related to the study product? ☐ YES ☐ NO

   Was death related to the study procedure? ☐ YES ☐ NO

2. Were any Adverse Events Reported during the course of the study?

   ☐ If YES, ensure the **Adverse Event Log** is up to date.

   ☐ NO

CRF Completion Acknowledgement

To be completed by the Investigator:

I have assumed responsibility for completeness and accuracy of all data recorded in these Case Report Forms.

Investigator's Name – Print Clearly	Investigator's Signature

Date: |___|___| |___|___| |___|___|___|___|
DD MM YYYY

Comment Log

Use this form to explain any subject, drug, or product related events that occurred during the study that are not noted elsewhere. Indicate the CRF page number(s) and if applicable study visits to which the comment refers in the appropriate column. Provide description of the event, initials of the study personnel, note the action taken, if any.

☐ Check if there are not any comments

CRF Page	Comment	Person Recording Comment

Concomitant Medications Log

Concomitant Medication #	Drug Name (Generic) **Reminder:** Include study medications such as aspirin and clopidogrel. Number all medications in chronological order.	Dose	Unit	Frequency (See * Below)	Route (See ** Below)	Indication (check one per line)				Start Date (DD/MM/ YYYY)	Stop Date (DD/MM/ YYYY)	Check if Continuing at Study Termination
						Existing Condition	Adverse Event	Prophylaxis	Study Medication			
						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐
						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐
						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐
						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐

						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐
						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐
						☐	☐	☐	☐	____/____/ _____ ☐Unknown	____/____/ _____ ☐Unknown	☐

*** Frequency:**		**** Route:**		**Instructions:** Each concomitant medication is to be numbered sequentially.
QD = once daily	BID = twice daily	IM = intramuscular	INH = inhalation	
TID = three times a day	QOD = every other day	IV = intravenous	PO = oral	
QID = four times a day	QHS = every night	SC = subcutaneous	SL = sublingual	
PRN = as needed	Other = not listed	TOP = topical	Other = not listed	

Site ID __ __ __ __ **Subject Number** __ __ **Birth Year** __ __ __ __

Adverse Event Log

AE Number	Study Limb	Adverse Event (Describe Event) **Reminder:** List adverse events in order by adverse event number.	Onset Date (DD/MM/YYYY)	Timing of Event (choose one)		Resolution Date (DD/MM/YYYY)	Severity (choose one)			Frequency See Codes Below	Serious Adverse Event (choose one)		Relationship See Codes Below			Outcome See Codes Below	Check if Transfusion due to AE
				Intra-Op	Post-Op		Mild	Moderate	Severe		No	If yes, See Codes Below	to Study Device	To Study Procedure			
			____/____/_____	☐	☐	____/____/_____	☐	☐	☐		☐						☐
			____/____/_____	☐	☐	____/____/_____	☐	☐	☐		☐						☐
			____/____/_____	☐	☐	____/____/_____	☐	☐	☐		☐						☐
			____/____/_____	☐	☐	____/____/_____	☐	☐	☐		☐						☐

Study Limb	Severity	Frequency	Serious Adverse Event Codes	Relationship	Outcome
Indicate if the event occurred in	**Mild** = Awareness of a sign or symptom that does not interfere with the subject's usual activity or	1 = Single episode 2 = Intermittent	A = Results in death B = Is life-threatening C = Permanent impairment of a	1 = Not Related 2 = Unlikely	1 = Recovered/resolved 2 = Recovered with sequelae

the study Limb. Y=Yes N=No NA=Not Applicable	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.	3 = Continuous	body structure or function D = In-patient or prolonged hospitalization E = Medical/surgical intervention to prevent life-threatening illness or injury or permanent impairment F = Led to fetal distress, fetal death or congenital abnormality or birth defect	3 = Possible 4 = Probable 5 = Highly Probable	3 = Not recovered/not resolved 4 = Ongoing (at study termination) 6 = Fatal 7 = Unknown

Site ID __ __ __ __ **Subject Number __ __** **Birth Year __ __ __ __**

Intervention/Revascularization Form

Revascularization #__________

1. Revascularization date: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

1. Was the revascularization involving the target lesion? ☐ YES ☐ NO ☐ Not Applicable

2. Was the target lesion revascularization ischemia driven? ☐ YES ☐ NO ☐ Not Applicable

Location 1=Right Coronary 2=Left Anterior Descending 3=Circumflex	**Intervention Performed** (mark only one) 1=Angioplasty 2=Stent (Bare) 3=Stent (Drug Eluting) 4=Other, specify	**Reason for Intervention** (mark only one) 1=Occlusion 2=Stenosis 3=Thrombosis 4=Other, specify	**Was the Intervention Successful?** (≤ 50% stenosis)	**Was the Intervention Clinically Driven?**
☐(1) ☐(2) ☐(3)	☐(1) ☐(2) ☐(3) ☐(4) _______________	☐(1) ☐(2) ☐(3) ☐(4) __________	☐(1) Yes ☐(2) No	☐(1) Yes ☐(2) No
☐(1) ☐(2) ☐(3)	☐(1) ☐(2) ☐(3) ☐(4) _______________	☐(1) ☐(2) ☐(3) ☐(4) __________	☐(1) Yes ☐(2) No	☐(1) Yes ☐(2) No
☐(1) ☐(2) ☐(3)	☐(1) ☐(2) ☐(3) ☐(4) _______________	☐(1) ☐(2) ☐(3) ☐(4) __________	☐(1) Yes ☐(2) No	☐(1) Yes ☐(2) No
☐(1) ☐(2) ☐(3)	☐(1) ☐(2) ☐(3) ☐(4) _______________	☐(1) ☐(2) ☐(3) ☐(4) __________	☐(1) Yes ☐(2) No	☐(1) Yes ☐(2) No

Angiographic Assessment

1. Was an angiogram of the study lesion(s) captured during this visit? ☐ YES ☐ NO

   1.1. Was the angiogram sent or uploaded to the core lab? ☐ YES ☐ NO

Serious Adverse Event Notification Form

Serious Adverse Type: _____

1. Reason for SAE: (choose one)
   - ☐ Resulted in Death
   - ☐ Is Life-threatening
   - ☐ Required inpatient hospitalization or prolongation of existing hospitalization
   - ☐ Resulted in persistent or significant disability/incapacity

2. Date of report: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

3. Date of adverse event onset: |___|___| |___|___| |___|___|___|___|
   DD MM YYYY

4. Type of report: ☐ Initial ☐ Follow-up

5. Diagnosis/Adverse Event (Name must match the AE found on the **Adverse Event Log**):

   _____

6. Symptoms (if applicable): _____ ☐ NA

Relationship to study device **(check only one):**

☐ Not Related ☐ Unlikely Related ☐ Possibly Related
☐ Probably Related ☐ Highly Probable Related

7. Relationship to study procedure **(check only one):**

   ☐ Not Related ☐ Unlikely Related ☐ Possibly Related
   ☐ Probably Related ☐ Highly Probable Related

8. Frequency of event: ☐ Single episode ☐ Intermittent ☐ Continuous

9. Outcome of event at this time: ☐ Recovered/resolved ☐ Recovered with sequelae
   ☐ Not recovered/not resolved ☐ Ongoing ☐ Fatal ☐ Unknown

Serious Adverse Event Notification Form (continued)

Note: if the event is later "Recovered/resolved" or "Recovered with sequelae" leave question 9 as is and indicate the date of resolution/recovery below.

9.1 If **Recovered/resolved** or **Recovered with sequelae** indicate the date resolved:

|___|___| |___|___| |___|___|___|___|
DD MM YYYY

10. If subject died, date of death: |___|___| |___|___| |___|___|___|___| ☐ NA
DD MM YYYY

If died, cause of death: _____

11. Treatment given (mark all that apply): ☐ None ☐ Medication ☐ Surgery
☐ Reintervention ☐ Other, specify: _____

12. Please describe event in chronological order (include relevant medical history, relevant dates [e.g., hospitalization], reasons for causality assessment, signs, symptoms, labs, and relative treatment):

_____

_____

_____

_____

_____

_____

_____ |___|___| |___|___| |___|___|___|___|
Investigator Signature DD MM YYYY