A Prospective Multi-Centre Registry of EvroSure (Everolimus Drug Eluting CoCr Coronary Stent) to Investigate Safety and Effectiveness

Name of Study: EverGreen

PROTOCOL

PROTOCOL APPROVAL PAGE

Registry title: A Prospective Multi-Centre Registry to Investigate Safety and Effectiveness of EvroSure (Everolimus Drug Eluting CoCr Coronary Stent).

Name of Study: EverGreen

Protocol version: ECS/FM/030622.

We, the undersigned, have read and approved the protocol specified above, and agree to adhere to its requirements outlined within:

A. Investigator

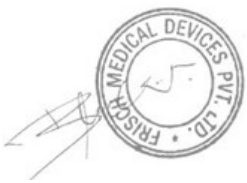
Dr. Rony M Santoso
Primaya Tangerang Hospital, Indonesia Email:
rony_msantoso@yahoo.com

08/12/2022

Signature Date

B. Sponsor Representative

Mr. Bhavin Oza
CEO
Frisch Medical Devices PVT LTD
Email: frischmedical@gmail.com
Email: info@frischmedical.com
Contact No.: 079-48006239



08/12/2022

Signature Date

TABLE OF CONTENTS

REGISTRY SUMMARY

OBJECTIVES

The primary objective of this Registry is to assess the safety and effectiveness of EvroSure - Everolimus Drug Eluting CoCr Coronary Stent in obstructive coronary artery disease.

INFORMED CONSENT FORM

Before signing this consent document, I have made sure that I have discussed my participation in the EverGreen Registry, with my doctor and that all of my questions/doubts have been addressed. I confirm having received both oral and written explanations of the Registry to be conducted. The aim of the Registry is to assess the safety and effectiveness of the EvroSure – Everolimus Drug Eluting CoCr Coronary Stent in coronary arteries. The Registry will include follow visits at 1 month, 6 months, and 12 months. The Primary Investigator has examined the project and given a favorable opinion. All documents belonging to my medical file are protected by professional secrecy and will remain strictly confidential.

I have read discussed and understood the patient information and hereby consent to voluntarily participate in the EverGreen Registry.

PATIENT ID:

DATE & TIME: **SIGNATURE:**

PHYSICIAN NAME:

REGISTRY DESIGN

This is a multi-Centre, prospective Registry. 888 (Or more) patients will be enrolled in the Registry. Patients will be followed up clinically for twelve months post-procedure at 1 month, 6 months & 12 months.

REGISTRY POPULATION

The Registry population will consist of 888 (Or more) patients with an obstructive coronary artery disease with few exclusion criteria. They would therefore be representative of "Real- Life patients" and practice.

TREATMENTS

Patients will receive the Everolimus Drug eluting CoCr Coronary stents in sizes of 8, 12, 14, 18, 22, 26, 30, 34, 38-, 42-, 46-, 50 & 54-mm lengths, and diameters of 2.25, 2.5, 2.75, 3.0, 3.50, 4.0 and 4.50 mm.

ENDPOINTS

The primary safety endpoint of the Registry is defined as Major Adverse Cardiac Events (MACE) at 30 days. MACE rate is defined as the incidence of the combined clinical endpoint: Composite of Death (Cardiac death as well as Non-Cardiac), Myocardial Infarction (Q-wave and non-Q-wave), Emergency **C**oronary **A**rtery **B**ypass **G**raft Surgery, clinically justified TLR within 30 days following index procedure.

The following secondary effectiveness endpoints will be as follows:

- Angiographic/Device Success (%) (Initial in hospital)
- Procedural Success (%)
- Clinically justified Target Lesion Revascularization (TLR) (%) at 12 months

The following secondary safety endpoints will be assessed:

- MACE (%) until 12 months (Clinically Justified)
- Device related SAEs until 12 months (Clinically Justified)

Refer to **Appendix I** for definitions.

1.0 INTRODUCTION

EvroSure stent is made up of unique hybrid cell design comprising of an intelligent mix of open and close cell designs resulting in a structure which provides excellent radial strength with a high degree of flexibility.

It has been known from experiences of Simon et al and Kastrati et al (ISAR – STEREO 1 & 2) that thin strut stent results in lower incidence of restenosis as opposed to thicker strut stents. The hybrid design configuration contains an intelligent mix of close cells at the edges and open cells which are mid segment. The resultant scaffolding has a highly competitive radial strength of 1.1 bars with the benefits of ultra-low strut thickness.

During Biomechanical tests, EvroSure demonstrates extremely competitive (if not superior) properties as follows-

- A metal to artery ratio ranging from 14% to 16% resulting in superior vessel wall coverage and thus ensuring better vessel wall coverage and uniform drug distribution. The 8 and 10 crown configurations ensure that there are more cells per diameter, resulting in low recoil (<3%) and superior acute gain.
- The unique design architecture ensures that foreshortening of the stent is < 0.29% (almost zero foreshortening).
- EvroSure uses semi-compliant PTCA balloon catheter which has abrupt shoulders to eliminate balloon-related edge injury. The manufacturing process ensures that there is low balloon overhang thus adding to the low injury solution.
- The catheter system is highly trackable and there is minimal loss in force transmission during navigation. Thus, reaching lesion sites through vessel tortuosity becomes easy with EvroSure
- An interesting technology advantage that gets added to EvroSure is the high stent dislodgement force. This translates into extreme comfort during navigation in tortuous anatomical situations without the fear of stent dislodgement.

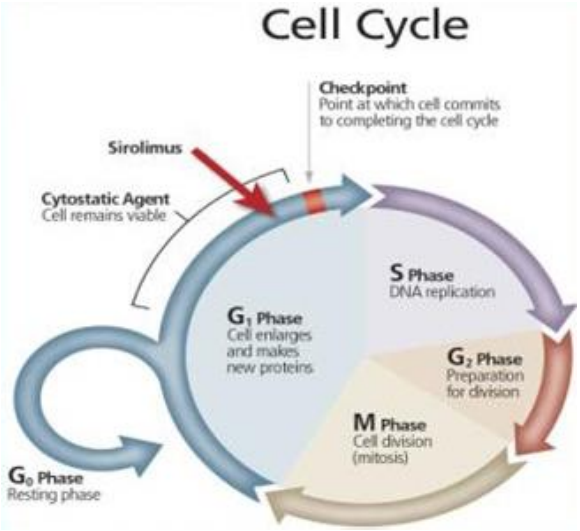
Finally, since EvroSure is created on L605 cobalt chromium stent, the density of the alloy transmits sufficient radiopacity to the final stent.

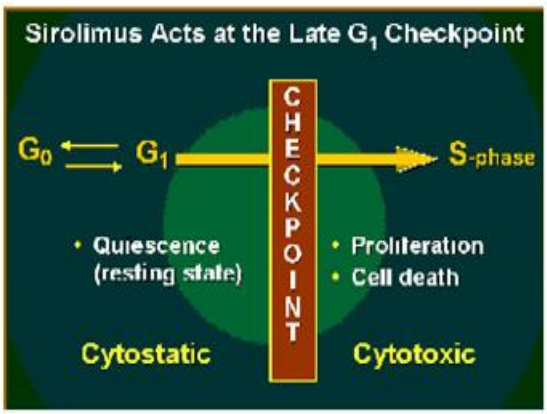
Drug Everolimus

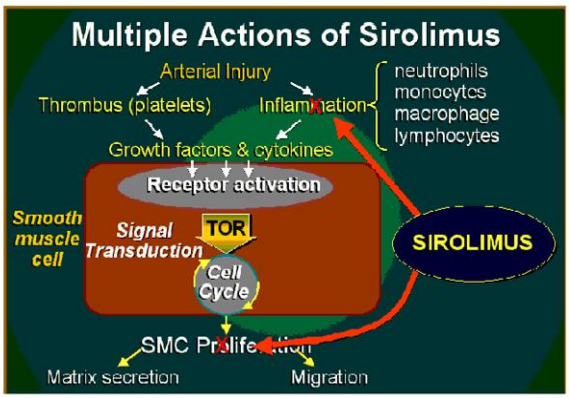
EvroSure Everolimus Drug Eluting CoCr Coronary Stent has a drug loading of 1.10µ g/mm^2 of stent surface area coated with Everolimus as the active anti-proliferative agent. An average 3.0 mm x 22 mm of EvroSure would have 190µ g of Everolimus. The drug is timed to release from the biodegradable polymer surface in approximately 28 days after implantation.

Mechanism of Action for Everolimus:

Everolimus has dual mode of action. It modulates inflammatory cell function and blocks smooth muscle cell proliferation. Everolimus is cytostatic. It stops proliferation prior to G1 check point returning cells to the G0 resting phase. In this way, by not killing cells, it prevents vessel damage and allows rapid and complete re-endothelialization within 30 days. It thereby minimizes the potential for thrombosis.







It inhibits growth factor & cytokine stimulated cell proliferation. DNA damage check point (G1 check):chk1-kinase inactivation before DNA replication and also inactivation of cdk2- cyclin a protein (growth factor).

Polymer

EvroSure uses a well-known and a well-documented co-polymer combination comprising of PLLA and PLGA which is biocompatible and biodegradable. The resultant polymer degrades in a period of 35- 45 days time and provides a uniformly thin coating of 1.5µm.

The coating is highly stable to EtO process and does not web, crack or lump on stent/balloon surface.

Safety and Device Biocompatibility

The pre-clinical evaluation of EvroSure Everolimus Drug Eluting CoCr Coronary Stent was carried out as follows; an anti-proliferative activity test was performed in vitro and in-vivo. In vitro toxicity was performed by using the Indirect Agar Diffusion Method (ISO 10993-5). The suppressive activity of Everolimus against the Intimal Layer In-Vitro was tested. Leukocyte adhesion studies were performed. The device passed all the tests.

Drug Biocompatibility and Safety

The Everolimus Drug eluting CoCr Coronary stents are tested to assess the loading/content and release kinetics over 48-50 days. The stents are coated with polymers loaded with Everolimus, sterilized and had Everolimus load calculated gravimetrically (120 ±10 µg) on 16-mm stents. Polymer coated stents were tested at 28 days in porcine coronary model and were found to be absent of fibrin, hemorrhage, necrosis, fibrinoid, or inflammation.

Conclusions

In short, the following conclusions can be stated:

- Indigenously developed and designed EvroSure is a
  - predictably safe & efficacious 3rd generation DES,
  - with a propensity to minimize vascular injury by use of an intelligent mix of ultra-low strut thickness Co-Cr stent,
  - highly documented drug Everolimus &
  - a biocompatible, biodegradable polymer

2.0 REGISTRY RATIONALE

This is a multi-center, prospective Registry aimed at evaluating the safety and effectiveness of the EvroSure - Everolimus Drug eluting CoCr Coronary stent in reducing neointimal hyperplasia and decreasing restenosis during PCI of stenotic coronary artery disease as well as intermediate term outcomes. The EvroSure- Everolimus Eluting Stent is a Drug Eluting Stent on a Cobalt Chromium platform with ultra-low strut thickness, High Radial Strength, Excellent conformability, Biodegradable polymer and Everolimus eluting characteristics. A stent of this type is expected to decrease restenosis following PCI and thereby improve the Clinical Outcomes.

3.0 OBJECTIVES

The main objective of this Registry is to assess the safety and effectiveness of the EvroSure Everolimus Drug eluting CoCr Coronary stent in obstructive coronary artery disease.

3.1 Primary objectives

The primary endpoint of the Registry is defined as Major Adverse Cardiac Events (MACE) at 30 days. MACE rate is defined as the incidence of the combined clinical endpoint: Composite of Death (Cardiac death as well as Non-Cardiac), Myocardial Infarction (Q-wave and non-Q-wave), Emergency **C**oronary **A**rtery **B**ypass **G**raft Surgery, clinically justified TLR within 30 days following index procedure.

3.2 Secondary objectives

The following secondary effectiveness endpoints will be as follows:

- Angiographic/Device Success (%) (Initial in hospital)
- Procedural Success (%)
- Clinically justified Target Lesion Revascularization (TLR) (%) at 12 months

The following secondary safety endpoints will be assessed:

- MACE (%) until 12 months (Clinically Justified)
- Device-related SAEs until 12 months (Clinically Justified)

4.0 REGISTRY DESIGN

This is a multi-Centre, prospective Registry. 888 (Or more) patients will be enrolled in the Registry. Patients will be followed up clinically for twelve months post-procedure at 1 month, 6 months & 12 months.

Approximately 888 patients with obstructive coronary artery disease with a vessel size between ≥2.5 to ≤4.50 mm in diameter by visual estimate and who meet all eligibility criteria will be treated with the Everolimus Drug Eluting CoCr Coronary Stent.

Total 888 patients will be enrolled.

It is anticipated that the total length of the Registry will be 24 months.

5.0 REGISTRY POPULATION

Total 888 patients eligible for coronary stenting and who meet the following entry criteria will be enrolled.

The Registry population will consist of 888 (Or more) patients with an obstructive coronary artery disease with few exclusion criteria. They would therefore be representative of "Real- Life patients" and practice.

5.1 Inclusion criteria

Patients must meet **ALL** of the following criteria:

1. The patient must be ≥ 18 years of age;
2. Patient was an acceptable candidate for PTCA, Stenting, or Emergent CABG;
3. Patient has clinical evidence of ischemic heart disease or a positive functional study
4. Patient and his or her treating physician agree that the patient will comply with all the required post-procedure follow-up.
5. Target lesion(s) present with ≥50% stenosis, in one or more vessels
6. Target lesions has to be de novo;
7. One or more target lesions require treatment
8. Reference vessel diameter of target lesion(s) must be ≥ 2.25mm and ≤ 4.5mm, by visual estimate.

5.2 Exclusion criteria

Patients will be excluded if **ANY** of the following conditions apply:

General exclusion criteria:

1. Previous PTCA with any stent
2. History of CVA or TIA within the last 3 months
3. Patient has active infection
4. Concurrent medical condition with a life expectancy of less than 12 months
5. Clinically relevant contraindication to aspirin, heparin, clopidogrel bisulphate, or ticlopidine including thrombocytopenia, neutropenia, or leukopenia

6. Active peptic ulcer or upper gastrointestinal bleeding
7. Current participation in an investigational drug or device trial that has not completed its primary endpoint follow-up period
8. Pregnancy or woman of childbearing potential who, in the opinion of the investigator, does not take adequate measures to prevent conception
9. Known hypersensitivity or contraindication to cobalt, chromium, or nickel

Angiographic Exclusion criteria

1. Angiographic evidence of thrombus (thrombus larger than half the diameter of the vessel and/or requiring other adjunctive interventions such as Angiojet, Exciser, Thrombolysis, etc.),
2. Saphenous Vein Graft Interventions, (S.V. G's)
3. Patients having undergone a PCI within 48 hours of an AMI episode.

5.3 Withdrawal, discontinuation, and/or replacement of subjects

All patients have the right to withdraw at any point during the period of the clinical Registry. It will be documented whether or not each patient completed the clinical Registry.

Every attempt should be made to collect follow-up information. Discontinued patients will not be replaced.

6.0 REGISTRY TREATMENT

6.1 Stents and delivery system

STENT:

The Everolimus Drug Eluting CoCr Coronary Stent is indicated for use in-patients with symptomatic ischemic heart disease due to obstructive coronary artery disease with a reference vessel diameter ranging from 2.25 mm to 4.50 mm and is intended to improve coronary luminal diameter.

Available Registry Stent Sizes

Diameters (mm)	Available Lengths (mm)												
2.25	8	12	14	18	22	26	30	34	38	42	46	50	54
2.50	8	12	14	18	22	26	30	34	38	42	46	50	54
2.75	8	12	16	20	24	28	32	36	40	42	46	50	54

3.00	8	12	16	20	24	28	32	36	40	42	46	50	54
3.50	8	12	16	20	24	28	32	36	40	42	46	50	54
4.00	8	12	16	20	24	28	32	36	40	42	46	50	54
4.50	8	12	16	20	24	28	32	36	40	42	46	50	54

Balloon

Balloon is made up of nylon material having PTFE coated stainless steel hypo tube shaft. Two radiopaque markers located underneath the balloon, fluoroscopically mark the working length of the balloon.

6.2 Stent placement

Using the Instructions for Use, the investigator should determine the appropriate diameter of the Everolimus Drug Eluting CoCr Coronary Stent to be implanted.

Preparation and percutaneous access should be performed according to standard hospital procedures. After percutaneous access is obtained, Heparin should be administered in accordance with the standard institutional procedures.

The target lesion should be crossed with a 0.014" exchange-length guide wire and predilated with an appropriately sized balloon. Balloon predilatation of the target lesion must be performed according to standard operational techniques. Investigators should use similar materials and techniques throughout the Registry to maintain consistency and standardisation of care.

The goal of stent implantation is to achieve an angiographic appearance of the stent expanded just outside the boundaries of the vessel filled with contrast medium.

To select the proper stent/balloon size, the investigator should:

1. Measure the reference vessel diameter;
2. Calculate the balloon size using compliance curves in the Instructions for Use to achieve stent/vessel ratio of 1.1:1, prior to stent placement;
3. Select the stent system that, at nominal pressure, provides this ratio.
   Example: A stent/vessel ratio of 1.1:1 for a reference vessel of 3.2 mm mean diameter implies the use of a balloon/stent system of 3.5mm (3.2mm x 1.1 = 3.5mm) using the nominal pressure as recommended.
4. Select the length of the stent such that lesion stent ratio is of at least 1: 1.1.

The delivery system is introduced over the exchange wire and advanced until the markers identifying the ends of the balloon catheter bracket the target lesion. The appropriate position of the stent is reconfirmed by contrast injection. The stent delivery balloon is then progressively inflated to the maximum recommended pressure as indicated in the Instructions for Use.

If stent/vessel ratio of 1.1:1 is not achieved, the stent may be re-crossed with an appropriate-sized balloon. Should resistance be experienced, withdraw the balloon catheter under fluoroscopic guidance. Center the balloon within the stent and re-dilate the stent to achieve the optimal result. Refer to the Instructions for Use for clarification, if necessary.

Following balloon deflation and withdrawal repeat angiography must be performed. Further stent expansion using a larger balloon at higher pressures may be used to achieve optimal sizing. Post-procedure, repeat angiograms must be taken from the original pre-procedural views after withdrawal of the guidewire(s) and after intracoronary injection of nitrates.

In the event of a failure to implant the stent (EvroSure) by using the required implantation method, the Investigator may choose to treat the target lesion with another approved device of his choice. This device will be appropriately recorded if it is not the Registry device

If a dissection occurs during predilatation or stent implantation an additional Registry stent should be used identical to the Registry treatment. **This will not be considered as a "Protocol Deviation".**

6.3 Criteria for good stent implantation

The investigator should strive for optimal result, using on-line QCA, if available. The following definitions will be used to describe treatment outcome:

Optimal stent result is obtained when both of the following criteria are applicable:

1. Diameter stenosis within the stent ≤ 20% by QCA
2. Mean reference diameter of the stent >1.1 with respect to the reference diameter of the adjacent segments.

6.4 End of procedure

The procedure ends when the guiding catheter has been removed and the patient is off the table. If thereafter the guiding catheter is reinserted and a dilatation is performed, this should be considered a repeat intervention and has to be recorded on the CRF.

6.5 Medication

Pre- and post-procedure medications to be given according to AHA guidelines and dual antiplatelet for post-procedure according to AHA guidelines

6.6 Instructions for return of damaged stents

The damaged stents should be returned to the local distributor.

Damaged stents:

Stents may get damaged because of improper handling before angioplasty.

Before opening, carefully stent delivery system package should be inspected, sterile barrier should be checked for any damages. Prior to using the device, the system should be carefully removed from the package and it should be inspected for bends, kinks, and other damage. Do not use the device if any damage to the packaging is noted.

In case of such damages, the stents are returned back to the factory where stringent inspection is done of the stent and root cause analysis is done.

If it is a case of improper handling at the Cath-lab site then proper instructions are given to the Cath-lab operator to avoid such incidents.

We perform 100% quality check i.e. on each and every stent & records of identification, traceability, and retrievability are maintained for each & every stent at production site.

Damage of Outer Box (Secondary Packing):

Stents are returned back to the factory if the outer box is damaged. The inner pouch is observed as per the in-house developed quality guideline such as any kind of damage to or indication of damage (integrity of seal, mechanical damage, etc.) to the primary packing and if it is found undamaged then they are packed in a new outer box.

Damage of Primary Packing:

If the inner pouch is also damaged or any indication of damage is observed, it is strongly recommended that the stent must not be used. And since drug coated stents are not subjected for re-sterilization, these stents are not used for their intended purpose.

7.0 ENDPOINTS

7.1 Primary endpoints

The primary endpoint of the Registry is defined as Major Adverse Cardiac Events (MACE) at 30 days. MACE rate is defined as the incidence of the combined clinical endpoint: Composite of Death (Cardiac death as well as Non-Cardiac), Myocardial Infarction (Q-wave and non-Q-wave), Emergency **C**oronary **A**rtery **B**ypass **G**raft Surgery, clinically justified TLR within 30 days following index procedure.

7.2 Secondary endpoints

The following secondary effectiveness endpoints will be as follows:

- Angiographic/Device Success (%) (Initial in hospital)
- Procedural Success (%)
- Clinically justified Target Lesion Revascularization (TLR) (%) at 12 months

The following secondary safety endpoints will be assessed:

- MACE (%) until 12 months (Clinically Justified)

- Device related SAEs until 12 months (Clinically Justified)-

1. A history of recurrent angina pectoris presumably related to the target vessel.
2. Objective signs of ischemia at rest (ECG changes) or during exercise test (or its equivalent) presumably related to the target vessel.
3. Abnormal results of any invasive functional diagnostic test (e.g. Doppler flow velocity reserve, fractional flow reserve).

8.0 REGISTRY PROCEDURES

8.1 Time and events schedule

All patients are asked to visit the clinic at 1 month (time window plus or minus 7 days), 6 month (time window plus or minus 15 days) and 12 months (time window plus or minus 30 days) after the procedure. OR they will be followed up by telephone OR by email at 1 month, 6 month, and 12 months. All efforts should be made to complete the required observations as much as possible. If the patient cannot be seen at the visit at 12 months, it is obligated to obtain information concerning possible events by a phone call to the patient or his general practitioner or family. A further extended clinical follow-up will be maintained for all patients at 36 and 60 months via phone call or a personal visit to the clinic if possible.

Figure 1: Investigations and measurements are carried out according to the following Schedule

	In- Hospital					
Event	**Screening**	**Pre**	**Post**	**1 Month**	**6 Months**	**12 Months**
Inclusion/Exclusion Criteria	**X**					
Physical Examination	**X**					
Medical History	**X**					
Anginal Status	**X**		**X**	**X**	**X**	**X**
Laboratory	**X**		**X**	**X**	**X**	**X**
CK/CK-MB/Troponin (optional)	**X**		**X**	**X**	**X**	**X**
Medication Regimen	**X**		**X**	**X**	**X**	**X**
Adverse Event Monitoring			**X**	**X**	**X**	**X**
Angiography		**X**	**X**			
Out of Clinic FUP				**X**	**X**	**X**

(Telephone, Mail, Others)						

- It is recommended that patients come back for a physician office visit at 1, 6-, 12-months post-procedure, but data could also be collected by telephone, mail or the referring cardiologist (including ECG) should a physician office visit not be possible.
- 1 Month follow-up Time Window ± 7 days
- 6 Months follow-up Time Window ± 15 days
- 12 Months follow-up Time Window ± 30 days

8.2 In/exclusion criteria

All general and medical inclusion and exclusion criteria will be screened before the patient enrolls in the registry. A qualifying Angiogram will be used to assess Inclusion and Exclusion criteria related to angiography.

8.3 Medication

Cardiac medications taken will be recorded at screening, at hospital discharge, and at all planned follow-up visits.

9.0 STATISTICAL DESIGN AND ANALYSIS

9.1 Power/size considerations

This is an observational, prospective, Registry. A total of 888 patients will be enrolled.

9.2 Analytical plan

The primary analysis will be performed according to the intention to treat principle.

Descriptive statistics will be performed for all relevant variables. Count variables will be summarised by the count and the percentage. Continuous various variables will be summarised by the mean, standard deviation, minimum and maximum. The event variables, such as MACE, will also be summarized as time-to-event variables and presented using the Kaplan-Meier method. The MACE per patient will be ranked according to the highest category on a scale ranging from (1) death, (2) MI, (3) CABG to (4) TLR.

9.3 Subgroup analysis

No subgroup analyses are planned.

9.4 Reporting

The primary analysis will be performed once the one-month follow-up of all the patient's results has been obtained. A final clinical report will be provided at the end of the registry.

10.0 ADVERSE EVENTS REPORTING

10.1 Definitions

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 undesirable clinical occurrence in a subject that can be attributed to the device, EvroSure Everolimus Drug Eluting CoCr Coronary Stent, procedure or medications required by this protocol (i.e., Aspirin, Clopidogrel Bisulfate [Plavix®], or other antiplatelet medication). The following **Anticipated Events** have been identified as possible complications of stent implantation:

Anticipated Events			
1	Abrupt stent closure	2	Allergic/immunologic reaction to anti-coagulant and/or antithrombotic therapy agents or contrast medium
3	Aneurysm	4	Arrhytmia's (bradycardia, rhythmical disturbances)
5	Arterial perforation	6	Bleeding complications
7	Cardiac tamponade	8	Cardiogenic shock
9	Death	10	Dissection
11	Drug reactions to antiplatelet agents/ anticoagulation agents/contrast medium	12	Emboli (tissue, air or thrombi emboli)
13	Embolization	14	Emergency CABG
15	Entry site complications	16	Fever
17	Fistulization	18	Heart Failure
19	Hemorrhage (hematoma)	20	Hypotension/hypertension
21	Infection (and pain at insertion site)	22	Myocardial infarction
23	Myocardial ischemia	24	Nausea and vomiting
25	Occlusion	26	Palpitations
27	Perforation or rupture	28	Pericardial effusion
29	Prolonged angina	30	Pseudoaneurysm
31	Renal failure	32	Respiratory Failure
33	Restenosis of the stented segment	34	Rupture of native coronary artery
35	Shock/pulmonary oedema	36	Stent compression
37	Stent dislodgment	38	Stent migration
39	Stroke	40	Thrombosis (acute, subacute or late)
41	Unstable Angina Pectoris	42	Vascular complications, which may require

	vessel repair
43 Ventricular fibrillation	44 Vessel spasm

The following **Anticipated Events** have been identified as possible complications of Everolimus coating:

Sl. No	Anticipated Events
1.	Allergic/immunologic reaction to drug or stent coating
2.	Alopecia
3.	Anemia
4.	Blood product transfusion
5.	Gastrointestinal symptoms
6.	Hematologic dyscrasia (including leukopenia, neutropenia, thrombocytopenia)
7.	Hepatic enzyme changes
8.	Histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
9.	Myalgia/Arthralgia
10.	Peripheral neuropathy

The following **Anticipated Events** have been identified as possible complications of the medicine Everolimus:

Anticipated Events	
1. Change in taste	2. Mouth blistering
3. Change in color of the nails	4. Nausea and vomiting
5. Change in normal bowel habits for more than 2 days	6. Pain in the joints of the arms or legs lasting 2-3 days
7. Chest pain	8. Pain redness, or swelling at the injection site
9. Chills	10. Severe exhaustion
11. Cough	12. Shortness of breath
13. Difficulty swallowing	14. Skin rash
15. Dizziness	16. Sore throat
17. Facial flushing	18. Tingling in the hands or toes
19. Fatigue	20. Thinned or brittle hair
21. Fever	22. Unusual bruising or bleeding
23. Loss of appetite	

Unanticipated Adverse Device Effects (ADEs) are defined as adverse effects on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Adverse Event (AE): An adverse event is defined as any undesirable clinical event occurring to a subject, during a clinical Registry, whether or not considered related to the investigational product(s).

Serious Adverse Event (SAE): an adverse event is defined as serious, whenever the adverse event results in the patient's death, is life-threatening, results in permanent or remarkable disability/dysfunction, requires in-patient hospitalization or prolongation of hospitalization, results in fetal death or distress, is a congenital anomaly/birth defect and in cases of cancer/malignancy or required surgical or medical intervention to prevent permanent impairment.

10.0 Reporting of (Serious) Adverse Events

All AEs and SAEs since randomization must be recorded in the CRF and source documents.

All SAEs or unanticipated adverse device effects (ADE) must be reported to Frisch Medical immediately (within 24 hours) by email

10.1 Follow-up of SAEs

All adverse events occurring during the Registry are to be followed up in accordance with good clinical practice until resolved or judged no longer clinically significant, or in case of a chronic condition until fully characterized. All follow-up results are to be reported to Frisch Medical Devices Pvt. Ltd.

11.0 ORGANIZATON

11.1 Sponsor

Sponsor:

Frisch Medical Devices Pvt. Ltd.

89, ACHHAD INDUSTRIAL AREA, ACHHAD, TA-TALASARI, Palghar, Maharashtra (India)- 401606

11.2 Investigator:

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Investigator Agreement

The Investigator agrees to conduct the clinical Registry in compliance with the protocol agreed to by the sponsor. The Investigator and the sponsor should sign the protocol to confirm this agreement.

The investigator agrees not to deviate from or make changes to the protocol without prior knowledge and approval of the sponsor except where necessary to eliminate an immediate hazard to clinical Registry patients. In this event, the Sponsor should be notified as soon as possible. The Investigator should document and explain any deviation or change from the approved protocol.

The Investigator agrees to allow monitoring and auditing of all essential clinical Registry documents by the Frisch Medical and inspection by the appropriate regulatory authorities. Monitoring and auditing visits by Frisch Medical should be scheduled at mutually agreeable times periodically throughout the Registry.

12.2 Monitoring

Trained and qualified personnel from the Sponsor **will** monitor the Registry throughout its duration by means of One personal visit to the Investigator's facilities and by other communication.

- the progress of the Registry~~,~~
- verify whether the reported clinical Registry data are accurate, complete, and verifiable from source documents,
- Whether the protocol and applicable amendments are being followed.

12.3 Record retention

The investigator should maintain the essential clinical Registry documents (including CRFs, source documents, device disposition records, adverse event reports, and other regulatory documents) as required by the applicable regulatory requirements. The investigator should take adequate measures to prevent accidental or premature destruction of these documents.

Essential clinical Registry documents should be retained for a minimum of two years after the last approval of the marketing application, or at least two years after 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.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the Registry records, custody must be transferred to a person who will accept responsibility.

12.4 Publication policy

The Sponsor and Investigators are committed to the publication and widespread dissemination of the results of the Registry. This Registry represents a joint effort between the Sponsor and Investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by Sponsor and Investigators or their personnel and associates resulting from or relating to the Registry must be submitted to the Steering Committee for review and approval prior to submission for publication or presentation.

If any such proposed publication or presentation contains patentable subject matter which in Sponsor's sole discretion, warrants intellectual proprietary protection, Sponsor may delay any publication or presentation for up to thirty (30) days after Steering Committee approval for the purpose of pursuing such protection.

13.0 REFERENCES

1. Sousa JE, Costa MA, Abizaid A, et al. Lack of Neo-intimal Proliferation After Implantation of Everolimus-Coated Stents in Human Coronary Arteries : A Quantitative Coronary Angiography and Three-Dimensional Intravascular Ultrasound Registry. *Circulation* 2001; 103:192-195.
2. Sousa JE, Costa MA, Abizaid AC et al. Sustained Suppression of Neo-intimal Proliferation by Everolimus-Eluting Stents: One-Year Angiographic and Intravascular Ultrasound Follow-Up. *Circulation* 2001; 104:2007-2011.
3. Rensing B, Vos J, Smits P et al. Coronary restenosis elimination with a Everolimus eluting stent. First European human experience with six month angiographic and intravascular ultrasonic follow-up. *Eur Heart J.* 2001; 22: 2125-2130.
4. De Jaegere P, Mudra H, Figulla H et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Registry (MUSIC Registry). *Eur Heart J.* 1998;19: 1214-23.
5. Albiero R, Nishida T, Adamian M et al. Edge restenosis after implantation of high activity (^{32}) P radioactive beta-emitting stents. *Circulation* 2000; 101: 2454-7.
6. Wardeh AJ, Knook AH, Kay IP et al. Clinical and angiographical follow-up after implantation of a 6-12 micro. Ci radioactive stent in patients with coronary artery disease. *Eur Heart J*. 2001; 22: 669-675.
7. Meerkin D, Tardif JC, Crocker IR, et al. Effects of intracoronary beta-radiation therapy after coronary angioplasty: an intravascular ultrasound Registry. *Circulation* 1999; 99: 1660-5.
8. Kay IP, Sabate M, Van Langenhove G et al. Outcome from balloon induced coronary artery dissection after intracoronary beta radiation. *Heart* 2000; 83: 332-7.
9. Kay IP, Sabate M, Costa MA et al. Positive Geometric Vascular Remodeling Is Seen After Catheter-Based Radiation Followed by Conventional Stent Implantation but Not After Radioactive Stent Implantation. *Circulation* 2000; 102: 1434-1439.
10. Sabate M, Serruys PW, van der Giessen WJ et al. Geometric vascular remodeling after balloon angioplasty and beta- radiation therapy: A three-dimensional intravascular ultrasound Registry. *Circulation* 1999; 100: 1182-8.

11. Kozuma K, Costa MA, Sabate M et al. Late Stent Malapposition Occurring After Intracoronary Beta-Irradiation Detected by Intravascular Ultrasound. *J Invasive Cardiol*.1999; 11: 651-655.

12. Waksman R, Bhargava B, Leon MB. Late thrombosis following intracoronary brachytherapy. *Catheter Cardiovasc Interv*. 2000; 49: 344-7.

13. Castagna MT, Mintz GS, Weissman N, Maehara A, Finet G, Waksman R. "Black hole": echolucent restenotic tissue after brachytherapy. *Circulation* 2001; 103: 778.

14. Kay IP, Wardeh AJ, Kozuma K et al. The pattern of restenosis and vascular remodelling after cold-end radioactive stent implantation. *Eur Heart J*. 2001; 22: 1311-7.

15. Morice MC, Serruys PW, Sousa JE et al. Revascularization with a Everolimus eluting versus an uncoated stent in patients with coronary artery disease. The RAVEL Registry. *N Eng J Med.* In press.

16. Rowinsky E K, Donehower R C. Everolimus (taxol). ***N Engl. J Med.*** 1995; 332:1004-1014.

17. Axel D I, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. ***Circulation*** 1994; 96:636-645.

18. Sollott SJ, Cheng L, Pauly RR, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. ***J Clin Invest.*** 1995; 95:1869-1876.

19. Heldman AW, Cheng L, Heller P, et al. Paclitaxel applied directly to stents inhibits neointimal growth without thrombotic complications in a porcine coronary artery model of restenosis. ***Circulation*** 1997; 96: I-288.

20. Kornowski R, Hong MK, Ragheb AO, Bramwell O, Leon MB. Slow Release paclitaxel coated GRII stents reduce neointimal formation in a porcine coronary in-stent restenosis model. ***Circulation*** 1997; 96: I-341.

21. Frab A, Heller PF, Carter AJ, et al. Paclitaxel polymer-coated stents reduce neointima. ***Circulation*** 1997; 96: I-608.

22. Wilensky RL, March KL, Gradus-Pizlo I, Speady AJ, Hathaway DR. Methods and devices for local drug delivery in coronary and peripheral arteries. *Trends Cardiovasc Med.* 1993; 3:163-170

APPENDIX I - DEFINITIONS AND ACRONYMS	
Acute gain	post-procedure minimal lumen diameter (MLD) minus the pre-procedure MLD measured by Quantitative Coronary Angiography (QCA).
ADE (Adverse Device Effect)	Adverse effects on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or IDE application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.
AE (Adverse Event)	Any undesirable clinical event occurring to a subject, during a clinical Registry, whether or not considered related to the investigational product(s).
Angiographic Stent Thrombosis/Occlusion	Angiographic stent thrombosis is defined as the angiographic documentation of either a complete occlusion (TIMI flow 0 or 1) or an angiographic documentation of a flow limiting thrombus (TIMI flow 1or 2). A Subacute Occlusion is defined as occurring after removal of the guiding catheter, before 30 days follow-up.
Angiographic success	Percentage of patients with a successful delivery and deployment of the Registry stent to the target lesion without use of a device outside the Registry treatment strategy and a final diameter stenosis after stenting £20% in the presence of grade 3 TIMI flow.
ASA	Acetylsalicylic acid: Chemical name for aspirin; a drug having antiplatelet, anti-inflammatory, analgesic, and antipyretic effects.
Bleeding complications	Bleeding will be considered major if: 1. it leads to death; 2. it leads to permanent disability; 3. it is clinically suspected or proven to be intracranial (see stroke) 4. it produces a fall in hemoglobin of at least 3 mmol/l; 5. it leads to transfusion of 2 or more units of whole blood of packed cells; 6. Peripheral vascular surgery is necessary. All other bleeding will be considered as minor.
Braunwald classification of unstable angina	**Severity** **Class 1:** 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. **Class 2:** 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. **Class 3:** Angina at rest, acute. Pts with one or more episodes of angina at rest within the

	preceding 48 hours. **Clinical circumstances in which unstable angina occurs:** **Class A:** Secondary unstable angina. Patients in whom unstable angina develops secondary to a clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia. Such conditions reduce myocardial oxygen supply or increase myocardial oxygen demand and include anemia, fever, infection, hypotension, uncontrolled hypertension, tachyarrhythmia, unusual emotional stress, thyrotoxicosis, and hypoxemia secondary to respiratory failure. **Class B:** Primary unstable angina. Patients who develop unstable angina pectoris in the absence of an extra cardiac condition that have intensified ischemia, as in class A. **Class C:** Post infarction unstable angina. Patients who develop unstable angina within the first 2 weeks after a documented acute myocardial infarction
CABG	Coronary Artery Bypass Graft.
CCS (Canadian Cardiovascular Society) classification	**Class I:** Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous, rapid, or prolonged exertion at work or recreation. **Class II:** Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking up hill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress or during the first few hours after awakening may cause pain. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions. **Class III:** Marked limitation of ordinary physical activity. Walking one-two blocks on a level and climbing one flight of stairs at normal pace results in angina. **Class IV:** Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.
Clinical Stent thrombosis	Composite 30 days ischemic endpoint including cardiac death, Q-wave MI or sub abrupt closure requiring revascularization. Stent thrombosis is defined as angiographic thrombus within the stented vessel at the time of the clinically driven angiographic restudy for documented ischemia (chest pain and ECG changes), representing abrupt or sub abrupt closure. Only angiographic stent thrombosis requiring target lesion revascularization during the first 30 days after stent placement was considered as an endpoint for the combined 30-days ischemic endpoint.
De novo lesion	A coronary lesion not previously treated.
Dissection NHLBI classification National Heart Lung and Blood Institute:	A – Intraluminal radiolucent defect B – Extraluminal “cap” (without staining) C – Extraluminal “cap” with persistence of dye (staining) D – Spiral defects E – Persistent filling defect F – Filling defect with total occlusion Note: Types E & F dissections may be caused by thrombus

DS (Diameter Stenosis)	Percent DS – Value calculated as 100 * (1 –(MLD/RVD). A 100 %DS is imputed for total occlusions.
Late loss	Late lumen loss is defined as the difference in minimal lumen diameter (MLD) between post-procedural and follow-up in mm
MACE (Major Adverse Cardiac Events)	Composite of Death (Both Cardiac & Non-Cardiac Death), MI (Q-wave and Non Q-wave), (emergent) CABG or clinically driven Target Lesion Revascularization (TLR).
Major vascular complications	All pseudoaneurysms, vascular access site bleeding associated with a decrease in hemoglobin ³3.0 mmol/L as well as vascular events which required surgical repair or transfusion of > 2 units within 30 days of the procedure.
MI (Myocardial Infarction)	Necrosis of the myocardium, as a result of interruption of the blood supply to the area, as in coronary thrombosis.
MI, non-Q-Wave	Elevation of post-procedure CK levels to >2 times normal with elevated CK-MB in the absence of pathological Q waves. If no assay for CK-MB was performed, elevation of CK levels to >2 times normal without new Q waves is also considered a non-Q-wave MI.
MI, Q-Wave	**MI, Q-Wave** Development of new, pathological Q waves in 2 or more contiguous leads (as assessed by the investigator and confirmed by the Clinical Endpoint Committee) with post-procedure CK-MB levels elevated above normal.
MLD (Minimal Lumen Diameter)	**MLD (Minimal Lumen Diameter)** Mean Minimal Lumen Diameter (mm).
Optimal stent results	1. Diameter stenosis within the stent £20%. 2. Ratio of reference diameter of the stent to the to the reference diameter of the vessel segments proximal and distal to the stented segment > 1.1
Percent in-stent volume obstruction	(Stent volume – lumen volume/stent volume) *100
Procedural success	the stents were deployed successfully without any adverse events or serious adverse events occurring.
Procedure success rate	Percentage of patients with angiographic success and without the occurrence of MACE during the index hospitalization.
QCA (Quantitative Coronary Angiography, off-line)	Off-line refers to assessment at the Angiographic Core Laboratory. The method is a quantitative estimate obtained with a digital angiographic computer utilizing an automatic edge detection algorithm.
RVD (Reference	Interpolated reference diameter

Vessel Diameter)	
SAE (Serious Adverse Event)	An adverse event is defined as serious, whenever the adverse event is fatal, life-threatening, results in persistent or significant disability/incapacity, requires inpatient hospitaliztion or prolongation of hospitalization, results in fetal death or distress, is a congenital anomaly/birth defect and in cases of cancer/malignancy.
Stroke	A focal neurological deficit, resulting from a vascular cause involving the CNS, of sudden onset that is not reversible within 24 hours (including death) and which is not due to a readily identifiable cause (i.e. brain tumor, trauma).
TLR (Target Lesion Revascularization)	Any repeat treatment of the stented segment including 5 mm proximal and 5 mm distal from the edge of the stent.
TVF (Target Vessel Failure)	Cardiac Death, MI (Q-wave and non-Q-wave) or Target Vessel Revascularization (TVR) that could not be clearly attributed to a vessel other than the target vessel.
TVR (Target Vessel Revascularization)	Revascularization of any segment of the index coronary artery, which was in physical contact with any component (guiding catheter, guidewire, balloon catheter, etc.) of the angioplasty hardware during the initial procedure
TWS (Technician's Work Sheet)	Part of the CRF used to specify the details of the angiographic procedure and the angiographic observations