CLINICAL INVESTIGATIONAL PLAN

A Prospective, Open label, Non-randomized, Single-Arm, Multicenter Study to Evaluate the Procedural Safety and Efficacy of ELCA® in Treatment of Patients with Single or Multivessel Coronary Artery Disease (CAD)

Protocol Number: ELCA - 1016

Version 1.0, 12 October 2016

SPONSOR

Spectranetics Corporation,
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CONTRACT RESEARCH ORGANIZATION

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This study will be conducted in compliance with the Protocol, Good Clinical Practice (GCP) as set forth in the International Council for harmonization (ICH) guidelines on GCP (ICH E6) and applicable local regulatory requirements

1. STUDY CONTACT INFORMATION DETAILS

Sponsor	**Spectranetics Corporation,** 9965, Federal Drive, Colorado Springs, CO 80921 Phone: 719-447-2452 Email: Amanda.johnson@spnc.com
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2. LIST OF PARTICIPATING INVESTIGATORS

This information will be provided as a separate document.

3. SPONSOR'S DECLARATION

Protocol Title: A Prospective, Open label, Non-randomized, Single-Arm, Multicenter Study to Evaluate the Procedural Safety and Efficacy of ELCA® in Treatment of Patients with Single or Multivessel Coronary Artery Disease (CAD)

Protocol Number: ELCA-1016

Version and Date: Version 1.0 dated 12 October 2016

I, on behalf of **Spectranetics Corporation** have read and understood this protocol and hereby approve the same. I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013), which are consistent with the ISO14155 (current version), ICH-GCP (E6-R1, Step 5) guidelines along with the local regulatory requirements of GCP for Clinical Research in India (2001), Schedule Y (all applicable amendments of Drug and Cosmetics Rules, 1945) and ICMR guidelines for Biomedical Research on Human Subjects (2006).

I also agree to comply with cGMP practices for providing the study device for human use.

10/17/2016

Signature **Date**

Christopher DeMorett,
Sr. Clinical Manager

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4. PROTOCOL SIGNATURE PAGE

Protocol Title: A Prospective, Open label, Non-randomized, Single-Arm, Multicenter Study to Evaluate the Procedural Safety and Efficacy of ELCA® in Treatment of Patients with Single or Multivessel Coronary Artery Disease (CAD)

Protocol Number: ELCA-1016

Version and Date: Version 1.0 dated 12 October 2016

I, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol complying all requirements regarding the obligations of investigators and all other pertinent requirements of the Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, October 2013), which are consistent with the ISO14155 (current version), ICH-GCP guidelines (E6-R1, Step 5) along with the local regulatory requirements of GCP for Clinical Research In India (2004, CDSCO), Schedule Y (all applicable amendments of Drug and Cosmetics Rules, 1945) , ICMR guidelines for Biomedical Research on Human Subjects (2006).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than evaluation or conduct of the clinical investigation without the prior consent of **Spectranetics Corporation**. I understand that the Sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial, I will communicate my intention immediately in writing to the Sponsor.

I further agree to ensure that all associates assisting in the conduct of this study are well informed regarding their obligations and confirm to conduct this study under my direction.

_____ _____

Principal Investigator Signature **Date**

_____

Principal Investigator Name (Print)

Address:

5. TABLE OF CONTENTS

6. STUDY SYNOPSIS

Title	A Prospective, Open label, Non-randomized, Single-Arm, Multicenter Study to Evaluate the Procedural Safety and Efficacy of ELCA® in Treatment of Patients with Single or Multivessel Coronary Artery Disease (CAD).
Trial Location	India
Name of the Sponsor	Spectranetics Corporation
Protocol Number	ELCA-1016
Development phase	III
Name of study device	Excimer Laser Coronary Atherectomy (ELCA®): Coronary Laser Atherectomy Catheters (OTW and RX) Mode of Application: Invasive Stand-alone modality or in conjunction with Percutaneous Transluminal Coronary Balloon Angioplasty (PTCA)
Indication	Single or Multi vessel Coronary Artery Disease (CAD)
Objective	**Primary Objective:** To evaluate the safety and efficacy of ELCA® in patients with single or multivessel CAD either as a stand-alone modality or in conjunction with (PTCA), **Secondary Objectives:** • To determine post-procedural TIMI Flow grade • Lesion Morphology • Device-related complications • Procedure-related complications
Study Endpoints	**Efficacy Endpoint:** • Device Success: Successful crossing of the Laser Catheter across the entire length of the stenotic lesion • Procedural Success: Target lesions with less than 50% residual stenosis after laser and adjunctive therapy.

	Safety Endpoint: • Freedom from Major Adverse Cardiac Events (MACE) through hospital discharge and at one month. MACE is defined as Death, Non-Q-wave and Q-wave myocardial infarction (MI), Target Lesion Revascularization, Cardiac Tamponade and Life-threatening arrhythmias • TIMI Flow • Lesion Morphology • Device-related complications • Procedure-related complications	
Device Failure/ Malfunctions	All failures and malfunctions of the study device must be sent to the CRO/Sponsor, preferably within 24 hours of knowledge of the event.	
Study design	Prospective, Open label, Non-randomized, Single-arm, Multicenter study.	
No. of centers	Total 05 sites in India. The center's compliance to the clinical investigation plan will be assessed on an ongoing basis. In case of serious non-compliance, the sponsor may decide to stop patient enrollment in a center based on its assessment.	
Sample Size	30	
Screening & Follow Up	Screening	Day -10 to 0
	Baseline (study procedure)	Day 0
	Clinic follow up visit	30 ± 7 days
	Protocol guided follow-up of patient is vital; Investigators and Site study management team should ensure minimizing follow up lapses and to avoid subjects becoming Lost-To-Follow-Up.	
Study Procedure/ Methodology	Each subject will be followed from enrollment through 30 days ± 7 days for the effectiveness and safety endpoints.	

	Upon enrollment after obtaining a written informed consent, each patient will be assigned a unique identification number. Only patients eligible to undergo cardiac catheterizations as per routine practice will be considered for the study. Premedication of patients will be as per the investigator's routine practice. All patient data will be recorded on patient data forms. **Screening:** This will be performed prior to the cardiac catheterization procedure. Only patients who have consented and fulfill the selection criteria will be enrolled. Additionally, ECG and Echocardiogram will be done using hospital equipment to ensure fulfillment of inclusion/exclusion criteria. **Procedure:** The entire procedure will be carried out as per the site routine practice and the device will be used as per the IFU. **Clinic follow up visit (30 ± 7 days):** The subject will return to the clinic at 1 month to evaluate angina status as per the CCS classification, AE assessments, concomitant medications and any coronary intervention that has occurred since the previous contact. An electrocardiogram (ECG) will be repeated during the clinic visit.
Key Inclusion Criteria	The subjects have to meet the following inclusion criteria: • Patient 18 years to 75 years, both inclusive • Have at least one severe stenotic lesion (greater than or equal to 80% diameter stenosis as assessed by visual estimation) • Hemodynamically stable patients coming to the site for cardiac catheterization and angiography who fulfill all the following criteria: ▪ Have no clinically significant cardiac arrhythmias, based on ECG results ▪ Have no evidence of valvular pathology, based on echocardiogram results ▪ Have ≥30% left ventricular ejection fraction

	(LVEF), based on echocardiogram results. • Angiographic evidence of calcification or a chronic total occlusion • Vessel reference diameter greater than or equal to 2.0 mm • Patient is willing and able to comply with study requirements • Women of child bearing potential , willing to use at least two methods of contraception
Key Exclusion Criteria	The subjects do not meet any of the following exclusion criteria: • Evidence of acute coronary syndrome within 3 months prior to index procedure • Evidence of acute ischemic events • Cardiogenic and non-cardiogenic shock • Active bleeding or coagulopathy • Previous coronary angioplasty within 6 months of the index procedure • Patients participating in trial for another investigational device/medicine within 1 month prior to enrolment in this study • Acute or Chronic renal failure, Impaired renal function (serum creatinine > 2.5 mg/dl or 221 μmol/l) determined within 72 hours prior to index procedure • Known allergies to the following: Aspirin, Clopidogrel or Ticlopidine, Heparin, Sirolimus or its derivatives, contrast agent (that cannot be adequately pre-medicated), or any metal • Planned surgery within 6 months of enrollment in this study • Life expectancy less than 6 months • Patients known to be suffering from substance abuse

	(alcohol or drug) • Patients with any other significant co-morbid illness which in the opinion of the investigator is not conducive of inclusion in the study. • Known or suspected Pregnancy • Patients not willing to provide written informed consent • In the investigators opinion subjects will not be able to comply with the follow-up requirements.
Data Collection	All requested data need to be reported by the centers into an electronic Case Record Form (eCRF).
Statistical analysis	As per the 25th SEC (Cardiovascular & Renal) meeting which deliberated the proposals on 30-10-2015 and recommended the firm (Spectranetics Corporation - Sponsor) shall conduct a Bridging study in Indian Population at least 25 patients. The directorate suggested that the sponsor submit a protocol for the study in India for clinical trial approval. Considering the 5 dropouts, Sponsor has set up this protocol to conduct the Excimer Laser Coronary Atherectomy (ELCA®) study in India on 30 eligible patients.

7. LIST OF ABBREVIATIONS

ACC	:	American College Of Cardiology
AE	:	Adverse Event
AHA	:	American Heart Association
AMI	:	Acute Myocardial Infarction
ASADE	:	Anticipated Serious Adverse Device Effect
CABG	:	Coronary Artery Bypass Graft
CAD	:	Coronary Artery Disease
CBC	:	Complete Blood Count
CCS	:	Canadian Cardiovascular Society
CDSCO	:	Central Drugs Standard Control Organization
CFR	:	Code Of Federal Regulations
CIP	:	Clinical Investigational Plan
CK	:	Creatine Kinase
CRO	:	Contract Research Organization
CRF	:	Case Record/Report Form
CRO	:	Clinical Research Orginazation
CV	:	Curriculum Vitae
DCG(I)	:	Drug Controller General Of India
ECG	:	Electrocardiogram
EDC	:	Electronic Data Capture System
ELCA	:	Excimer Laser Coronary Atherectomy
EOT	:	End Of Therapy
FDA	:	Food And Drug Administration
GCP	:	Good Clinical Practice
ICF	:	Informed Consent Form
ICH	:	International Council for Harmonization
IEC	:	Institutional Ethics Committee
IFU	:	Instruction For Use
IHD	:	Ischemic Heart Disease
IRB	:	Institutional Review Board
ISO	:	International Organization Of Standardization
LARS	:	Laser Angioplasty For Restenotic Stents
LVEF	:	Left Ventricular Ejection Fraction
MACE	:	Major Cardiac Adverse Events
mg	:	Milli Gram
MI	:	Myocardial Infarction
mL	:	Milli Litre
OTW	:	Over-The-Wire
PCI	:	Percutaneous Coronary Intervention
PLLA	:	Poly-L-lactic acid
PTCA	:	Percutaneous Transluminal Coronary Balloon Angioplasty

RX	:	Rapid Exchange
SAE	:	Serious Adverse Event
SAT	:	Sub Acute Thrombosis
SEC	:	Subject Expert Committee
SOP	:	Standard Operating Procedure
SVG	:	Saphenous Vein Bypass Grafts
TIA	:	Transient Ischemic Attack
TIMI	:	Thrombolysis In Myocardial Infarction
TMF	:	Trial Master File
Trop I	:	Troponin I
ULN	:	Upper Limit of Normal
UPT	:	Urine Pregnancy Test
WMA	:	World Medical Association

The following terms will be used synonymously:

- Clinical Investigation Plan (CIP) = Clinical Protocol = Study Plan
- Clinical Investigation = (clinical) Study = (clinical) Trial
- CRF = eCRF
- Study Device = Excimer Laser Coronary Atherectomy (ELCA ®) Products
- Spectranetics Corporation = Spectranetics = SPNC= Sponsor

8. STUDY PROCEDURE OVERVIEW

Procedure		Screening (Day -10 to 0)	Coronary Atherectomy	Post Procedure Assessment	30 Days Clinic Follow Up (± 7 Days)	Unscheduled Visit
Informed Consent Signed		X				
Assessment of Eligibility Criteria		X				
Review of Medical History		X				
Review of Concomitant Medications		X	X	X	X	X
Physical Exam	Complete	X				X
	Angina Class (CCS)	X			X	X
	Vital Signs	X		X	X	X
Clinical Laboratory	Chemistry[1]	X[2]				
	Cardiac Biomarkers (CK, CK-MB and Trop I)	X[3]		X[5], X[6]		
	Pregnancy Test	X[9]				
12 Lead Electrocardiogram (ECG)		X[3]		X[4]	X[7]	X
LVEF measured through the Echo or LV Angiogram		X[2]				
Coronary Angiogram		X				X[8]
Device evaluation by Investigators				X		
Adverse Event Assessment			X	X	X	X

1	Blood chemistry includes Complete Blood Count (CBC) and platelet count, serum sodium, potassium, urea, creatinine, and Random Blood Sugar (RBS)
2	72 hrs prior to the index procedure.
3	24 hours prior to index procedure.
4	24 hours post procedure
5	6 - 24 hours post-procedure or at discharge whichever is earlier.
6	**Cardiac Markers:** If cardiac biomarkers (CK-MB or Trop I) > 3 time Upper Limit of Normal (ULN) or SAT, CK, CK-MB & Trop I post procedure, the levels must be evaluated every 8 hours until it returns to normal or until hospital discharge.
7	**ECG:** To be obtained for any suspicious episode of coronary ischemia or SAT during the baseline hospitalization.
8	If angiogram is performed during the unscheduled visit, may be collected.
9	Urine Pregnancy Test to be performed only for women of child bearing potential, within 72 hours before angiography

9. BACKGROUND AND INTRODUCTION

Ischemic Heart Disease (IHD) has been recognized as a leading cause of death globally. According to the most recent health statistics, WHO's Global Health Statistics 2008, coronary artery disease (CAD) will be the number one *killer* in 2030, causing 14.2% of all deaths worldwide. Acute coronary syndrome (ACS) is an acute clinical presentation of CAD; it refers to a range of acute myocardial ischemic states.[2,3] It encompasses unstable angina, non-ST segment elevation myocardial infarction (ST segment elevation generally absent), and ST segment elevation myocardial infarction (persistent ST segment elevation usually present).

Since its inception in 1977, balloon angioplasty has undergone major improvements but has persistent shortcomings in the form of abrupt closure and restenosis. Balloon angioplasty has lower success rates in management of long lesions, calcified vessels, bifurcation lesions, saphenous vein graft stenosis and ostial narrowings. It is possible that some of these angiographic characteristics, which have been identified as relatively complex by American College of Cardiology /American Heart Association (ACC/AHA) task force may be handled more effectively by a procedure that removes atherosclerotic plaque such as excimer laser coronary angioplasty. Studies have reported that excimer laser – facilitated coronary angioplasty, in contrast to balloon angioplasty is equally successful in treating simple and complex lesions.[4]

Atherectomy is a procedure which is performed to remove atherosclerotic plaque from diseased coronary and peripheral arterial vasculature. Atherectomy devices are designed to cut, shave, sand or vaporize these plaques and have different indications.

Various available techniques for atherectomy are:

1. Directional atherectomy where the direction can be adjusted, which is useful for eccentric lesions,
2. Rotational atherectomy where the burr spins concentrically and is mostly used in calcified coronaries,
3. Orbital atherectomy where the crown orbits the wire and is used in both coronary and peripheral arterial disease and,
4. Excimer Laser atherectomy which ablates the tissue and is used in both coronary and peripheral arterial disease.

When excimer laser irradiation is used in the setting of PTCA, the major advantage of this technique is thought to be ablation of the atherosclerotic plaque with minimal thermal and mechanical injury

to the adjacent vessel wall structures[9].

As opposed to the mandatory fissuring and cracking of the plaque and over distending the arterial wall using conventional coronary angioplasty[10], laser atherectomy might have the theoretical potential of reducing complications and probably as a result of reduced injury, of decreasing the incidence of restenosis.

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. Although the history of laser begins in 1951, the first medical application is reported by Goldman in 1962 and used in 1963 for the experimental ablation of atherosclerotic plaques. The first clinical applications were performed by Choy and Ginsburg in 1983.

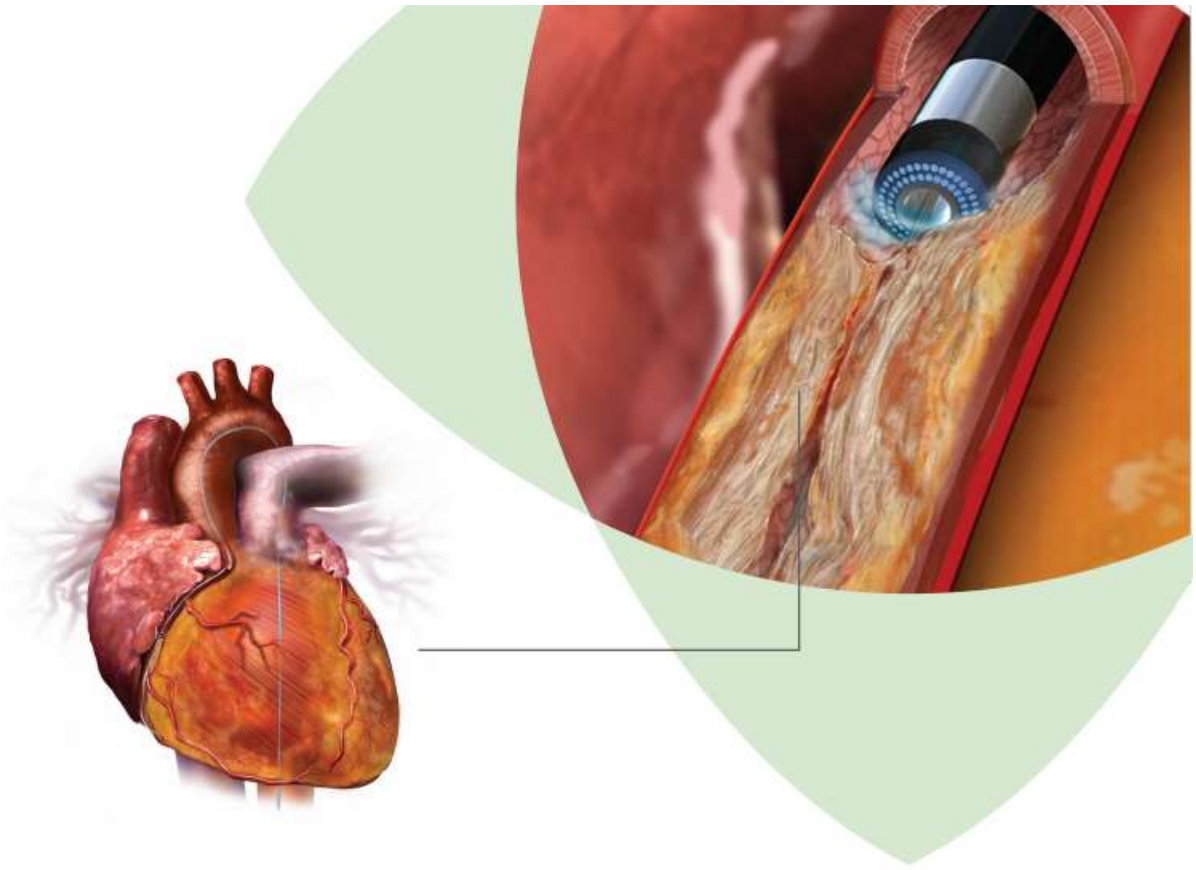

Figure 1: ELCA® Mode of Action

Excimer Laser Coronary Atherectomy (ELCA ®) uses the high energy, monochromatic light beam to alter or dissolve (vaporize) the plaque without damaging the surrounding tissue. Fiber-optic catheters are used to deliver this light beam. For endovascular applications, Xenon Chloride excimer laser is used and its fiber-optic catheter has multiple small fibers, rather than just a few large fibers, in order to be flexible enough to navigate in the arterial tree.

Laser can be used in both coronary and peripheral applications. In coronaries, excimer laser can be used to remove thrombi; to vaporize pro coagulant reactants in addition to debulking the underlying plaque; and to facilitate stent delivery. In the CARMEL multicenter study, excimer laser angioplasty was successfully used in more than 90% of the enrolled 151 acute myocardial infarction (AMI) patients with a large thrombus burden with a relatively low rate (8.6%) of major cardiac adverse events (MACE). It has been also used for in-stent restenosis: in the Laser Angioplasty for Restenotic Stents multicenter registry (LARS), laser angioplasty reduced 30-day repeat-target-site coronary intervention, but it did not decrease in 1 year. Balloon-resistant lesions, chronic total occlusions, calcified lesions, and under expanded stents in calcified lesions are some other scenarios in which excimer laser coronary atherectomy can be successfully used.

The original excimer laser coronary angioplasty (ELCA) devices Model numbers PC1014 and PC1017, known as the “Soft Rim” versions were originally submitted to the FDA through the PMA approval process in 1991 Submission P910001. The devices were indicated for use in patients with single or multivessel coronary artery disease either as a stand-alone treatment or in conjunction with percutaneous transluminal coronary angioplasty (PTCA) and in patients who are acceptable candidates for coronary artery bypass graft (CABG) disease. These models obtained approval from the FDA for use in 1993. CE mark was granted in 1996.

10. INVESTIGATIONAL DEVICE

10.1 DEVICE NAME

Excimer Laser Coronary Atherectomy (ELCA®) Products

Excimer Laser Coronary Atherectomy (ELCA®): Coronary Laser Atherectomy Catheters (OTW and RX)

Mode of Application: Invasive

Stand-alone modality or in conjunction with Percutaneous Transluminal Coronary Balloon Angioplasty (PTCA)

Coronary Laser Atherectomy Catheters (Over-The-Wire [OTW] and Rapid Exchange [RX])

10.2 MODELS:

- 110-001 ELCA 0.9mm Extreme OTW Laser Catheter
- 110-002 ELCA 0.9mm 80 Hz Extreme OTW Laser Catheter
- 110-003 ELCA 0.9mm Vitesse RX Laser Catheter
- 110-004 ELCA 0.9mm 80 Hz Extreme RX Laser Catheter
- 114-009 ELCA 1.4mm Vitesse RX Laser Catheter
- 117-016 ELCA 1.7mm Vitesse RX Laser Catheter
- 120-009 ELCA 2.0mm Vitesse RX Laser Catheter
- 117-205 ELCA 1.7mm Vitesse-E RX Laser Catheter
- 120-008 ELCA 2.0mm Vitesse-E RX Laser Catheter

ELCA products are percutaneous, single use, disposable medical devices designed for excimer laser coronary atherectomy within native coronary arteries and saphenous vein bypass grafts (SVG). ELCA products are typically employed, as a precursor treatment or in conjunction with percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) techniques that employ balloon catheter dilatation and/or stenting, to reduce, minimize or alleviate flow-limiting stenoses or occlusions following placement of a guidewire across the target treatment site.

ELCA products are approved for use in conjunction with the Spectranetics CVX-300® Excimer Laser System (CVX-300) and are intended for use in patients with single or multivessel coronary artery disease (CAD) or SVG disease as a stand-alone modality or in conjunction with PCI techniques.

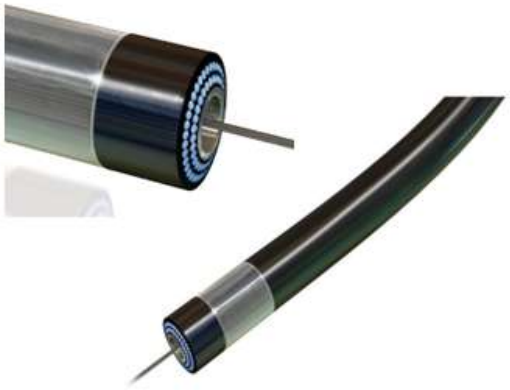

Figure 2: ELCACatheter

Figure 2: CVX-300 Excimer Laser

10.3 INDICATIONS FOR USE

ELCA products are typically employed as a precursor interventional treatment for patients presenting with a variety of obstructive CAD and SVG indications (e.g., complex lesion patterns, subtotal and total occlusions, small vessel disease, resistant lesions, acute thrombosis) and a range of comorbid conditions (e.g., coronary insufficiency, acute coronary syndrome, acute myocardial infarction, heart failure, arrhythmia).

ELCA indications for use are based on lesion, stenosis and/or occlusion physical descriptors versus the clinical presentation of the patient. The ELCA indications are identical for CE mark (EU) and FDA (US) product labeling. The current indications include;

- Occluded saphenous vein bypass grafts
- Ostial lesions
- Long lesions - (greater than 20 mm in length)
- Moderately calcified stenoses - (Heavily calcified stenoses are those lesions that demonstrate complete calcification when identified under fluoroscopy by angiography prior to the procedure. Moderately and slightly calcified stenoses are all others.)
- Total occlusions traversable by a guidewire

- Lesions which previously failed balloon angioplasty - (This includes those lesions that were treated unsuccessfully by PTCA. Lesions that have undergone a complicated PTCA procedure are not included in this category.)
- ONLY ELCA, NOT ELCA X-80: Restenosis in 316L stainless steel stents, prior to the administration of intravascular brachytherapy.

Contraindications

- Lesion is in an unprotected left main artery.
- Lesion is beyond acute bends or is in a location within the coronary anatomy where the catheter cannot traverse.
- Guidewire cannot be passed through the lesion.
- Lesion is located within a bifurcation.
- Patient is not an acceptable candidate for bypass graft surgery.

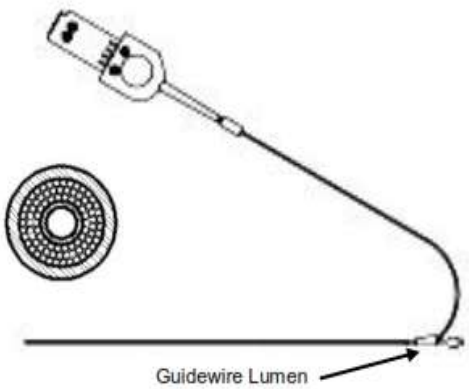

Figure 1: Over the Wire

Table 1.1 ELCA® Coronary Laser Atherectomy Catheter Models

Device Description	Model Number	Max. Guidewire Compatibility (in.)	Max. Tip Diameter (in.)	Max. Tip Diameter (mm)	Sheath Compatibility (Fr)	Working Length (cm)
OTW Catheter Specifications						
0.9 mm	110-001	0.014	0.038	0.97	4	135 ± 5

Glossary of Special Terms

Antegrade Fashion = In the direction of blood flow.

Baseline Angiography = Record of the cardiac muscle and blood vessels prior to a given interventional angioplasty procedure.

Retrograde Fashion = In the direction opposite to blood flow.

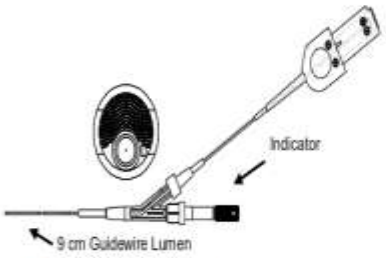

Figure 2: Rapid Exchange Eccentric

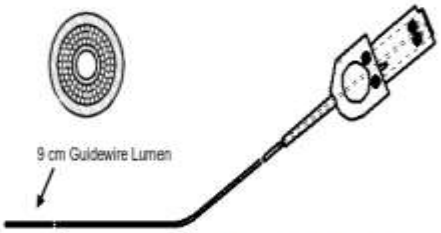

Figure 3: Rapid Exchange

Device Description	Model Number	Max. Guidewire Compatibility (in.)	Max. Tip Diameter (in.)	Max. Tip Diameter (mm)	Sheath Compatibility (Fr)	Working Length (cm)
RX Catheter Specifications						
0.9 mm	110-003	0.014	0.038	0.97	4	135 ± 5
1.4 mm	114-009	0.014	0.057	1.45	5	135 ± 5
1.7 mm	117-016	0.014	0.069	1.75	6	135 ± 5
1.7 mm E	117-205	0.014	0.065	1.65	6	135 ± 5
2.0 mm E	120-008	0.018	0.079	2.0	7	135 ± 5
2.0 mm	120-009	0.014	0.080	2.0	7	135 ± 5

10.4 DEVICE FAILURE/ MALFUNCTIONS

In case of device failure or malfunction, Investigator should attempt again with the new study device to treat the target lesion.

All failures and malfunctions of the study device must be sent to the CRO/Sponsor, preferably within 24 hours of knowledge of the event. The investigator must return any damaged study device to the Sponsor with an explanation of why the study device was opened but unused. All device failure and malfunctions will be reported in the Clinical Study Report.

10.5 DEVICE SUPPLY & DEVICE LABELING

Where applicable, the investigational device and its associated components will have a label according to ISO14155 (current version) that will be visible on the pertinent shipping cartons and storage containers. The required labels or instructions for use (IFU) will bear the following information:

- Name, model and lot number of the Excimer Laser Coronary Atherectomy (ELCA ®) Products
- Name and addresses of the manufacturer and distributor
- Labeling statement: “FOR CLINICAL INVESTIGATION ONLY”
- Quantity of contents

- All relevant contraindications, hazards, adverse device effects, interfering substances or devices, warnings and precautions
- Expiration date

10.6 DEVICE STORAGE

Store according to *Instruction for Use*, the study device has to be stored in a cool, dark and dry location at maximum temperature of 25 °C.

10.7 DEVICE ACCOUNTABILITY

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the CIP.

The sponsor or designee shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The principal investigator or an authorized designee shall complete the Investigational Device Accountability Log in order to keep records of the receipt, use, return and disposal of the investigational devices, which shall include:

- Date of receipt
- Identification of each investigational device (batch/serial number or unique code)
- Expiry date, if applicable
- Date or dates of use
- Subjects identification code, if applicable
- Date on which the investigational device was returned/explanted from subjects, if applicable
- Date of return of unused, expired or malfunctioning investigational devices, if applicable

11. RISK BENEFITS EVALUATIONS

The risk assessment, to support the safety of Excimer Laser Coronary Atherectomy (ELCA®) Product are documented in the previous clinical evaluations of the device. Study subjects will be informed of all known potential side effects and complications associated with study treatment and evaluations prior to enrollment in the study.

The treatment will be performed according to routine hospital practice. Excimer Laser Coronary Atherectomy (ELCA®) Product is CE mark approved.

No patient identifier information will be collected during the study. Each patient will be assigned a unique identifier via Remote Data Capture system. This information is then pooled with all the data for analysis and reporting.

The risks of using this device in coronary lesions may be similar to risks encountered with other marketed stainless steel stents/drug eluting stents/ atherectomy catheter. Excimer Laser Coronary Atherectomy (ELCA®) Product is not commercially available in Indian market for its use. Information about risk and risk mitigation may include, but is not limited to;

- **Cardiac events:**
  Myocardial infarction or ischemia, abrupt closure of coronary artery, restenosis of treated artery (greater than 50% obstruction), cardiogenic shock, angina, tamponade, perforation or dissection of coronary artery or aorta, cardiac perforation, emergency cardiac surgery, pericardial effusion, aneurysm formation.
- **Arrhythmic events:**
  Ventricular tachycardia, ventricular fibrillation, atrial fibrillation, bradycardia.
- **Respiratory events:**
  Acute pulmonary edema, congestive heart failure, respiratory insufficiency or failure.
- **Vascular events:**
  Access site hematoma, hypotension/hypertension, pseudoaneurysm, arteriovenous fistula formation, retroperitoneal hematoma, vessel dissection or perforation, thrombosis or occlusion, compromise of side branch patency, vasospasm, peripheral

ischemia, dissection, distal embolization (air, tissue debris, thrombus).

- **Neurologic events:**
  Permanent (stroke) or reversible (TIA) neurologic event, femoral nerve injury, peripheral nerve injury.
- **Bleeding events:**
  Access site bleeding or hemorrhage, hemorrhage requiring transfusion or other treatment. Allergic reactions to contrast media, antiplatelets, anticoagulants, to the drug carrier (PLLA), to Sirolimus and/or Magnesium, Yttrium, Neodymium, Zirconium, Gadolinium and Dysprosium.
- **Infection and sepsis.**
- **Death**.

The following complications may be associated with the use of coronary stenting devices or PTCA:

- Allergic reaction to contrast medium
- Bleeding complications
- Cardiac tamponade
- Cerebrovascular accident
- Dissection of coronary artery
- Drug reactions to antiplatelet agents, anticoagulation agents and/or contrast media
- Emboli, distal (tissue, air or thrombotic emboli)
- Endocarditis
- Failure to deliver the required therapy
- Fever
- Hematoma
- Hemorrhage
- Injury of the coronary artery
- Pain and tenderness
- Pyrogenic reaction
- Renal failure
- Emergency CABG

Based upon the existing experience with the Excimer Laser Coronary Atherectomy (ELCA®), it can be concluded that the risks associated with the use of the ELCA® are acceptable under the conditions outlined in this study protocol, and that the potential benefits may outweigh the risks.

Moreover, subjects will be monitored closely throughout the clinical investigation duration.

Subjects will be evaluated clinically at pre-determined time points to assess their clinical status till the end of study.

Potential Benefits

Participation in this study is voluntary. Subjects potentially could benefit through the procedure of study device, as compared to the routine angioplasty for the patient population under consideration in this study. As already mentioned, several studies have shown the benefits of standalone ELCA atherectomy and ELCA atherectomy with stent implantation has better patient outcome in similar patient population. Information gathered from this study will help confirm the safety and performance of the Excimer Laser Coronary Atherectomy (ELCA®) in subjects with coronary artery disease (CAD).

12. CLINICAL INVESTIGATION

12.1 STUDY DESIGN

This is a Prospective, Open label, Non-randomized, Single-Arm, Multicenter Study to Evaluate the Procedural Safety and Efficacy of ELCA® in Treatment of Patients with Single or Multivessel Coronary Artery Disease (CAD).

12.2 STUDY POPULATION

Up to 30 patients will be enrolled at up to 05 Indian study sites. Patients will be followed from enrollment through 30 days ± 7 days for the effectiveness and safety endpoints at the study centre.

The center's compliance to the clinical investigation plan will be assessed on an ongoing basis. In case of serious non-compliance, the sponsor may decide to stop patient enrollment in a center based on its assessment

12.3 STUDY DURATION

Duration of this clinical study is up to 12 months which includes trial set-up, enrollment period, study procedures, follow-up visits, data analysis and release of the clinical study report.

Study will start upon the receipt of the central Indian regulatory authority's approval as well as Ethics Committee approval at respective sites. Up to 30 eligible subjects will be enrolled in the study. All subjects will be followed clinically until one month (30±7 days), post-procedure.

12.4 STUDY OBJECTIVES

Primary Objective

To evaluate the safety and efficacy of ELCA® in patients with single or multivessel CAD either as a stand-alone modality or in conjunction with Percutaneous Transluminal Coronary Balloon Angioplasty (PTCA).

Secondary Objectives:

- To determine post-procedural TIMI Flow grade
- Lesion Morphology
- Device-related complications
- Procedure-related complications

12.5 STUDY ENDPOINTS

Efficacy Endpoint:

- Device Success: Successful crossing of the ELCA Catheter across the entire length of the stenotic lesion
- Procedural Success: Target lesions with less than 50% residual stenosis after laser and adjunctive therapy

Safety Endpoint:

- Freedom from major adverse cardiac events (MACE) through hospital discharge and at one month

  MACE is defined as Death, Non-Q-wave and Q-wave myocardial infarction (MI), Target Lesion Revascularization, Cardiac Tamponade and Life-threatening arrhythmias
- TIMI Flow
- Lesion Morphology
- Device-related complications
- Procedure-related complications

In order to fully characterize the procedure, information of all treated lesions will be collected irrespective of whether the lesion has been treated with ELCA® product.

Electronic Case Report Forms will be utilized to collect relevant information.

13. CLINICAL INVESTIGATION PROCEDURES

Up to 30 subjects with documented clinical symptoms, ECG changes and study lesion identified by angiography requiring Coronary Atherectomy will be enrolled in this study.

A written informed consent form will be obtained for enrollment. Each patient will be assigned a unique identification number. Only patients eligible to undergo cardiac catheterizations as per routine practice will be considered for the study. Premedication of patients will be as per the investigator's routine practice. All data will be captured in Case Record Form.

13.1 SCREEN FAILURE:

There may be a provisionally enrolled subject who withdraws consent prior to the index procedure or is unsuitable for the Excimer Laser Coronary Atherectomy (ELCA®) following laboratory assessments, pre-procedure ECG or any study specific invasive or non-invasive treatment as pre-specified in the Clinical Investigation Plan. These subjects will be exited from the study once screen failure is confirmed. Subject informed consent forms will be kept in the site's administrative files. These subjects will not be considered as part of the 30 patients for the analysis.

13.2 ENROLLED:

The investigator must ensure that all patients being considered for the study meet the study criteria (all of the inclusion and none of the exclusion criteria). The investigator should apply no additional exclusions, in order that the study population will be representative of all eligible patients. Patient selection is to be established by checking through all inclusion/ exclusion criteria at screening and baseline. A relevant record (e.g. checklist) must be stored with the source documentation at the study site. Deviation/Violation from any entry criterion excludes patients from enrollment into the study.

13.3 INCLUSION CRITERIA

Subjects will be enrolled in the study if ALL of the following conditions are met:

1. Patient 18 years to 75 years, both inclusive
2. Have at least one severely stenotic lesion (greater than or equal to 80% diameter stenosis as assessed by visual estimation)
3. Haemodynamically stable patients coming to the site for cardiac catheterization and angiography for various indications and who fulfill all the following criteria:

- Have no clinically significant cardiac arrhythmias, based on ECG results
- Have no evidence of valvular pathology, based on echocardiogram results
- Have ≥30% left ventricular ejection fraction (LVEF), based on echocardiogram results.

4. Angiographic evidence of calcification or a chronic total occlusion
5. Vessel reference diameter greater than or equal to 2.0 mm
6. Patient is willing and able to comply with study requirements
7. Women of child bearing potential , willing to use at least two methods of contraception

13.4 EXCLUSION CRITERIA

Subjects will not be enrolled in the study if ANY of the following conditions are present in the subject:

1. Evidence of acute coronary syndrome within 3 months prior to index procedure
2. Evidence of acute ischemic events
3. Cardiogenic and non-cardiogenic shock
4. Active bleeding or coagulopathy
5. Previous coronary angioplasty within 6 months of the index procedure
6. Patients participating in trial for another investigational device/medicine within 1 month prior to enrolment in this study
7. Acute or Chronic renal failure, Impaired renal function (serum creatinine > 2.5 mg/dl or 221 μmol/l) determined within 72 hours prior to index procedure.
8. Known allergies to the following: Aspirin, Clopidogrel or Ticlopidine, Heparin, Sirolimus or its derivatives, contrast agent (that cannot be adequately pre-medicated), or any metal
9. Planned surgery within 6 months of enrollment in this study
10. Life expectancy less than 6 months
11. Patients known to be suffering from substance abuse (alcohol or drug)
12. Patients with any other significant co-morbid illness which in the opinion of the investigator is not conducive of inclusion in the study.
13. Known or suspected Pregnancy
14. Patients not willing to provide written informed consent
15. In the investigators opinion subjects will not be able to comply with the follow-up requirements.

13.5 SCHEDULE AND PROCEDURES

Prescreening Evaluation, Informed Consent & Enrollment

The subjects being considered for percutaneous coronary interventions should be pre-screened via a general review of inclusion/exclusion criteria without any study related assessment.

After the subject signed the IRB/IEC approved informed consent, study specific screening assessments can be started and the subject is provisionally enrolled.

Each potential subject who meets the inclusion criteria and has none of the exclusion criteria will be explained about the study and study device, informed about the objective, potential risks-benefits and alternatives of the study and then invited to voluntarily participate in the study. Subjects will be informed about the one month (30±7 days) follow up visit to assess the safety and efficacy endpoints. Investigator will answer each questions asked by subject and/or subject's representative during the informed consent process.

Investigator will give ample time to subject and/or subject's representative to read and understand the informed consent form. If a subject and/or subject's representative voluntarily agrees to participate in the study, subject and/or subject's representative will sign and date the written subject informed consent form prior to any study procedure. Each subject is free to withdraw from the study at any time during the study period.

Informed consent should be obtained in accordance with the applicable Indian regulations - Schedule Y and all applicable amendments (Drugs and Cosmetics Rules, 1945), GCP for Clinical Research in India (2001), ICMR guidelines for Biomedical Research on Human Subjects (2006), and current versions of Declaration of Helsinki, ICH-GCP and ISO 14155. If a subject might be eligible for the study, the investigator or delegated staff should approach the subject to obtain the written informed consent. During the consent process the background of the proposed study, the benefits and risks of study participation should be explained in detail to the subject.

It has to be emphasized that a subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled. The subject must be given ample time to read the subject information and to address questions before signing the consent form. The Patient Information Sheet and a copy of the EC approved signed consent form (by investigator and subject) will be handed over to the subject.

13.6 SCREENING/BASELINE EXAMINATIONS

After signature of the informed consent, the subjects will undergo a baseline examination in order to assess their eligibility through the following tests and examinations

- Physical examination and relevant medical history, including angina status or myocardial ischemia assessment as per Canadian Cardiovascular Society (CCS) Classification, medication list, vital signs and subjects demographic information;
- Baseline cardiac biomarkers (CK, CK-MB and Trop I) must be obtained 24 hours prior to the index procedure;
- Routine clinical laboratory testing including Complete Blood Count (CBC) and platelet count and blood chemistry include serum sodium, potassium, urea, creatinine, and random blood sugar (RBS) must be obtained, 72 hours prior to the index procedure;
- For women of child bearing potential, urine pregnancy test must be performed 72 hours prior to the index procedure and it must be negative;
- 12-lead electrocardiogram must be obtained 24 hours prior to the index procedure.
- Documented LVEF through the Echocardiography or LV angiography to assess Left Ventricular function 72 hours prior to the index procedure.
- Review of inclusion and exclusion criteria

13.7 ANTI PLATELET MEDICATIONS

Before the procedure and in the follow-up period, the subjects will be treated with anti-platelet medications, or vasodilators, according to the standard institutional practice. Pre medication & Post medication will be recorded in Study Medication Form in eCRF.

13.8 TREATMENT PROCEDURE

The entire procedure will be carried out as per the site routine practice and the device will be used as per the 'Instruction for Use', available with Excimer Laser Coronary Atherectomy (ELCA®) Products.

All study investigators and site personnel involved in the clinical trial have to sign the Site Signature and Responsibility log (Delegation Log) and provide signed and dated curriculum vitae (CV).

Treating physicians/ study investigators will be trained by the study Sponsor on the study protocol and procedures prior to clinical investigation procedure.

Subject preparation and percutaneous access should be performed according to the standard hospital practice. Both femoral and radial accesses are accepted. The procedure begins once percutaneous access has been made.

13.9 POST PROCEDURE ASSESSMENT (UNTIL DISCHARGE)

The index procedure will be considered as complete, when the guiding catheter has been removed from the subject and the subject has left the cardiac catheterization laboratory. If a guiding catheter is reinserted thereafter, it will be considered as a re-intervention. Relevant CRF will be completed for such re-intervention. Following post procedure parameters will be assessed after the Coronary Atherectomy:

1. Vital Signs

Subject's vitals will be assessed immediately post PCI as per the Investigator's discretion.

2. Laboratory Evaluation

Cardiac biomarkers (CK, CK-MB and Trop I) will be performed 06-24 hours / or at discharge of post-procedure whichever is earlier. If the cardiac biomarkers (CK-MB or Trop I) are 3 times above the upper limit of normal or incase of Sub Acute Thrombosis (SAT), CK, CK-MB & Trop I must be evaluated every 8 hours until it returns to normal or until hospital discharge.

3. Electrocardiogram

12-lead electrocardiogram will be obtained 24 hours post procedure. Electrocardiograms should also be obtained for any episodes suspicious for coronary ischemia or SAT during the baseline hospitalization.

13.10 SUBJECT FOLLOW-UP

After study procedure, all enrolled subjects will be followed through hospital discharge and will undergo on-site follow-up evaluations at one month (30±7 days). The investigator may examine the subject at any time post-device placement if there is any concern about the device or subject. In addition, the investigator will inform the subject and/or subject's representative that they should report any discomfort immediately.

13.11 CLINIC FOLLOW UP VISIT (30 ± 7 DAYS)

The subject will return to the clinic at one month (30 ± 7 days) and Study subjects will undergo the following clinical evaluation:

- Assessment of the ischemic/angina status (CCS, Braunwald or silent ischemia)

- Monitoring and documentation of adverse and serious adverse events,
- Documentation of any change to anti-platelet/anti-coagulant medical therapy.

An electrocardiogram will be repeated during the clinic visit as per the investigator's discretion.

13.12 UNSCHEDULED CLINIC VISIT

If the subject is seen by the investigator between scheduled follow-up visits (not a study required visit), unscheduled follow-up CRF must be completed. The subject will still be required to come for the next scheduled follow-up visit if the unscheduled visit is out of the compliance follow-up window. If the subject has complications attributable to the study procedure and seeks medical advice from the Investigator between scheduled follow-up visits, an Event Reporting CRF must be completed in addition to a Follow-up CRF.

13.13 UNSCHEDULED CORONARY INTERVENTION

The indication for an unscheduled coronary intervention could be an abnormal electrocardiogram, positive exercises test, raised biomarkers or symptoms suggestive of coronary ischemia. Symptoms, stress testing and other appropriate evidence should be documented on the relevant CRF. In case of an unscheduled coronary angiogram in the follow up period during the study participation, the event must be reported on the relevant CRF.

If the subject is treated by a health-care professional other than the study investigator for treatment related to complications, the investigator must request copies of the medical records and, if necessary, complete an Event Reporting CRF.

13.14 SUBJECT LOST TO FOLLOW-UP

Subjects who do not complete the scheduled follow-up visits and have not officially withdrawn from the study are considered lost to follow-up. If a subject is lost to follow-up, an End of Study CRF must be completed and sent to the Sponsor/CRO as soon as possible, after subject status has been determined. If a subject fails to comply with follow-up evaluations, the study site must make repeated attempts (minimum three attempts) to contact the subject. Each attempt to contact the subject and the method used to contact (e.g., telephone contact, registered letter), must be documented in the subject's records.

13.15 EARLY DISCONTINUATION OF STUDY

The study may be discontinued/ terminated at any time at the request of the Sponsor, the Ethics Committee, Principal Investigator or Regulatory Authority, with appropriate and timely notification to all parties concerned, otherwise, the study is terminated upon completion of all enrolled subjects through one month (30±7 days) of clinic/angiographic follow-up.

13.16 STUDY EXIT

Every subject should be encouraged to remain in the study until they have completed the CIP required follow-up period of one month (30±7 days). If a subject prematurely discontinues the study, the reason for discontinuation should be documented in Case Report Form (CRF). Possible reasons for premature discontinuation may include, but are not limited to the following:

- For any reason determined by judgment of the investigator that the subject should no longer participate in this trial.
- Subject non-compliance with the CIP
- Subject lost to follow-up.
- Voluntary decision by the subject.
- Death

13.17 STUDY COMPLETION

Subject who completes all protocol-required study procedures.

13.18 DATA COLLECTION AND FOLLOW-UP FOR WITHDRAWN PATIENTS

Investigator will have to follow the patient who has been withdrawn from the study. Investigator should try to obtain the reason, if patient withdraws his/her consent. Reason for withdrawal from the study shall be documented, whenever possible. It is vital to collect safety data on any patient discontinued because of an adverse event (AE) or serious adverse event (SAE). In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the patient should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

14. ADVERSE EVENT & DEVICE DEFICIENCIES

During the course of this clinical investigation adverse events (AE) might occur.

Adverse event information will be collected throughout the clinical investigation in the CRF by the investigator or designee.

Any adverse event will be followed until study end.

14.1 ADVERSE EVENT DEFINITION AND CLASSIFICATION

Adverse Events are defined and classified in this section according to the current version of ISO 14155.

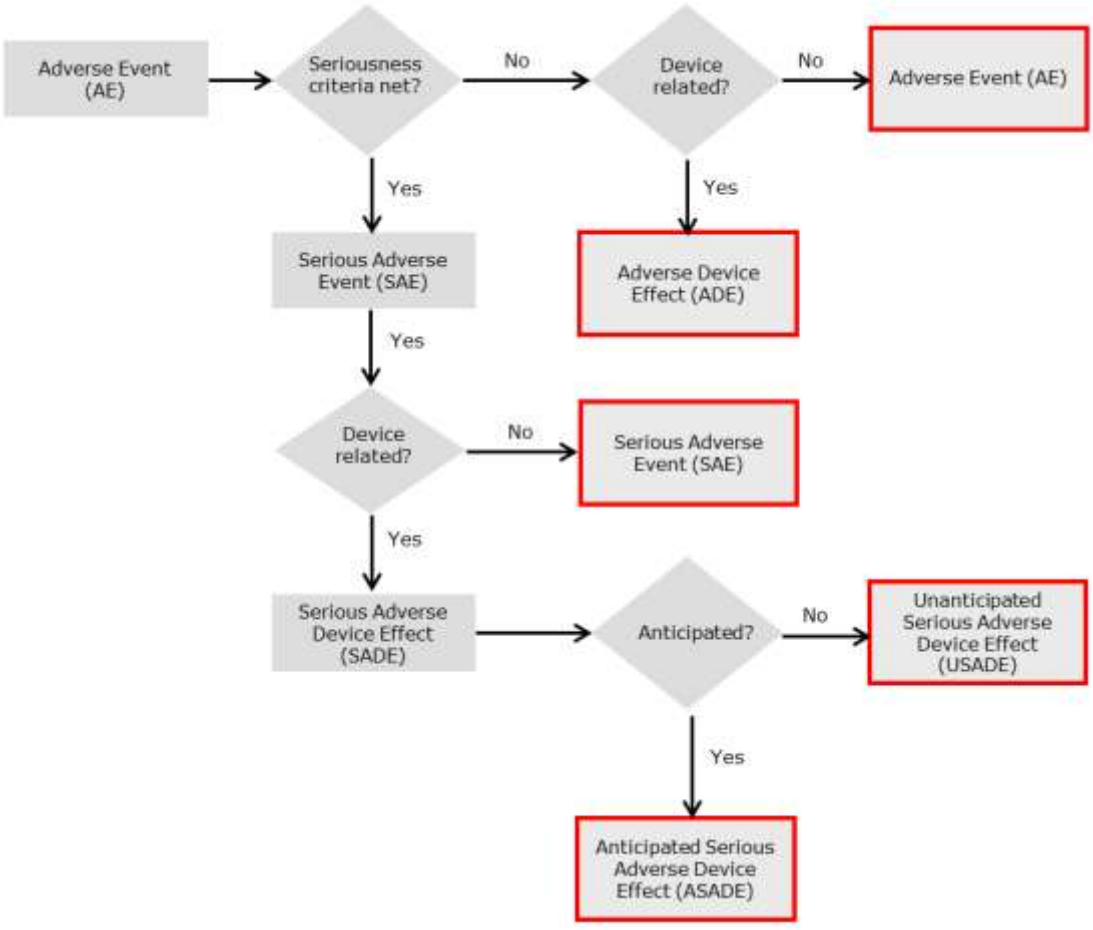

Figure 4 – Adverse event definition and classification

Adapted from ISO 14155

AE – Adverse event:

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.

Note: This definition includes events related to the investigational medical device

Note: This definition includes events related to the procedures involved

Note: For users or other persons, this definition is restricted to events related to investigational medical devices

ADE – Adverse Device Effect:

An *adverse event* related to the use of an investigational medical device.

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

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

SAE – Serious Adverse Event:

An *adverse event* that

a) led to death,

b) led to serious deterioration in the health of the subjects, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-subject or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

SADE – Serious Adverse Device Effect:

An *adverse device effect* that has resulted in any of the consequences characteristic of a serious adverse event.

USADE – Unanticipated Serious Adverse Device Effect:

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

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

Device Deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors and inadequate labelling.

Use error

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Note: Use error includes slips, lapses, and mistakes.

Note: An unexpected physiological response of the subject does not in itself constitute a use error. [ISO 14971:2007, definition 2.27]

14.2 ADVERSE EVENT REPORTING

Adverse events have to be reported in accordance to ISO14155 (current version), Schedule Y and all applicable amendments (Drugs and Cosmetics Rules, 1945), GCP for Clinical Research in India (2001, CDSCO), ICMR guidelines for Biomedical Research on Human Subjects (2006).

An adverse event occurring within this clinical trial will only be reported for enrolled subjects, as defined above.

Reporting of adverse events for enrolled subjects will be conducted until either study exit or study completion.

According to ISO14155 (current version), the investigator shall:

- Record every adverse event and observed device deficiency, together with an assessment
- Report to the sponsor or designee, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports
- Report to the IRB/IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or IRB/IEC
- Report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by national regulations.
- Supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

Adverse events classified to be serious and/or with a relation to the investigational device have to be reported to Spectranetics Corporation/CRO without unjustified delay after awareness by the investigator or by the investigator's designee.

Reporting should be done using the Adverse Event Form in the CRF. This report should deliver any information available at the time of reporting. Utmost effort has to be made to collect as much information as possible during initial reporting. Follow-up information has to be delivered as fast as possible to ensure timely completion of the report.

The investigator is obliged to provide copies of blinded source documents from the medical record, for all SAEs and ADEs, as requested by Spectranetics Corporation/CRO. Angiographic films and technical worksheets must be sent to Spectranetics Corporation/CRO by courier within 5 business days after assessment.

If additional information or documentation is needed, the clinical project manager / safety officer or designee will contact the investigator to retrieve the necessary information.

Primary contact for reporting Serious Adverse Events: Safety Reporting:

CBCC-Vibgyor Research Pvt. Ltd.
811, Iscon Elegance, Opp. Karnavati Club, S. G. Highway,
Ahmedabad - 380 015, India
Phone: +91 79 6616 8812/13/14
Fax: +91 79 6616 8811
E-mail: elca@vibgyorcare.com

14.3 SERIOUS ADVERSE EVENT

As per ICH-GCP (E6, step 5) guidelines, serious adverse event (SAE) or serious adverse drug reaction is any medical occurrence that at any dose:

No.	Description
1	Results in death
2	Is life threatening: refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.
3	Requires inpatient hospitalization or prolongation of existing hospitalization*
4	Results in persistent or significant disability/incapacity: is defined as a substantial disruption in a person's ability to conduct normal life functions
5	is a congenital anomaly or birth defect
6	Is an important medical event: A medical event that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

* Examples of situations which do not fulfill this criterion in the absence of an AE include, but are not limited to, are as follows:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the site (e.g., stent removal after surgery). This should be recorded in the study file

- A hospitalization for a pre-existing condition that has not worsened
- Hospitalization for social reasons

All SAEs will be recorded on the appropriate SAE form, followed through resolution by the study investigator and must be reviewed and evaluated by a study investigator.

14.4 ABNORMAL LABORATORY VALUES OR ABNORMAL CLINICAL FINDINGS

Collection of laboratory data should be limited to those laboratory parameters that are relevant to safety, study outcome measures, and/or clinical outcome. Investigator or designee will record and report only those abnormal laboratory values, which are clinically significant considering the change from the baseline value.

14.5 SEVERITY OF AN ADVERSE EVENT

For evaluating severity of an AE / SAE, following classification will be used to quantify intensity as per the clinical judgment of the investigator:

- Mild: The event is transient and easily tolerated by the subject. Does not generally warrant medical intervention;
- Moderate: The event causes the subject discomfort and interrupts the subject's usual activities. May warrant medical intervention; or
- Severe: The event usually incapacitating and causes considerable interference with the subject's usual activities. Warrants systemic drug therapy or other treatment Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

14.6 CAUSAL RELATIONSHIP OF ADVERSE EVENT

The investigator should use his medical judgment to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRFs and in SAE form (in case of SAEs).

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

No.	Description
1	*Unrelated*: The Adverse Event is clearly not related to the investigational agent, disease, concomitant medication, or other contributing cause.
2	*Unlikely*: The Adverse Event is doubtfully related to the investigational agent, disease, concomitant medication, or other contributing cause.
3	*Possible*: The Adverse Event may be related to the investigational agent, disease, concomitant medication, or other contributing cause.
4	*Probable*: The Adverse Event is likely related to the investigational agent, disease, concomitant medication, or other contributing cause.
5	*Definite*: The Adverse Event is clearly related to the investigational agent, disease, concomitant medication, or other contributing cause.

For causality assessments, events meeting the categories of probable or possible will be considered "related." Events that are reported as unlikely will be considered "not related."

If an investigator's opinion of possible, probable, or unrelated to study drug is given, another cause of event must be provided by the investigator for the serious adverse event.

14.7 ASSESSMENT OF OUTCOME OF ADVERSE EVENTS

The outcome of the AEs will be assessed and recorded as per the following categories:

- Recovered/resolved;
- Ongoing (Not resolved or stabilized on follow-up);
- Recovered with sequelae;
- Unknown;
- Death.

14.8 REPORTING OF SERIOUS ADVERSE EVENTS

SAE Reporting Requirements according to Indian Regulatory Requirements (Schedule Y):

Investigator's Responsibility

- Investigator(s) shall report all serious adverse events to the Licensing Authority defined under clause (b) of rule 21(Drug & Cosmetics rules, 1945), the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurrence.
- In case, the Investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Licensing Authority along with the report of the serious adverse event.
- The report of the serious adverse event, after due analysis, shall be forwarded by Investigator to the Licensing Authority as referred to in clause (b) of rule 21(Drug & Cosmetics rules, 1945), the Chairman of the Ethics Committee and the Head of Institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event.

Sponsor's Responsibility

- Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor or designee to the Licensing Authority (DCGI) as referred to in clause (b) of rule 21, the Chairman of the Ethics Committee and the head of the institution where the trial has been conducted, within fourteen days of the occurrence of the serious adverse event.

Ethics committee that accorded approval for the protocol will send its review report to DCGI for all SAEs within 30 days of its occurrence.

The above mentioned process and timelines for initial SAE reporting will also be followed for reporting of all follow-up information received for the SAE.

In the event of a SAE, the investigator will notify / contact the Medical Monitor. Additionally, detailed safety reporting procedures will be described in safety management plan for the study.

The further course of action for all SAEs; shall be observed as per current local applicable rules and regulations.

14.9 MEDICAL MONITORING

It is the responsibility of the investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and implementation of site data and safety-monitoring plan. For any subject

safety or eligibility concerns or protocol related queries, the investigator should contact the sponsor's medical monitor.

Detailed medical monitoring procedures will be described in the relevant section of the project management plan.

15. STATISTICAL ANALYSIS

As per the 25th SEC (Cardiovascular & Renal) meeting which deliberated the proposals on 30-10-2015 and recommended the firm (Spectranetics Corporation - Sponsor) shall conduct a Bridging study in Indian Population at least 25 patients. The directorate suggested that the sponsor submit a protocol for the study in India for clinical trial approval. Considering the 5 dropouts, Sponsor has set up this protocol to conduct the Excimer Laser Coronary Atherectomy (ELCA®) study in India on 30 eligible patients.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All sites conducting research under the sponsorship of the **Spectranetics Corporation** are required to have a plan in place for assuring the quality of the research being conducted. Each site should have standard operating procedures (SOPs for clinical trial activities) and methods of training for staff should be specified.

16.1 INFORMED CONSENT PROCESS

The investigator or a person designated by the investigator should completely inform the patients and/or their families describing this study and study related procedures providing sufficient information to them for making an informed decision about their participation in this study.

All the patients should be informed to the complete extent possible about the study, in language and terms they are able to understand. Consent form must be IRB/IEC approved and the patient will be provided the same in local language(s).

Prior to patient's participation in this study, the written informed consent form must be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative / impartial witness (along with patient's thumb impression in case when he/she is illiterate) and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

16.2 MONITORING

Monitoring will be performed by Sponsor or Sponsor designees, to ensure that the investigator and the clinical investigation team conduct the clinical investigation in accordance with the CIP, current versions of Declaration of Helsinki, ISO 14155, International conference of harmonization-Good clinical practice (ICH-GCP) and applicable Indian regulations (Schedule Y and all applicable amendments - Drugs and Cosmetics Rules, 1945), GCP for Clinical Research in India (2004, CDSCO), ICMR guidelines for Biomedical Research on Human Subjects (2006).) to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

Periodic monitoring visits will assure that the facilities are still acceptable; that the CIP is being followed, that the IEC/IRB has been informed about approved CIP changes as required, that records on study conduct and data collection are complete and present, that appropriate and timely reports have been made to the sponsor and the authorities, that device inventory is controlled, and that the investigator is carrying out all agreed activities.

During monitoring visits, 100% Patient informed consents and 100% source data related to inclusion exclusion criteria, Primary and secondary endpoints and AE and SAEs will be verified as defined in the monitoring plan. For this purpose, the investigator must permit access to medical records of the subjects (source data) throughout the study. In case of electronic medical records, the investigator has to ensure that the monitor receives access or print outs of all study relevant source documents. The documents must be signed and dated by the investigator or other designated staff.

If a monitor becomes aware that an investigator is not complying with the requirements as outlined in the CIP, the monitor is obliged to notify Sponsor or Sponsor designees for the study management. Sponsor or Sponsor designees will evaluate the non-compliance and issue corrective actions, discontinue enrollment or as a last measure close the clinical investigation site. The investigator must in such case return all unused devices to Sponsor or Sponsor designees.

16.3 SOURCE DATA

Original or signed and dated copies of all clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled subject. For data documented in the CRF respective source data in the medical record (source document) must be available.

The medical record/subjects record (source document) must contain, but is not limited to:

- Executed informed consent
- Subjects participation in the clinical investigation
- Demographics
- Documentation of medical history
- Intervention report
- Vessel and lesion sizes and characteristics
- All angiographies, ECGs, laboratory examination outcomes including reference values
- Discharge letter
- All adverse events: diagnosis, symptoms, onset date, severity, device and procedure relationship, action taken, outcome
- Concomitant medication
- Follow-up information
- Date of clinical investigation completion

16.4 DATA COLLECTION

The investigator or an individual designated by the investigator is responsible for recording all data from the study in the electronic Case Report Form (CRF).

The data will be entered in an electronic Case Record Form (CRF), compliant with the 21 CFR Part 11. The site staff must be trained on CRF completion before they are given access for data entry. Data should be entered within 7 days of the study visit and the data queries should be responded to promptly. All CRF pages must be electronically signed by the investigator or a person designated by the investigator at each site.

Subjects will be identified in the CRFs by a unique reference number only, a composition of letters and numbers. CRFs are confidential documents and will only be available to Sponsor (including Sponsor designees), the investigator, the clinical investigation statistician, and the regulatory authorities. The investigator or a person designated by the investigator will maintain subject identification log of the subjects participating in the clinical investigation at the clinical investigation site which will be maintained in the Investigative site file.

16.5 DATA MANAGEMENT

The data manager is responsible for providing a clean data set at the end of the clinical investigation. Queries should be resolved by the investigator or a person designated by the investigator in a timely manner. Data snapshots will be taken for interim analysis. When all data is complete, the database will be locked and data will be analyzed.

After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity, and validity of the database against the CRFs. These should include:

- Missing value checks
- Range checks
- Consistency checks
- Sequence checks
- Probabilistic checks and
- Protocol adherence checks

All data will be entered into the EDC system. When the database is complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the sponsor or Sponsor's designee, the Trial Statistician and the Data Manager.

It is the responsibility of the study site and investigator to resolve all data queries that arise during data management in a timely manner.

16.6 PROTOCOL COMPLIANCE

The investigator is required to conduct the study in accordance with the signed investigator agreement and clinical protocol.

The investigator shall notify Sponsor or Sponsor's designee and the reviewing IRB/IEC in writing, no later than 5 working days after any significant violations from the study plan, conducted to protect the life or physical well-being of a subject in an emergency. Except in such emergency, prior approval by Sponsor or Sponsor's designee and, if applicable, IRB/IEC approval is required for significant violations from the study plan. Such an approval will be documented in writing and maintained in the study files.

Sponsor or Sponsor's designee categorizes instances of protocol non-compliance as either violations or deviations.

16.7 PROTOCOL VIOLATIONS

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the study and/or the rights, safety or welfare of subjects.

Protocol violations include, but are not limited to:

- Failure to obtain informed consent
- An unapproved (Sponsor or Sponsor's designee and IRB/IEC) investigator using Excimer Laser Coronary Atherectomy (ELCA®) products for study purposes
- Violation of relevant inclusion/exclusion criteria
- Protocol requirement violations that affect the primary endpoints analysis

In some instances, compliance issues with the consent process may occur. The investigator should seek guidance from the site's IRB/IEC to ensure the subject received appropriate information to

consider their participation in the study. The investigator is obliged to take any action the IRB/IEC feels is necessary, including subjects removal from the study. Please note that subjects who haven't signed informed consent prior to implantation will not be included in the study analysis, even if informed consent could be obtained retrospectively.

All violations will be reported to the competent authority in accordance with applicable regulatory timelines. The study site should report the protocol violation to the reviewing IRB/IEC and provide a copy of the notification to Sponsor or Sponsor's designee. The site should also report the protocol violation to Sponsor or Sponsor's designee on the applicable CRF.

16.8 PROTOCOL DEVIATIONS

Protocol deviations are defined as instances where protocol requirements are not followed in such a manner whereby data is unusable or unavailable.

Protocol deviations are less serious in nature and do not require IRB/IEC notification, as long as they do not have an effect on the rights, safety or welfare of the study subjects.

Protocol deviations include, but are not limited to:

- Procedure not performed within the allowed follow-up window
- Required data not obtained
- Follow-up procedure performed at an unapproved location

The study site should report the protocol deviation on the applicable CRF.

16.9 PROTOCOL AMENDMENTS

Any change or addition to the protocol, other than administrative ones (i.e. typographical or logistical), can only be made in a written protocol amendment that must be approved by Sponsor, DCGI where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a violation of the protocol. In such cases, CRO and Sponsor should be notified of this action and the IRB/IEC at the study site should be informed within 7 working days.

Changes to the protocol affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval but the IRB/IEC must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC approval that can be treated as administrative amendments include:

- Changes in the staff used to monitor trials
- Changes in shipping address for CRFs

16.10 AUDITS / INSPECTIONS

Study centre's may be audited during the course of and after completion of the clinical investigation by Sponsor or Sponsor's designee, IRB/IEC, competent authority or other applicable regulatory authorities.

The investigator must provide the auditors/inspectors with all clinical investigation documents including the medical records for all enrolled subjects.

Sponsor or Sponsor's designee will evaluate any non-compliance and issue corrective actions, discontinue enrolment or at last measure close the clinical investigation site

17. REGULATORY REQUIREMENTS

17.1 COMPLIANCE STATEMENT

The clinical trial will be conducted as per the principles and requirements of Declaration of Helsinki (Ethical principles for medical research involving human subjects, revised by the 64th WMA General Assembly, Brazil, 2013), and ICH-GCP (E6-R1, Step 5) guidelines along with the local regulatory requirements of Good Clinical Practices for Clinical Research in India (2001, CDSCO) ICMR guidelines for Biomedical Research on Human Subjects (2006) and Schedule Y (all applicable amendment) and ISO 14155 (current version).

17.2 ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

The clinical investigation plan as well as other relevant study documents required will be submitted for approval by the IRB/IEC and DCGI (Drug Controller General of India, CDSCO) competent authority of India prior to study start.

Sponsor or each participating institution/hospital must provide this protocol (protocol amendment, if applicable) and essential documents for the review and approval to Institutional Ethics Committee (IEC) or Institutional Review Board (IRB), Registered with DCGI, for the formal approval of the study conduct. The decision of the IEC/IRB signed by its chairman with IEC composition, concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IEC/IRB members and their affiliation to the sponsor. All major amendments to the CIP, ICF, or other written information provided to subjects, and/or study procedures directly affecting the subject, must be approved in writing by the respective site IEC/IRB. The Investigator shall report in writing to the IEC/IRB, any SAE and SADE whether procedure related or not, according to the IEC/IRB required timelines, but no longer than 7 days after the investigator is aware of event(s) occurrence.

If requested, a progress report during the trial and a final study report at the end of the clinical trial will be submitted to the IEC/IRB.

Sponsor or Sponsor's designee will record changes to the clinical investigation plan in amendments. Amendments will be submitted to the involved IRB/IEC and respective competent authorities as applicable according to international or local regulations. Investigators and study personnel will be trained on all amendments.

All subjects must be provided with a written informed consent which is approved by the site's IRB/IEC. Sponsor or Sponsor's designee will provide a master English informed consent form and subject information sheet to be used in the study. Each site must provide Sponsor or Sponsor's designee with a copy of the clinical site's IEC/IRB approval letter or vote and the IRB/IEC approved informed consent. The approval letter must specify the documents for which approval has been granted. Otherwise it is the obligation of the investigator to inquire about a new document giving the necessary details. In addition the composition of the IRB/IEC and a statement about its compliance to GCP is required. Approvals for the continuation of the trial at each clinical site must be kept current and notifications forwarded to Sponsor or Sponsor's designee.

17.3 INSURANCE

Subjects who participate in this study will be insured for study related injury according to local regulatory requirements. Sponsor or Sponsor's designee will organize appropriate insurance coverage which will be available throughout the entire study.

The sponsor certifies that it has taken a liability insurance policy covering this clinical trial . The insurance policy is in accordance with local laws and requirements. A copy of the insurance certificate will be provided to the IEC/IRB.

17.4 PATIENT AND DATA CONFIDENTIALITY

Patient confidentiality along with the information disclosed/provided/produced during the clinical trial, including, but not limited to the CRFs, ICFs and results are strictly held in trust by the sponsor, sponsor's authorized personnel, investigators and their staff members. Subjects will not be identified by any personal identity and name in any published study reports.

No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit direct access to such records.

The submission of this clinical trial protocol and other necessary documentation to the ethics committee (IEC/IRB) is expressly permitted, the IRB/IEC members having the same obligation of

confidentiality. Subject's confidentiality will be maintained throughout the study. It will be ensured that the information can always be tracked back to the source data, if required. For this purpose, a unique subject identification code (i.e. subject number) will be used that allows identification of all data reported for each subject.

Data relating to the study might be made available to third parties (e.g. in case of an audits or regulatory inspections) preconditioned that the data are treated confidentially and that the subject's privacy is guaranteed.

17.5 RECORDS

Records to be maintained by the investigator include, but are not limited to:

- Clinical trial investigational plan/Protocol and all amendments
- Investigators Brochure or equivalent document
- Contact list sponsor/study site
- Signed clinical trial agreement
- IRB/IEC correspondence, approval letter, including informed consent
- IRB/IEC membership list
- Regulatory authority notification, correspondence and approval
- Insurance certificate
- If applicable, device shipping records, device accountability
- Correspondence relating to the trial
- CVs for all investigators and key members of the investigation site team
- Training records
- Site personnel signature list and delegation of authority form
- Blank set of CRFs and instructions for completion
- Subjects screening/enrollment log
- Subjects identification log
- Lab certification and lab test normal ranges
- Adverse event forms
- Applicable study logs & forms
- Reports (including interim reports, final reports from investigator and sponsor)

Sponsor or Sponsor's designee will retain relevant study documentation in the Trial Master File (TMF) according to national legislation and Sponsor or Sponsor's designee Standard Operating Procedure (SOPs).

17.6 RECORD RETENTION

All study records and reports will remain in file at the sites for a minimum of 3 years after completion of the trial and will further be retained in accordance with local and international guidelines as identified in the clinical trial agreement.

The investigator must contact Sponsor or Sponsor's designee before destruction of any records and reports related to the clinical investigation. Sponsor or Sponsor's designee must be informed if the investigator plans to leave the clinical investigation site. In such case the site must name a new contact person before the investigator parts from the clinical investigation site.

17.7 STUDY TERMINATION

Sponsor or Sponsor's designee will monitor the progression of the clinical investigation. If warranted, the clinical investigation may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the clinical investigation population.

Sponsor or Sponsor's designee may terminate investigator and site participation in the clinical investigation if there is evidence of failure to maintain adequate clinical standards, failure to comply with the clinical investigational plan, fraud or any other forms of misconduct.

In the event of clinical investigation termination or suspension, Sponsor or Sponsor's designee will send a report outlining the circumstances to the corresponding IRB/IEC, regulatory authority and all investigators. A suspended or terminated clinical investigation may not be re-initiated without approval of the corresponding IRB/IEC and regulatory authority.

Reasons for termination include, but not limited to, following:

a) Any clinical adverse event (AE), laboratory abnormality, situation occurs such that continued participation in the study would not be in the best interest of the patients.
b) The study can be terminated if the aim of the clinical trial has become out dated or is no longer of interest.

c) If the investigator has received from the sponsor all study drugs, means and information necessary to perform the clinical trial and has not included any subject after a reasonable period of time mutually agreed upon, site can be prematurely closed.

d) If the sponsor is not scientifically convinced regarding results of the clinical trial, it may close-out the site pre-maturely.

e) The site can be prematurely closed if there is an event of breach by the investigator of the fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the applicable guidelines for GCP.

f) Additionally, IRB/IEC can terminate the study for the safety of subjects.

Subsequent review of serious, unexpected, and related AEs by the medical monitor, IEC/IRB, the sponsor(s), or local regulatory authorities may also result in suspension of further trial interventions/administration of study product at a site. The study sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

17.8 INVESTIGATOR REIMBURSEMENT AND CONTRACTING

Sponsor or Sponsor's designee will reimburse efforts undertaken for inclusion and follow up of subjects, and documentation of subject data within the study. A contract (Clinical Trial Agreement) with the principal investigator and/or the respective hospital will be agreed on and signed prior to study start. Within this an overall fee per subjects broken down to individual visits will be included.

This subject fee will cover all expenses for material used and procedures to be performed according to the CIP. The CIP and any future changes thereof will be part of the contract.

17.9 RESPONSIBILITIES OF INVESTIGATORS

The investigator(s) undertake(s) to perform the clinical trial in compliance and accordance with this clinical trial protocol and pertinent requirements of guidelines and regulations. The investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of CRF, DCF or other appropriate mode of communication) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by sponsor representatives. The investigator may appoint such other individuals as he/she may deem appropriate as sub-investigators to assist in the conduct of the clinical trial in accordance with the

clinical trial protocol. All sub-investigators shall be appointed and listed in a timely manner. The sub-investigators will be supervised by and under the responsibility of the investigator. The investigator will provide them with a copy of the clinical trial protocol and all necessary information.

17.10 RESPONSIBILITIES OF SPONSOR AND STUDY MANAGEMENT

The sponsor of this clinical trial is responsible for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards of ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main role of the clinical monitoring team is to help the investigator and the sponsor in maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

The detailed Project Management Plan, incorporating monitoring plan, safety management plan, IP (Investigational Product) management plan will be generated outlining further management of the study related activities of sponsor and CRO.

17.11 CLINICAL STUDY REPORT

A final clinical study Report will be prepared according to the Schedule Y Appendix II and ICH guideline on structure and content of Clinical Study Report. A Final Clinical study Report will be prepared regardless of whether the study is completed or prematurely terminated.

18. PUBLICATION POLICY

It is the responsibility of Sponsor or Sponsor's designee to register this trial in an acceptable registry. On the basis of the statistical and clinical evaluation of the pooled results across the study centers, a clinical study report will be prepared by Sponsor or Sponsor's designee. This can form the basis of a manuscript for publication in a peer-reviewed journal. The sponsor will hold the right to publish the results of present study at any time.

Sponsor or Sponsor's designee intends to publish the results of this clinical investigation. Sponsor or Sponsor's designee reserves the right to include the report of this clinical investigation in any regulatory documentation or submission or in any informational materials prepared for the medical profession. The ownership of the data shall at all times be held by Sponsor or Sponsor's designee.

No publication of results from single center experience will be allowed until the primary endpoint is analysed in order to allow for preparation and publication of the multicentre results.

Sponsor or Sponsor's designee agrees that investigators shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the clinical investigation after the first publication. Any prior publication in any way or form is not permitted, without approval by Sponsor or Sponsor's designee.

The investigator should provide Sponsor or Sponsor's designee with a copy of any publication in journals, theses or dissertations at least 4 weeks prior to submission.

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20. APPENDICES

- **SPNC_ELCA STUDY : Patient Information Sheet And Informed Consent Form**