A Prospective Randomized single blind Multicenter Study to Assess the Safety and Effectiveness of the SELUTION SLR* 014 Drug Eluting Balloon in the Treatment of Subjects with In-stent Restenosis

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To demonstrate the safety and efficacy of the SELUTION SLR* 014 DEB for treatment of bare-metal or drug-eluting in-stent restenosis (ISR).

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON54574

Source
ToetsingOnline

Brief title
Selution SLR014 ISR

Condition

- Coronary artery disorders

Synonym
in-stent restenosis, reocclusion of coronary vessels

Research involving
Human

Sponsors and support

Primary sponsor: MedAlliance LLC
Source(s) of monetary or material Support: Industry: Med Alliance LLC

Intervention

Keyword: cardiovascular, drug-coated balloon, in-stent restenosis

Outcome measures

Primary outcome

The primary endpoint for effectiveness is TLF rate at 12 months post-index procedure. TLF is defined as all cardiac death, target vessel myocardial infarction (SCAI definition), or clinically driven TLR.

Secondary outcome

Powered: Follow-up in-segment minimum lumen diameter (MLD) at 12 months (angiographic follow-up subset).

Other:

Secondary endpoints will include:

• Device success

• Lesion success

• Procedure success

The following secondary clinical endpoints will be evaluated prior to discharge, at 1, 6 and 12 months and annually thereafter through 5 years follow-up:

• Composite safety endpoint: defined as any death, any MI (SCAI), or any repeat

revascularization.

• All-cause mortality

• Cardiovascular mortality

• MI (SCAI, UDMI 3/4, ARC2)

• TLR

• Target vessel revascularization (TVR)

• Target vessel failure (TVF), defined as composite of cardiac death, MI, or TVR.

• Stent thrombosis (ST, Academic Research Consortium [ARC] definite or probable)

• Bleeding (Bleeding Academic Research Consortium [BARC] classification)

• Patient- oriented composite defined as any death, any MI, or any repeat revascularization

• Net adverse clinical events defined as Death, MI, TVR, ST, or Bleeding (BARC 2-5)

The following secondary angiographic and imaging endpoints will be evaluated in the designated subsets.

• Binary angiographic restenosis

• In-stent percent diameter stenosis

• In-segment percent diameter stenosis

• In-stent late loss

• In-stent MLD

• OCT assessment of neointimal hyperplasia, neo-atherosclerosis, and stent

malapposition at 12-13 months (OCT subset)

Study description

Background summary

In-stent restenosis (ISR) is a key measure of success in percutaneous coronary intervention (PCI) and remains a widespread therapeutic challenge.
Bare-metal stents (BMS) improved procedural results and reduced restenosis compared with balloon angioplasty (BA), but a requirement for repeat target lesion revascularization remained in range of 15-20% due to neointimal hyperplasia.
the use of Drug-eluting stents (DES) resulted in a highly significant 50-75% decrease in restenosis rates due to near elimination of neointima, however leading to late stent thrombosis due to ongoing inflammation and absent or delayed healing, lading to required prolonged dual antiplatelet therapy (DAPT) and ongoing risk of restenosis.
Target Lesion Revascularization is still necessary for about 4% of patients by one year after stenting.

Treatment with DES for in-stent restenosis creates layers of stens give risk of uncertain healing, thrombosis, recurrent ISR and bleeding complications due to dual antiplatelet therapy. Therefore drug-coated balloons (DCB) have re-emerged as therapy for ISR.
DCB allow patients to avoid additional stent layers and to minimize the use of DAPT while providing a superior treatment result to current BA.

Sirolimus is able to stop cell growth without killing the cells that line the blood vessels. Paclitaxel is more toxic to cells lining the blood vessels, particularly in higher doses, and it can kill some of these cells. Sirolimus is therefore considered a safer alternative to paclitaxel.

Study objective

To demonstrate the safety and efficacy of the SELUTION SLR* 014 DEB for treatment of bare-metal or drug-eluting in-stent restenosis (ISR).

Study design

Prospective, multi-center, single blind, randomized, controlled, noninferiority clinical trial.

Subjects with previous bare-metal or drug-eluting coronary stent and qualifying evidence for ISR will be screened per the protocol inclusion

and exclusion criteria to achieve a maximum of 418 randomized subjects (includes 5% allowance for loss to follow-up). Eligible subjects will be randomized 1:1 to treatment with either the SELUTION SLR* DEB or SOC to include contemporary DES (zotarolimus-eluting stents and everolimus-eluting stents only) or non-DEB BA. A maximum of 20% of patients randomized to SOC will be treated with BA.
This is a single blind trial, meaning that the patient but not the treating clinician will be blinded to the treatment given after randomization. The patient will remain blinded until they reach primary endpoint at 12 months and all protocol mandated assessments have been completed.

Intervention

Subject preparation and percutaneous access should be performed according to standard hospital.
After confirming all clinical and target lesion inclusion and exclusion criteria, pre-dilatation may be performed: a visually estimated residual diameter stenosis < 30% must be achieved prior to randomization. IVUS and/or OCT will be performed in all subjects after determining angiographic eligibility and prior to randomization.
Prior to randomization the SOC treatment choice must be declared; either DES or BA. If subject is randomized in the control group, they will be treated with the pre-declared treatment: DES (otarolimus-eluting stent or an everolimus-eluting stent) or BA.
If the subject is randomized in the study group, they will be treated with the study SELUTION SLR* DEB.

Study burden and risks

The risks of the PTCA procedure are the same as for the study device group or the standard of care
group.

The potential risks related to conducting PTCA procedures for the treatment of coronary artery lesions include, but are not limited to the following:
• Allergic reaction to contrast medium, anticoagulants, and antiplatelets
• Aneurysm or pseudoaneurysm
• Arrhythmias
• Arteriovenous (AV) fistula
• Death
• Embolization
• Fever
• Hematoma
• Hemorrhage, incl. bleeding at puncture site
• Hypotension/hypertension
• Increased Procedure Time/Additional Interventions

• Ineffective Anti*Restenotic Therapy
• Inflammation
• Ischemic Heart Disease
• Myocardial Infarction
• Occlusion
• Pain or tenderness
• Hemothorax
• Renal failure
• Sepsis/infection
• Shock
• Stroke
• Thrombosis
• Vessel dissection, occlusion, perforation, recoil, restenosis, rupture, or spasm

Potential adverse events that may be unique to the SELUTION SLR* PTCA DEB Sirolimus drug coating or the active pharmaceutical ingredient (sirolimus) include, but are not limited to:
• Abnormal liver function tests
• Anemia
• Arthralgias
• Diarrhea
• Hypercholesterolemia
• Hypersensitivity, including anaphylactic/anaphylactoid type reactions
• Hypertriglyceridemia
• Hypokalemia
• Interstitial lung disease
• Leukopenia
• Lymphoma and other malignancies
• Thrombocytopenia
The potential adverse events listed above are related to the oral administration of Sirolimus at significantly higher doses than what would be delivered by the SELUTION SLR* PTCA DEB locally to the vessel wall. Therefore, due to the local administration and low dosage, these pharmacological interactions are deemed possible but unlikely.

The first 60 patients who consent to participate in the imaging sub cohort will receive angiography and OCT at 12-month follow-up.
The total exposure as a result of these imaging studies is approximately 4.4 mSv. In comparison: the background
radiation in the Netherlands is ~2.5 mSv, per year. Cumulative exposure to radiation can increase your risk of
developing certain types of cancer in the future. The estimated additional risk of cancer is 1 in 9,000 for these
additional procedures.

Contacts

Public
MedAlliance LLC

Jenner 4, Suite 180/190
Irvine CA 92618
US
Scientific
MedAlliance LLC

Jenner 4, Suite 180/190
Irvine CA 92618
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects must meet all of the following clinical criteria to participate in the trial:
1. Subject age is >= 18 years or minimum legal age as required by local regulations.
2. Female subjects of childbearing potential have a negative pregnancy test <= 7 days before
the procedure.
3. Subject presents with chronic coronary syndrome (CCS) (manifest as documented angina or positive functional testing), unstable angina or stabilized non-ST elevation MI (NSTEMI) (biomarkers stabilized or down trending) with an indication for PCI and planned intervention.
4. Subject is eligible for DAPT treatment with aspirin plus either,

Clopidogrel, Prasugrel, or Ticagrelor. Note: Subjects who require continued oral anticoagulant therapy may omit aspirin at discretion of investigator.
5. Life expectancy > 1 year in opinion of investigator.
6. Subject is willing and able to provide informed consent and comply with study procedures and required follow-up evaluations.

Subjects must meet all the following imaging criteria to participate in the trial:
1. Target lesion is within a native coronary artery or major branch.
2. Target lesion is within a previously placed BMS or DES and does not extend further than 5 mm beyond either the proximal or distal edge of the stent.
3. Up to two (2) non-target lesions in non-target vessels may be treated, but successful PCI of the non-target lesions must be completed before treatment of the target lesion. Successful treatment is defined as no greater than 30% residual stenosis by visual estimate, no dissection greater than National Heart, Lung, Blood Institute (NHLBI) type C, and Thrombolysis in Myocardial Infarction (TIMI) grade flow in the non-target lesion > 2.
4. Target lesion is < 26 mm in length.
5. Target lesion has diameter stenosis > 50% and <= 99% by visual estimate.
6. RVD is >= 2.00 mm and <= 4.50 mm.
7. Target lesion must be successfully pre-dilated/pre-treated. Note: Successful pre-dilation/pre-treatment is defined as dilation or pre-treatment that achieves stent expansion of approximately 80% of the distal RVD (at the discretion of the investigator) based on intravascular ultrasound (IVUS)/optical coherence tomography (OCT) and no greater than 30% residual stenosis by visual estimate and no dissection greater than NHLBI type C. TIMI grade flow in the target lesion must be > 2. Note: Atherectomy and cutting balloon are permitted for pre-treatment.

Exclusion criteria

Clinical exclusion criteria:

1.Known hypersensitivity or allergy to Sirolimus or other pharmacologic agents required for the procedure.
2. STEMI within 30 days.
3. Planned treatment of additional lesions in the target vessel, or more than two (2) non-target lesions within non-target vessels, during the index procedure.
4. Target lesion is located within a bifurcation with planned treatment of side branch vessel.
5. Target lesion is the more than 3rd or greater stent failure (i.e., more than two [2] layers of
stent are present at any segment of the target lesion).
6. Target vessel had any previous vascular brachytherapy treatment or is

planned to undergo brachytherapy at index procedure.
7. Previous PCI of the target vessel within 30 days.
8. Planned PCI of a non-target vessel, or a non-target lesion in the target vessel, within 30 days of randomization.
9. Subject has chronic renal insufficiency (dialysis dependent, or glomerular filtration rate [GFR] <= 30 ml/min/1.73 m2 within 30 days of index procedure) or has undergone renal transplantation.
10. Subject has acute renal insufficiency confirmed by 50% increase of serum creatinine within 48 hours before procedure and/or decrease in urine output.
11. History of active peptic ulcer or gastrointestinal bleeding within prior 6 months or other inability to comply with the recommended duration of DAPT.
12. Subject is pregnant, breast-feeding, or a woman of childbearing potential who is not using appropriate contraceptives to avoid becoming pregnant.
13. Documented left ventricular ejection fraction (LVEF) < 25%.
14. Currently participating in another investigational drug or device study that has not completed primary endpoint follow-up.

Imaging exclusion criteria:
1. Target lesion is total occlusion or has evidence of thrombus.
2. Target lesion involves an unprotected left main.
3. Target lesion has > 30% residual stenosis by visual estimate or dissection greater than NHLBI type C after pre-dilation/pre-treatment.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-03-2021
Enrollment:	40

Type:	Actual

Medical products/devices used

Generic name:	SELUTION Sustained Limus Release (SLR)TM 014 Drug-Eluting Balloon (DEB)
Registration:	No

Ethics review

Approved WMO Date:	17-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2023
Application type:	Amendment

Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	17-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	10-01-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	23-08-2024

Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04280029
CCMO	NL71862.018.19