



SELUTION SLR™ 014 ISR:

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

Clinical Study Protocol Number: SEL-003-2019

Version 08

07 July 2023

NCT Number: NCT04280029

Study Sponsor:

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Sponsor Signature Page

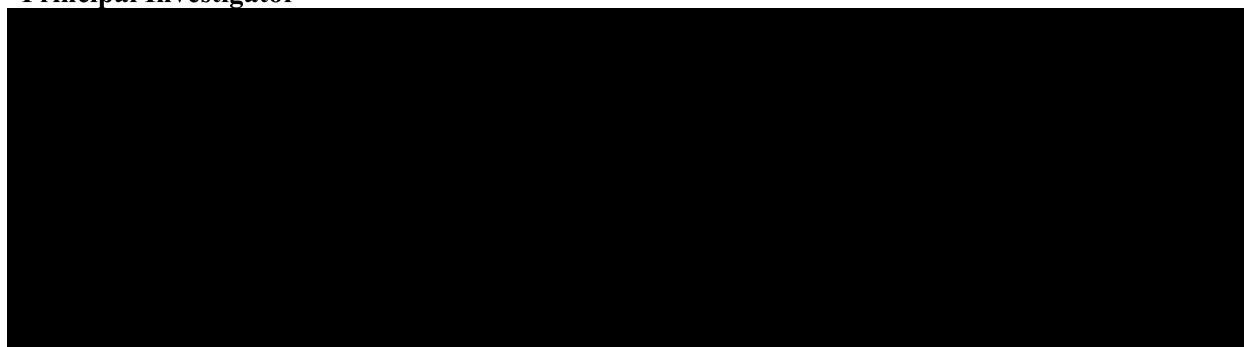
Study Title: SELUTION SLR™ 014 ISR:
A Prospective Randomized Single Blind Multicenter Study to Assess
the Safety and Effectiveness of the SELUTION SLR™ 014 Drug
Eluting Balloon in the Treatment of Subjects with In-stent Restenosis

Short Title: SELUTION SLR 014 ISR

CIP No: SEL-003-2019

CIP Version and Date: Version 08, 07 July 2023

Principal Investigator



Investigator Signature Page

Protocol No. [SEL-003-2019]

I have reviewed this protocol for the study entitled:

<p style="text-align: center;">SELUTION SLR™ 014 ISR:</p> <p style="text-align: center;">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</p>
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I agree to conduct this study according to the requirements described in the protocol, the principles of GCP and ISO 14155.

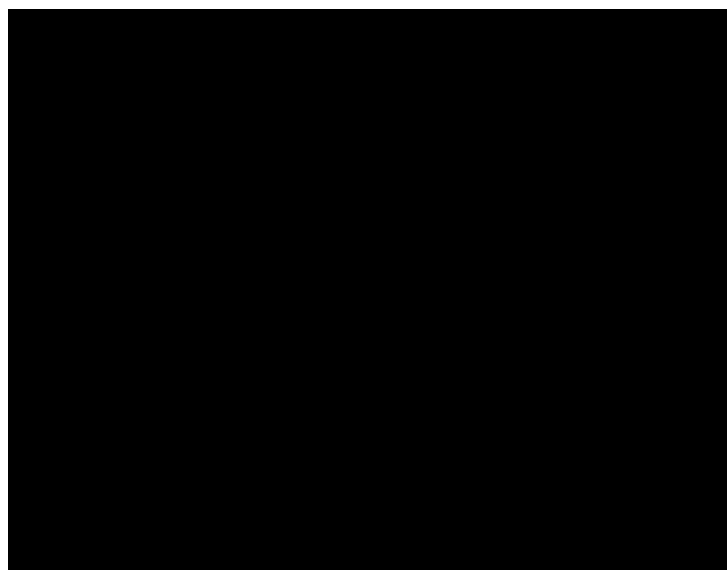
Investigator Name (print or type):

Investigator's Signature:

Date:

Site Number:

Site Address:



CIP Revision History

Version no.	Version Date	Section amended	Description of amendment	Justification/Explanation for amendment
01	07 Dec 2019	-	First release	-
02	31 Dec 2019	3.3	Remove Orsiro stent from control device list	Stent is not an EES or ZES stent
		6.1.2	Updated angiographic exclusion criteria to include pre-dilation criteria	Previously referenced in the body of the protocol but not included in the exclusion criteria
		7.4.1	No guidewire in angio imaging fields	Clarification of procedures to avoid imaging artifact
		7.4.5	Clarification of DEB inflation guidelines and clarification of stent procedures	Clarification of procedures
		7.4.6	End of procedure OCT required for OCT sub-group	Clarification of procedure
		7.7.7	SELUTION patients requiring revascularization should receive DES	Clarification of procedures
		8.3.4	Sub-analysis added based on lesion length and lesion diameter	Additional planned analysis added
		13	Added section describing CIP amendment procedures	Clarification of administrative procedures for CIP amendments
		15	Added section specifying end of study procedures	Clarification of administrative procedures for ending the study
		Figure 3	Updated to clearer format	Clearer presentation of information
		Figure 4	Updated to clearer format	Clearer presentation of information
		Synopsis	Updated per above changes	updated to align with protocol changes
03	14 Mar 2020	1- synopsis	Approx. 50% of patients recruited in US. Other updates to reflect changes in the main body of the protocol	Clarification – detail contained in main body of protocol
		2 - Admin	Updated SAE e-mail address	Typo correction
		3.2	Removed incorrect address	Typo correction
		3.2.4	Device training at SIV	Clarified timing of device training
		4.4	Patient oriented composite	Included in synopsis, but missing from main body of protocol
		5 – study design, and multiple other locations	Added single blinding	Per FDA request
		7.1	Angio requirements for patients requiring early reintervention	Updated Table 2 to reflect wording in the text of the protocol
		7.4.5	Remove use of SELUTION SLR to treat dissection or residual stenosis	Per FDA request
		7.7.4	Device related AE follow-up	Clarified follow-up requirements
		8.1 Sample size determination and multiple other locations	Sample size calculation update to include additional test of non-inferiority for DES vs DEB	Per FDA request
		8.3.2	Sequential testing of powered secondary endpoint and superiority of primary endpoint	Clarification

Version no.	Version Date	Section amended	Description of amendment	Justification/Explanation for amendment
04	24 JUL 20	8.5	Added additional sub-analysis: DEB vs POBA, DEB vs DES, 2 stent layers ISR vs 1 stent ISR, Focal vs Diffuse lesion, ISR<1yr vs ISR>1yr	DEB vs POBA, DEB vs DES, 2 stent layers ISR vs 1 stent ISR, – FDA request Focal vs Diffuse lesion, ISR<1yr vs ISR>1yr – Sponsor addition
		App B	TLR typo correction	Typographic error correction
		1- synopsis	Updated with changes below	Updated to match main body of protocol
		3.2	Figure 1 updated with new image Removed 40mm long devices	40mm long devices removed due to restriction in treated lesion length
		3.4	Lesion lengths restricted to 26mm.	More focused trial patient population.
		5 – Study design	Lesion lengths restricted to 26mm and within stent only. IVUS/OCT required pre-procedure for sizing. Pre-dilation 1.1-1.2 times RVD.	More focused trial patient population. Amended procedure details to match best practice for DEB.
		6.1.1.2	Angiographic inclusion updated to restrict lesion length to <26mm and within stent only	More focused trial patient population
		7.4.1	OCT/IVUS required for sizing	Changed from recommendation to requirement
		7.4.2	Pre-dilation 1.1-1.2 times RVD	Correction of required predilation for DEB
		7.4.5	No use of IVUS/OCT after DEB treatment	Potential for IVUS/OCT to damage DEB coating on the vessel wall
		7.4.6	No use of IVUS/OCT after DEB treatment	Potential for IVUS/OCT to damage DEB coating on the vessel wall
		7.1, 7.2.1, 7.7, 8.5	COVID-19 status and sub-analysis added	COVID-19 patient status and sub-analysis added due to viral pandemic
		8.1	Analysis will be conducted on both PP and ITT populations for both DEB vs SOC and DEB vs DES	Clarification
		8.2	PP definition to include only patients that satisfy inclusion/exclusion criteria	Clarification
05	11 SEP 20	Table 2, 6, 7, 9 Sections 7.4.6, 9.1.7, 9.4, 9.5	Clarification of reporting requirements in EU	EU reporting requirements were not clear
		12.1	Alignment of identified risks with IB data	Discrepancy between CIP and IB risks
06	13 MAY 2021	Sections 9.1.3., 9.3., 15	SAE definition, relatedness, and reporting requirements to be compliant with EU MDR 2017/745	New EU Medical Device Regulation (EU MDR 2017/745)
		Section 2	Study Administration	Updated to reflect new Sponsor contacts and to add EU Representative per New EU Medical Device Regulation
		Protocol Synopsis and Section 6.1.1.2	Imaging Inclusion Criteria Update	Imaging Inclusion Criteria updated to include target lesions within a previously placed BMS or DES that do not extend to outside 5mm of

Version no.	Version Date	Section amended	Description of amendment	Justification/Explanation for amendment
				either the proximal or distal edge of the stent.
		Section2- and multiple other locations	CRO name and contact information changed	CRO Name and contact information updated from Genae to IQVIA MedTech
		Figure 3, Figure 4	418 patients randomized, remove post-procedure imaging in OCT subgroup	Typo correction
07	03 AUG 2021	Figure 3	Location of text boxes in flow chart figure corrected	Formatting correction
		Table 6, 7	UADEs/USADEs and SAE definition and reporting timeframe updated.	Updated to be in compliance with new EU Medical Device Regulation (EU MDR 2017/745).
08	07 July 2023	1	Revised for consistency with changes to body of the protocol.	Revised based on FDA Study Design Considerations, with additional editorial and administrative updates.
		2	Study contacts updated	Administrative update
		3.4	Clarified that DES in control group are FDA-approved -limus eluting stents	Editorial clarification
		3.5	Indications for use and contraindications revised to match current IFU	Administrative update
		4.2	Clarified that periprocedural MI will be adjudicated according to both SCAI (primary) and ARC 2 (additional) definitions. Spontaneous MI will be adjudicated using 4th Universal Definition of Myocardial Infarction	Revised based on US FDA recommendation
		4.3	Hypothesis-driven secondary endpoint revised to TLF at 12 months in DEB vs. DES among subjects with one previous layer of stent; MLD endpoint moved to exploratory endpoints.	Revised based on discussions with US FDA; the revised design is expected to provide a clinically relevant additional evaluation of DEB safety and efficacy to inform interpretation of the primary study results.
		4.4	Minor clarifications and additions to secondary exploratory endpoints. Bleeding data collection limited to clinically significant bleeds (BARC 2-5) to 12 months only.	Improved clarity and expanded endpoint reporting.
		4.5	Added reporting of cardiac biomarker elevations by various thresholds.	Additional reporting per US FDA recommendation.
		5	Imaging substudy design changed from 120 angiographic (with 60 subject OCT subset) to 60 total subjects undergoing both angiographic and OCT at baseline and follow-up. Additional minor changes for consistency.	Minimizes the number of subjects required to undergo additional imaging while ensuring adequate imaging data to guide interpretation of primary study results.
		5.1	Number of clinical sites increased from up to 60 to up to 80; Canada and Brazil regions added.	Recruitment of additional clinical sites will accelerate availability of study results.

Version no.	Version Date	Section amended	Description of amendment	Justification/Explanation for amendment
		5.2	Enrollment cap per site set at 15% of total randomized cohort.	Revised based on US FDA recommendation
		5.3.1	Added status definition for imaging substudy subjects.	Administrative update
		6	Clarified requirements for pre-randomization imaging and point of enrolment for imaging substudy cohort.	Editorial clarification
		6.1.1.1	Revised Clinical Inclusion Criteria: <ul style="list-style-type: none"> IC #3 – Clarified that NSTEMI subjects must be stabilized and that subjects must have an indication for PCI and planned intervention IC #4 (DAPT) – Added note to clarify that subjects who require continued oral anticoagulant therapy may omit aspirin at discretion of investigator 	The changes will improve the consistency of the application of study eligibility criteria.
		6.1.1.2	Revised Imaging Inclusion Criteria: <ul style="list-style-type: none"> IC #3 (non-target lesions) – Expanded to define successful treatment. IC #7 – Added to define requirement for successful target lesion pre-treatment. 	The changes will improve the consistency of the application of study eligibility criteria.
		6.1.2.1	Revised Clinical Exclusion Criteria: <ul style="list-style-type: none"> EC #4 – Clarified that bifurcation exclusion applies to those for which side branch treatment is planned EC #6 – Added planned target vessel brachytherapy at index procedure to exclusion EC # 9-10 – Added exclusions for acute or chronic renal insufficiency 	Improved consistency of eligibility criteria, reduced confounding by pre-existing renal disease and improved safety for imaging subgroup.
		6.1.2.2	Revised Imaging Exclusion Criteria to exclude unprotected left main but allow severely calcified lesions.	Revised for consistency with clinical practice.
		Fig 4.	Revised to better depict procedural flow and to reflect changes in imaging substudy	Administrative update, consistency.
		7.1	6-month and 2-, 3-, 4-, and 5-year follow up visit modalities revised to telephone contact (with optional clinic visit)	Improved follow-up compliance while maintaining clinic visits for full ascertainment at the critical time points of 30 days and 1 year.
		7.4.2	Atherectomy permitted for target lesion pre-treatment.	Revised to reflect standard of care, pre-treatment occurs prior to randomization.
		7.5.2	Cardiac biomarkers revised to specify that CKMB or Troponin T are preferred, and Troponin I is not accepted.	Revised based on US FDA recommendation.

Version no.	Version Date	Section amended	Description of amendment	Justification/Explanation for amendment
			Post-procedure biomarker timing window expanded from 6-12 to 4-24 hours.	Timing update to improve compliance and assessment of peri-procedural MI
		7.7	Added that absence of COVID-19 status will not be considered a protocol deviation.	COVID testing is performed only per SOC, but status will be collected if known.
		8	Statistical hypotheses revised to reflect modified secondary hypothesis-driven endpoint. Additional details of statistical methods provided and additional prespecified subgroup analyses added.	Revised based on US FDA recommendations
		9.4	Updated contacts for AE reporting.	Administrative update.
		11.18	Added Medicare Population Statement	US reimbursement requirement.
		12.1	Potential risks revised to match current IFU.	Administrative update, consistency.
		App. B	Specified that biomarker elevations will be adjudicated according to manufacturer-defined URL rather than site-specific ULNs	Revised based on US FDA recommendation

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1 Protocol Synopsis

STUDY TITLE	SELUTION SLR™ 014 ISR: 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																																																											
DEVICE DESCRIPTION	SELUTION Sustained Limus Release (SLR) 014 Drug-Eluting Balloon (DEB) <table><tr><td></td><td colspan="9">Balloon diameter (mm)</td></tr><tr><td>Balloon Length</td><td>2.00</td><td>2.25</td><td>2.50</td><td>2.75</td><td>3.00</td><td>3.25</td><td>3.50</td><td>4.00</td><td>4.50</td></tr><tr><td>15 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr><tr><td>20 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr><tr><td>30 mm</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr></table>											Balloon diameter (mm)									Balloon Length	2.00	2.25	2.50	2.75	3.00	3.25	3.50	4.00	4.50	15 mm	X	X	X	X	X	X	X	X	X	20 mm	X	X	X	X	X	X	X	X	X	30 mm	X	X	X	X	X	X	X	X	X
	Balloon diameter (mm)																																																											
Balloon Length	2.00	2.25	2.50	2.75	3.00	3.25	3.50	4.00	4.50																																																			
15 mm	X	X	X	X	X	X	X	X	X																																																			
20 mm	X	X	X	X	X	X	X	X	X																																																			
30 mm	X	X	X	X	X	X	X	X	X																																																			
COMPARATOR DEVICE	A standard of care (SOC) control group using contemporary drug eluting stent (DES) or non-DEB balloon angioplasty (BA).																																																											
OBJECTIVES	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	<p>Prospective, multi-center, randomized, single blind, controlled, noninferiority clinical trial will enroll up to 418 randomized subjects (including up to 60 subjects in an angiographic and optical coherence tomography [OCT] sub-study) at up to 80 sites in the United States (US), Canada, Brazil, and Europe (EU). A minimum of 50% of the subjects will be enrolled in the US.</p> <p>Subjects with previous bare-metal stent (BMS) or DES and qualifying evidence for ISR will be screened per the protocol inclusion and exclusion criteria. Eligible subjects will be randomized 1:1 to treatment with either the SELUTION SLR 014 DEB or SOC to include contemporary DES (zotarolimus-eluting stents [ZES] and everolimus-eluting stents [EES] only) or BA. A maximum of 20% of patients randomized to SOC will be treated with BA.</p> <p>Randomization will be stratified by DES or BMS ISR and whether there are currently 1 (first stent restenosis) or 2 (second stent restenosis) implanted stent layers at the target lesion. Subjects with more than 2 previous stent layers (3rd or greater stent restenosis) involving the target lesion will be excluded.</p>																																																											

The primary endpoint will be Target Lesion Failure (TLF) at 12-months in the SOC group vs. the SELUTION SLR 014 DEB group.

After initial randomized treatment, subjects in the SOC group may receive DEB (including SELUTION SLR 014 DEB) treatment for recurrent restenosis requiring a repeat target lesion revascularization (TLR) (i.e., after the study primary endpoint has been met). Patients in the SELUTION SLR 014 DEB group who require revascularization should receive a commercially available DES as the preferred treatment choice. However, BA treatment is an acceptable alternative if clinically justified.

A subset of up to 60 subjects will be enrolled in the angiographic and OCT substudy and undergo planned angiographic and OCT follow-up within 30 days after completion of the 12-month primary endpoint clinical follow-up/assessment.

BLINDING	<p>This randomized trial is a single-blind study. The physician performing the index procedure as well as study site personnel present at the index procedure will not be blinded; however, every effort will be made to maintain blinding for the following:</p> <ul style="list-style-type: none">• Subjects and their families• Site personnel involved in conducting study assessments during follow-up• The Clinical Events Committee (CEC) will be blinded to the treatment arm during the adjudication process. <p>Unblinding will only occur to protect subject rights, welfare, or well-being.</p>
SUBJECT POPULATIONS	<p>Patients with cardiovascular disease who have BMS or DES ISR involving a native coronary artery with reference vessel diameter (RVD) of 2.00-4.50 mm and lesion length < 26 mm associated with clinical symptoms or functional evidence of myocardial ischemia.</p>
NUMBER OF SUBJECTS AND SITES	<p>Accounting for an assumed 5% loss to follow up, up to 418 subjects will be randomized in the study. Enrollment will occur at up to 80 sites across the US, Canada, Brazil, and Europe. Enrollment per site is limited to a maximum of 63 randomized subjects (~15% of the total randomized subjects). Approximately 50% of subjects will be recruited in the US.</p>
CLINICAL INCLUSION CRITERIA	<p>Subjects must meet all of the following criteria to participate in the trial:</p> <ol style="list-style-type: none">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 myocardial infarction (NSTEMI) (biomarkers stabilized or down trending) with an indication for percutaneous coronary intervention (PCI) and planned intervention.
4. Subject is eligible for dual antiplatelet therapy (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.

**IMAGING
INCLUSION
CRITERIA**

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 $\leq 99\%$ by visual estimate.
6. Reference vessel diameter (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.

**CLINICAL
EXCLUSION
CRITERIA**

1. Known hypersensitivity or allergy to Sirolimus or other pharmacologic agents required for the procedure.
2. ST-elevation myocardial infarction (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 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 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 a 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.

**POINT OF
RANDOMIZATION**

Subjects will undergo randomization after Informed Consent is signed, all clinical and angiographic inclusion and exclusion criteria are met, any non-target lesion(s) have been treated successfully with commercially approved devices, and the target lesion has been successfully pre-treated.

**PRIMARY
ENDPOINT**

The primary safety and efficacy endpoint is TLF at 12 months post-index procedure for SELUTION SLR 014 DEB versus SOC in all

patients. TLF is defined as all cardiac death, target vessel myocardial infarction (MI) or clinically driven TLR.

MI includes spontaneous (Type 1) MI using the 4th Universal Definition of Myocardial Infarction (UDMI) and peri-procedural MI using the Society for Cardiac Angiography and Intervention (SCAI) definition.

**HYPOTHESIS-
DRIVEN
SECONDARY
ENDPOINT**

If the primary endpoint is met, the following secondary endpoint will be tested in a sequential manner for non-inferiority:

- TLF at 12 months post-index procedure for SELUTION SLR 014 DEB versus DES among subjects with one previous layer of stent.

**OTHER
SECONDARY
ENDPOINTS**

Secondary Clinical Endpoints

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 the patient-oriented composite of any death, any MI (spontaneous or peri-procedural), or any repeat revascularization.
- All-cause mortality
- Cardiovascular mortality
- MI (spontaneous MI using the 4th UDMI; peri-procedural MI using SCAI, Academic Research Consortium [ARC]-2 definitions)
- Clinically driven TLR, all TLR
- Clinically driven Target Vessel Revascularization (TVR), all TVR, non-TVR
- TLF defined as all cardiac death, target vessel MI or clinically driven TLR.
- Target vessel failure (TVF), defined as cardiovascular death, target vessel MI (spontaneous or peri-procedural) and clinically driven TVR
- Stent thrombosis (definite or probable) according to the ARC criteria, subclassified as acute, subacute, late, very late, and cumulative stent thrombosis
- Bleeding according to Bleeding Academic Research Consortium (BARC) Classification 2 to 5 (assessed to 12 months)
- Net adverse clinical events, defined as death, MI (spontaneous or peri-procedural), TVR, stent/target lesion segment thrombosis, or bleeding (BARC types 2-5) (assessed to 12 months)

Secondary Performance Endpoints

The following secondary performance endpoints will be evaluated concluding the index procedure:

- Device success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study device only.
- Lesion success, defined as attainment of < 30% residual stenosis of target lesion using any percutaneous method.
- Procedure success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study device only without the occurrence of in-hospital major adverse cardiac events (MACE), a composite of all-cause death, MI or clinically driven TLR.

Secondary Imaging Endpoints

The following secondary endpoints will be evaluated at 12 months in the angiographic and OCT sub-study subjects only:

- Binary angiographic restenosis
- In-stent percent diameter stenosis
- In-segment percent diameter stenosis
- In-stent late lumen loss (LLL)
- In-segment LLL
- In-stent minimum lumen diameter (MLD)
- In-segment MLD
- OCT assessment of neointimal hyperplasia, neo-atherosclerosis, and stent malapposition

OTHER MEASURES

Exploratory Cardiac Biomarker Analysis

The study will provide detailed analyses of site reported peri-procedural cardiac biomarker elevations including creatine kinase-muscle/brain (CKMB) and troponin T. Troponin I will not be permitted. Biomarkers will be summarized by type and the following thresholds: ≥ 1 ; ≥ 5 ; ≥ 10 ; ≥ 35 ; ≥ 70 ; ≥ 100 ; ≥ 250 .

SUBJECT

FOLLOW-UP

Randomized subjects will be followed through 5 years post-index procedure, with clinical follow-up at 1 month, 6 months, 12 months, and annually thereafter through 5 years. Clinic visits are required at 1 month and 12 months. Six-month follow-up and annual follow-visits at 2 to 5 years may be conducted by phone call or optional clinic visit.

Subjects in the imaging substudy will undergo angiographic and OCT follow-up at approximately 12 months post-procedure (after the 12-month clinical follow-up has been completed).

**TREATMENT
STRATEGY**

- Pre-dilation/pre-treatment to achieve residual stenosis < 30% by visual estimate is required prior to randomization.
- IVUS or OCT assessment is required prior to delivery of randomized treatment with stent expansion of approximately 80% of the distal RVD based upon investigator assessment.
- Pre-dilation/pre-treatment can include use of cutting or scoring balloons, atherectomy, and non-compliant balloons sized 1.1-1.2 times RVD to optimize results.
- For subjects randomized to the SELUTION SLR 014 DEB group:

After appropriate pre-dilation/pre-treatment, a SELUTION SLR 014 DEB with balloon diameter 1.0-1.1 times the RVD and a length 2.00 mm greater than target lesion length should be inflated to nominal pressure for 60 seconds.
- For subjects randomized to the control group (SOC):

The operator may choose to implant a commercially available DES (EES or ZES), or they may leave the BA result rather than implant an additional layer of stent. It is expected that patients with one prior stent will receive DES and patients with two prior stents will receive BA.
- In either treatment group, bailout stenting using a commercially approved DES is recommended for residual stenosis > 50% or angiographic complications that may be flow limiting (e.g., dissections greater than NHLBI grade C).
- At least one (1) blood sample will be obtained for CKMB or troponin T (Troponin I is not accepted) 4-24 hours after the procedure. If the value is elevated, then additional samples should be obtained until the peak level has been determined.

**ANTIPLATELET
AND
ANTICOAGULANT
THERAPY**

Subjects will be prescribed anti-platelet therapy as follows:

- SELUTION SLR 014 DEB group: Aspirin minimum 75 mg daily indefinitely plus P2Y12 inhibitor for minimum 1 month.
- Control group (SOC):
 - For DES subjects, aspirin minimum 75 mg daily indefinitely plus P2Y12 inhibitor for minimum 6 months (3 months or in accordance with local guidelines if high bleeding risk).
 - For BA patients, aspirin minimum 75 mg daily indefinitely plus P2Y12 inhibitor for minimum 1 month.

For subjects with requirement for uninterrupted oral anticoagulation therapy, aspirin may be omitted during the minimum period of P2Y12 inhibitor requirement.

**STATISTICAL
CONSIDERATIONS**

The proposed investigational device exemption (IDE) study will assess noninferiority of the 12-month TLF rate in subjects treated with the SELUTION SLR 014 DEB versus the 12-month TLF rate in subjects treated with SOC.

We estimate that at least 80% of patients in SOC will undergo DES implantation and a maximum of 20% will undergo POBA alone.

Hypotheses

1. The primary efficacy objective is to demonstrate the non-inferiority of DEB over SOC. This will be assessed through testing the following hypotheses:

$$H_0^1: p_B^{\text{Eff}} - p_S^{\text{Eff}} \geq \delta^{\text{Eff}}$$

$$H_1^1: p_B^{\text{Eff}} - p_S^{\text{Eff}} < \delta^{\text{Eff}}$$

where p_B^{Eff} and p_S^{Eff} are the 12-month TLF rates in the SELUTION SLR 014 DEB group and comparator SOC group, respectively, and $\delta^{\text{Eff}} = 10\%$ is the noninferiority margin.

Statistical Methods:

Statistical assessment for the primary hypothesis will be conducted using a statistical test for noninferiority of proportions based on posterior probability. The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of noninferiority being met). The SELUTION SLR 014 DEB group will be declared noninferior to the SOC group if the posterior probability of the alternative hypothesis H_1^1 is large, that is

$$P(H_1^1 | \text{Data}) = P(p_B^{\text{Eff}} - p_S^{\text{Eff}} < \delta^{\text{Eff}} | \text{Data}) > \pi^1$$

The threshold, $\pi^1 = 0.975$, is a pre-specified level of evidence we require to declare the alternative hypothesis true.

It is selected such that the one-sided type I rate for testing the primary hypotheses of noninferiority is bounded by 2.5%.

Sample Size Assumptions:

- True 12-month TLF rate is 12.0% in both SOC and DEB treatment groups (all subjects – i.e., both 1 and 2 previous layers of stent)
 - True 12-month TLF rate is 9.0% in DES and DEB treatment group in subjects with one layer of previous stent
-

- 1:1 randomization of SELUTION SLR 014 DEB versus SOC assuming 80% DES use and 20% POBA use
- 10.0% is the absolute noninferiority margin

assuming $\pi^1 = 0.975$, a sample size of 396 (198 randomized to SELUTION SLR 014 DEB group and 198 randomized to SOC group) evaluable subjects will lead to a power level of 85% to reject H_0^1 at the final analysis. Accounting for an assumed 5% loss to follow up, 418 subjects will be randomized in the study.

**EVENT
ADJUDICATION
AND SAFETY
MONITORING**

All potential endpoint events will be adjudicated by an independent CEC.

An independent Data Safety Monitoring Board (DSMB) will review aggregate safety data regularly throughout the study follow-up period.

2 Study Administration

Sponsor	<p>MedAlliance LLC 4 Jenner, Suite 190 Irvine, CA 92618 USA</p> <p><u>Representative:</u></p> <div></div> <p><u>Other Contact:</u></p> <div></div> <p><u>EU Legal Representative:</u></p> <div></div>
Device Legal Manufacturer	<p>M.A. MedAlliance SA. Rue de Rive 5, 1260 Nyon, Switzerland</p>
Principal Investigator	
US Co Principal Investigator	
Contract Research Organization	<p>IQVIA MedTech Justitiestraat 6B 2018 Antwerp Belgium (Relevant contact details will be provided to individual sites)</p>

Emergency contact for SAE reporting	Email: SelutionISR.medtech@iqvia.com AND selutionisr@medalliance.com
Biostatistics	Baim Institute for Clinical Research 930 Commonwealth Avenue, #3 Boston, MA 02115, USA Gheorghe Doros, PhD
Protocol Development	Baim Institute for Clinical Research 930 Commonwealth Avenue, #3 Boston, MA 02115, USA
Angiographic and Optical Coherence Tomography Core Laboratory	Baim Institute for Clinical Research 930 Commonwealth Avenue, #3 Boston, MA 02115, USA

3 Introduction

3.1 Background

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 (TLR) remained in the range of 15-20% due to increased neointimal hyperplasia¹. The advent of drug-eluting stents (DES) in 2003 resulted in a highly significant 50-75% decrease in restenosis rates due to near elimination of neointima. This effect was accompanied, however, by ongoing inflammation and absent or delayed healing leading to late and very late stent thrombosis, a requirement for prolonged dual antiplatelet therapy (DAPT), and an ongoing risk of restenosis, such that TLR rates exceeded 15% by 5 years². The deficiencies of first-generation DES have been corrected by contemporary DES with improved early healing and a reduced DAPT requirement. Nevertheless, TLR is still necessary for about 4% of patients by one year after stenting and a persistent hazard of approximately 1-1.2%/year has been demonstrated even with the latest devices³. As a result, from 2009-2017, ISR was responsible for 10.6% of all PCIs reported in the National Cardiovascular Data Registry (NCDR) registry⁴. With continued accrual and treatment of increasingly complex lesions it is likely this prevalence will increase.

Biologic failure with neointimal hyperplasia or late development of neo-atherosclerosis and mechanical failures related to stent under-expansion or stent fracture account for this ongoing ISR risk⁵. When restenosis occurs, repeat DES has proven to be the most effective treatment, with significantly lower risk for repeat restenosis compared with vascular brachytherapy or BA^{6, 7}. Unfortunately, additional layers of stent and polymer carry an added hazard due to risk of uncertain healing, thrombosis, recurrent ISR and the bleeding complications of DAPT. Added stent layers can also decrease vessel flexibility and worsen occlusion of branch coronary vessels. Furthermore, the mechanism of restenosis in individual cases, based on intracoronary imaging study, may indicate that non-stent therapy is preferred or required in addition to repeat stenting in many cases⁵.

Interest in drug-coated balloons (DCB) has reemerged in the setting of ongoing risk and the challenges to treatment of DES ISR. This technology allows for the short-term transfer of anti-neoplastic medications to the arterial wall. There are numerous potential advantages of DCB, including their ability to allow patients to avoid additional stent layers and to minimize the use of DAPT while providing a superior treatment result to current BA. Despite superior safety and effectiveness for Sirolimus and related compounds as the active drugs of DES, complexities in drug delivery and tissue uptake for non-stent delivery have resulted in use of paclitaxel as the active drug for most of these devices studied to date. In these studies, paclitaxel DCB have shown encouraging results with outcomes only slightly worse than DES and superior to BA and vascular brachytherapy⁶⁻¹⁴. Nevertheless, there are concerns with efficiency of tissue delivery requiring loading high doses on the balloon due to loss during delivery and distal wash-out as well as prolonged tissue retention raising concerns for local and possibly systemic toxicity¹⁵.

Development of DCBs that elute Sirolimus would be advantageous based on the favorable therapeutic window and previous success in DES use. Such development requires overcoming the issues of low lipophilicity and reversible binding to the therapeutic target, in order to maintain consistent tissue levels for a prolonged period^{15, 16}. The delivery mechanism must also avoid the potential risk of distal embolization of particulates. Limited data with one Sirolimus eluting balloon was able to demonstrate noninferiority compared to a paclitaxel-coated balloon¹⁷.

ISR remains an important challenge. In addition to the prevalence as noted, there is increasing recognition of clinical importance. Symptomatic ISR can manifest as acute coronary syndrome in up to 71% of presenting patients¹⁸ and can present with non-ST elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) in 19% and 9% of cases, respectively⁴. Late mortality is also increased after a restenosis clinical event¹⁹. Effective treatment of initial restenosis and reducing recurrent events is essential to improving overall safety of PCI. DCBs along with routine imaging to help identify principal mechanisms of restenosis to optimize treatment success may be an important part of this strategy.

3.2 Investigational Device Description

The SELUTION Sustained Limus Release (SLR)TM 014 drug-eluting balloon (DEB) catheter is a combination product consisting of a standard percutaneous transluminal angioplasty (PTA) balloon catheter coated with a drug (Sirolimus) at 1 µg/mm². The drug coating is formulated with Sirolimus loaded into poly (lactic-co-glycolic acid) (PLGA) microspheres suspended in a phospholipid blend.

The balloon catheter component of the SELUTION SLR 014 DEB is a conventional single use, sterile, rapid exchange catheter to dilate vascular lesions. The semi-compliant balloon is inflated for 60 seconds (minimum of 30 seconds) to transfer the Sirolimus loaded microspheres to the target vessel wall. The balloon is then deflated and removed from the body.



The following device sizes are available:

Balloon Length	Balloon diameter (mm)								
	2.00	2.25	2.50	2.75	3.00	3.25	3.50	4.00	4.50
15 mm	X	X	X	X	X	X	X	X	X
20 mm	X	X	X	X	X	X	X	X	X
30 mm	X	X	X	X	X	X	X	X	X

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The active pharmaceutical ingredient in the SELUTION SLR 014 DEB coating is Sirolimus, also known as rapamycin. Sirolimus is a macrocyclic lactone produced by streptomyces hygroscopicus. Sirolimus has a long history of safe and efficacious use as an anti-restenotic compound in DES such as the Cypher Sirolimus-eluting coronary stent. It is anticipated that anti-proliferative and anti-inflammatory properties of Sirolimus will also reduce the tendency for restenosis following BA. Sirolimus is an anti-proliferative drug by virtue of its effects on ubiquitous cell cycle proteins²⁰. It binds to FK506-binding protein 12 (FKBP12). The rapamycin-FKBP12 dimeric molecule inhibits the mammalian target of rapamycin (mTOR). mTOR is one of the key regulatory proteins that directs cell metabolism and cell growth, in part, by

upregulating the cyclin-dependent kinase inhibitor p27. Upregulation of p27 leads to inhibition of cell cycle progression at the juncture of G1 to S phase. Thus, in most cells, therapeutic concentrations of Sirolimus will arrest cell division at the late G1 stage. Because this is prior to initiation of mitosis, the arrest at G1 causes a cytostatic rather than cytotoxic inhibition of cell growth.

[REDACTED] The anti-proliferative properties of Sirolimus make it a useful agent to reduce the risk of restenosis for several months post-angioplasty. In this capacity it interferes with fibroblast and smooth muscle cell proliferation as well as the proliferation of inflammatory cells. These three cell types are largely responsible for the neointimal hyperplasia resulting from the tissue response to vascular injury secondary to angioplasty. Numerous clinical trials have demonstrated a reduced neointimal hyperplasia following implantation of stents coated with Sirolimus²⁰⁻²³.

Details of the device materials, manufacturer, manufacturing process and exposure routes can be found in the accompanying Investigators Brochure.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

3.2.3 Human Clinical Data from Other Applications

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

More extensive descriptions of the clinical studies performed to date are available in the accompanying Investigator Brochure for this study.

3.3 Device training / use

General training on the unique features of the device and the key elements of the instructions for use (IFU) will be provided at the Site Initiation Visit. All participating investigators must be experienced in conducting PCI. No specific additional training is required to use the study device.

3.4 Control Device Description

Control devices potentially include any of the following, to be determined by the specialist performing the PCI:

- Any commercially-available angioplasty balloon without a drug coating – Plain Old Balloon Angioplasty (POBA)
- Any commercially available scoring/cutting balloon
- FDA-approved commercially available -limus eluting DES systems, including stents from the following categories (manufacturer listed in parentheses):

- Everolimus eluting stents: Xience™ (Abbott Vascular®), Promus™ or Synergy™ (Boston Scientific®)
- Zotarolimus eluting stents: Endeavor™ and Resolute™ (Medtronic®).

The choice of comparator group has been dictated by the standard of care (SOC) treatment used throughout the United States (US) for treating the target patient group. Any commercially available device that meets the descriptions above and is appropriately indicated may be used. In the US, no DCB/DEB's are currently approved for use in coronary applications, therefore although devices are available in Europe these will be excluded from use in the SOC group in order to ensure that European and US data is poolable.

3.5 Indications for Use

The SELUTION SLR 014 DEB is indicated for balloon dilatation of in-stent restenotic coronary lesions, for the purpose of improving myocardial perfusion and decreasing the incidence of restenosis.

3.6 Contraindications

The SELUTION SLR 014 DEB is contraindicated in:

- Patient with known allergies or hypersensitivities to Sirolimus (or analogs)
- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patients with a known sensitivity to contrast agents
- Pregnant or breast-feeding women
- Lesions that cannot be crossed with a guidewire and suitably predilated
- Subjects who would be considered unsuitable candidates for standard PCI

4 Study Objectives and Endpoints

4.1 Study Objectives

The objective of the study is to demonstrate the safety and efficacy of the SELUTION SLR 014 DEB for treatment of bare-metal or drug-eluting ISR.

4.2 Primary Endpoint

The primary safety and efficacy endpoint is target lesion failure (TLF) at 12 months post-index procedure for SELUTION SLR 014 DEB versus SOC in all patients. TLF is defined as all cardiac death, target vessel myocardial infarction or clinically driven TLR.

MI includes spontaneous (Type 1) MI using the 4th Universal Definition of Myocardial Infarction (UDMI) and peri-procedural MI using the Society for Cardiac Angiography and Intervention (SCAI) definition.

4.3 Hypothesis-driven Secondary Endpoint

If the primary endpoint is met, the following secondary endpoint will be tested in a sequential manner for non-inferiority:

- TLF at 12 months post-index procedure for SELUTION SLR 014 DEB versus DES among subjects with one previous layer of stent.

4.4 Secondary Endpoints

4.4.1 Secondary Clinical Endpoints

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 the patient-oriented composite of any death, any myocardial infarction (MI) (spontaneous or peri-procedural), or any repeat revascularization.
- All-cause mortality
- Cardiovascular mortality
- MI (spontaneous MI using the 4th Universal Definition of Myocardial Infarction [UDMI]; peri-procedural MI using Society for Cardiac Angiography and Intervention [SCAI], Academic Research Consortium [ARC]-2 definitions)
- Clinically driven TLR, all TLR
- Clinically driven TVR, all TVR, non-TVR
- TLF defined as all cardiac death, target vessel MI or clinically driven TLR
- Target vessel failure (TVF), defined as cardiovascular death, target vessel MI (spontaneous or peri-procedural) and any clinically driven TVR
- Stent thrombosis (definite or probable) according to the ARC criteria, subclassified as acute, subacute, late, very late, and cumulative stent thrombosis²⁴
- Bleeding according to Bleeding Academic Research Consortium (BARC) classification 2-5 (assessed to 12 months).²⁵
- Net adverse clinical events defined as death, MI (spontaneous or peri-procedural), TVR, stent/target lesion stent thrombosis, or bleeding (BARC types 2-5) (assessed to 12 months)

4.4.2 Secondary Performance Endpoints

The following performance endpoints will be evaluated concluding the index procedure:

- Device success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study device only
- Lesion success, defined as attainment of < 30% residual stenosis of target lesion using any percutaneous method

- Procedure success, defined as attainment of < 30% residual stenosis of the target lesion using the assigned study device only without the occurrence of in-hospital major adverse cardiac events (MACE), a composite of all-cause death, MI or clinically driven TLR

4.4.3 Secondary Imaging Endpoints

The following secondary endpoints will be evaluated at 12 months in the angiographic and OCT sub-study subjects only:

- Binary angiographic restenosis
- In-stent percent diameter stenosis
- In-segment percent diameter stenosis
- In-stent LLL
- In-segment LLL
- In-stent MLD
- In-segment MLD
- OCT assessment of neointimal hyperplasia, neo-atherosclerosis, and stent malapposition

4.5 Other Measures

As an exploratory additional measure for cardiac biomarkers, the study will provide detailed analyses of site reported peri-procedural cardiac biomarker elevations including creatine kinase-muscle/brain (CKMB) and troponin T. Troponin I will not be permitted. Biomarkers will be summarized by type and the following thresholds: ≥ 1 ; ≥ 5 ; ≥ 10 ; ≥ 35 ; ≥ 70 ; ≥ 100 ; ≥ 250 .

5 Study Design

The SELUTION SLR 014 DEB ISR clinical trial is a prospective, multi-center, randomized, single blind, controlled, noninferiority trial. The trial will enroll up to 418 randomized subjects (including up to 60 subjects in an angiographic and OCT sub-study) at up to 80 sites in the US, Canada, Brazil, and EU. A minimum of 50% of the subjects will be enrolled in the US.

Subjects with previous BMS or DES and qualifying evidence for ISR will be screened per the protocol inclusion and exclusion. Eligible subjects will be randomized 1:1 to treatment with either the SELUTION SLR 014 DEB or SOC to include contemporary DES or non-DEB BA. The choice of DES is open to the treating investigator but must be either a zotarolimus-eluting stents (ZES) or an everolimus-eluting stents (EES). Investigators are required to declare which SOC treatment option they will use prior to randomization. It is expected that patients with one prior stent will receive DES and patients with two prior stents will receive BA. The treating investigator may deviate from this recommendation if he/she believes that it is in the best interest of the patient, however any deviation from the recommendation must be clinically justified and recorded in the eCRF.

Randomization will be stratified by DES or BMS ISR and whether there are currently 1 (first stent restenosis) or 2 (second stent restenosis) implanted stent layers at the target lesion. Subjects with more than 2 previous stent layers (3rd or greater stent restenosis) involving the

target lesion will be excluded. A maximum of 20% (42) of patients randomized to SOC will be treated with BA. If this limit is reached prior to completion of enrollment, then any subsequent patients who are determined to require BA treatment if they are randomized to SOC will be declared as screen failures prior to randomization and excluded from the trial.

The target lesion must be within a previously placed BMS or DES and must not extend further than 5 mm beyond either the proximal or distal stent edge. The target lesion will also be < 26 mm in length and have a diameter stenosis of > 50%. Prior to treatment with the control or investigational device, flow distal to the lesion must be greater than Thrombolysis in Myocardial Infarction (TIMI) 2. Pre-dilation/treatment of residual stenosis to < 30% will be required prior to randomization. Pre-dilation/treatment can include the use of cutting balloon, scoring balloons, atherectomy, and/or non-compliant balloon sized 1.1-1.2 times the reference vessel diameter (RVD). Intravascular ultrasound (IVUS) or OCT must be used prior to randomization to optimize stent expansion to approximately 80% of the distal RVD based upon investigator assessment and to determine accurate vessel sizing for treatment devices (DEB, DES or POBA). Subjects may undergo treatment of up to two (2) non-target lesions in non-target vessels at the time of the index procedure, but successful PCI of these non-target lesions must be completed prior to treatment of the target lesion.

Randomized subjects will have clinical follow-up at 1 month, 6 months, 12 months and at 2, 3, 4, and 5 years following the index procedure. Primary endpoint clinical follow-up will be at 12 months. A subset of up to 60 subjects will be enrolled in the angiographic and OCT substudy and undergo planned angiographic and OCT follow-up within 30 days after completion of the 12-month primary endpoint clinical follow-up/assessment.

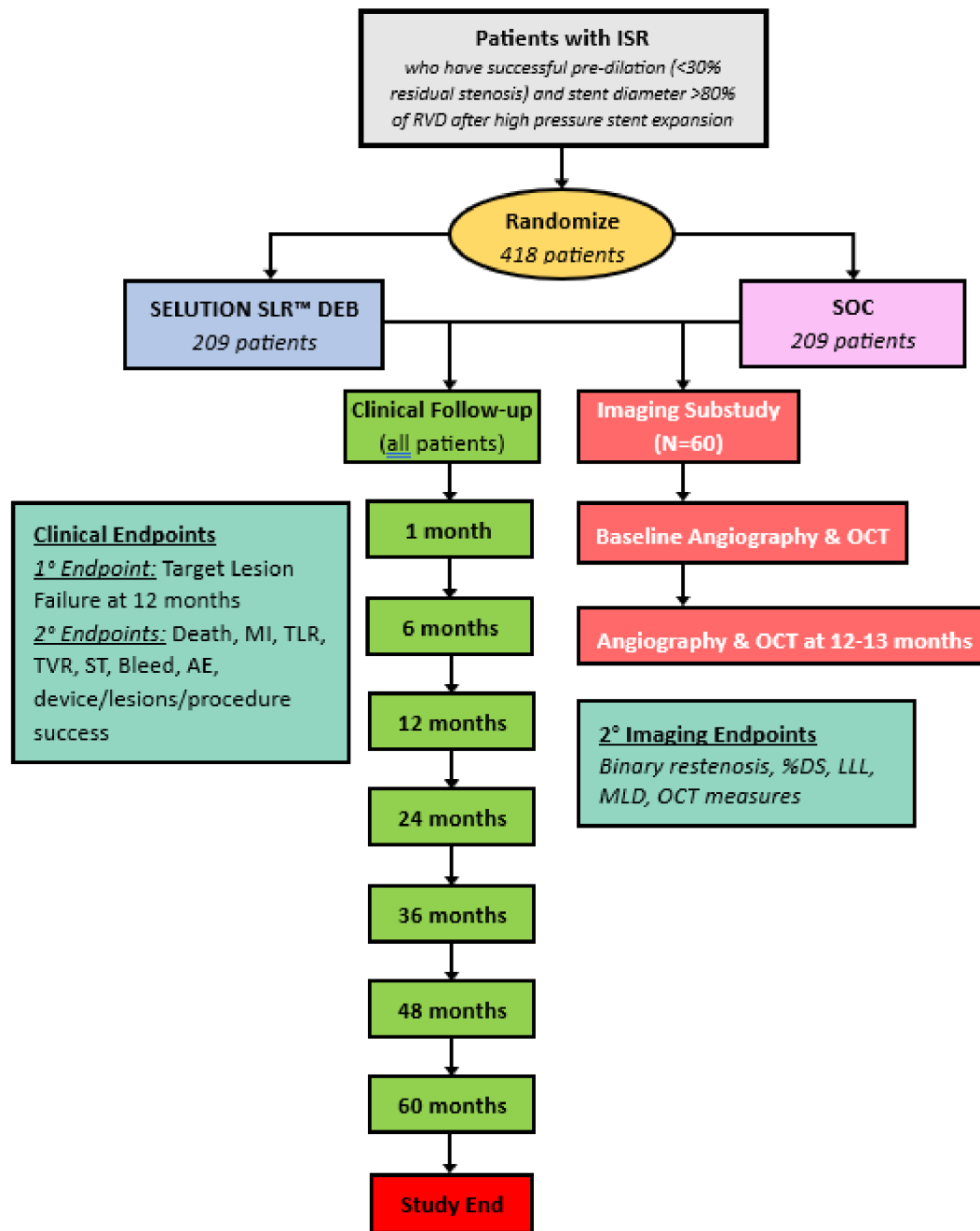
This is a single blind trial, meaning that the patient but not the treating clinician will be blinded to the treatment given after randomization. The patient will remain blinded until all protocol mandated assessments have been completed.

Subjects in the SOC group may receive DEB (including SELUTION SLR 014 DEB) for recurrent restenosis requiring a repeat TLR (after the study primary endpoint has been met). Patients in the SELUTION SLR 014 DEB group who require revascularization should receive a commercially available DES as the preferred treatment choice. However, BA treatment is an acceptable alternative if clinically justified.

The study will test for noninferiority of SELUTION SLR 014 DEB versus SOC. The trial design is shown in **Figure 3**.

Based on the evaluation of available pre-clinical data and existing relevant clinical data, the Sponsor believes that the use of the investigational device in human subjects is justified and that the design of the clinical trial will provide meaningful safety and efficacy data.

Figure 3. Trial Design of SELUTION ISR



5.1 Clinical Sites

The trial will be conducted at up to 80 sites across the US, Canada, Brazil, and Europe.

A separate list of participating sites, Principal Investigators (PIs) and Institutions will be maintained by the Sponsor.

5.2 Number of Subjects

A sufficient number of subjects will be provisionally enrolled to achieve a maximum of 418 randomized subjects (including 5% to account for lost to follow-up). Enrollment is limited to a maximum of 63 randomized subject (~15% of the total randomized subjects) per site. It is expected that approximately 50% of subjects will be enrolled in the US.

5.3 Study Participation Status

5.3.1 Status Definitions

Provisionally enrolled: Subject who is fully informed about the specifics of the study by authorized site personnel and provides informed consent by properly signing an informed consent form (ICF) after the confirmation of the initial enrollment criteria. Subjects for whom consent was not obtained prior to participation in the study will not be considered provisionally enrolled. No data collected from these “subjects” will be included in any analysis. Failure to obtain consent will be reported as a protocol deviation.

Screen failure: Provisionally enrolled subject who withdraws consent prior to randomization or is unsuitable for randomization following a diagnostic angiogram, an unsuccessful crossing of the target lesion with a guide wire, or unsuccessful pre-dilation/pre-treatment (> 30% residual stenosis), or subject who randomized to SOC who requires BA treatment after the overall study limit of 20% of subjects treated with BA has been reached. These subjects will be exited from the study once screen failure is confirmed.

Enrolled (Randomized): Provisionally enrolled subject who meets all clinical and angiographic eligibility criteria and has been randomized. These subjects will be followed in accordance with protocol requirements.

Enrolled Angiographic and OCT substudy (Randomized): Provisionally enrolled subject who meets all clinical and angiographic eligibility criteria, agrees to angiographic and OCT follow-up, has undergone baseline angiography and OCT, and has been randomized. These subjects will be followed in accordance with protocol requirements and have angiographic follow-up after the 12-month clinical visit.

Study exit: Early termination of study participation applicable to subjects that have signed an ICF.

Study completion: Subject who completes all protocol-required study procedures.

5.4 Subject Study Exit

Investigators should make every effort to ensure subjects complete all protocol-required procedures, including study follow-up visits. However, subjects may be required to exit the study, despite an investigator’s best efforts. Good clinical practice (GCP) guidelines describe the need for clear subject exit procedures, to include when and how to exit subjects from the study, as well as to outline the type and timing of the follow-up and data collection for these subjects.

Subjects may be exited from this study in the following limited situations:

- Subject Death

- Subject withdrawal of informed consent
- Investigator believes it is in the best medical interest of the subject to discontinue study participation
- Subject is considered a screen failure

In the event of major protocol non-compliance, each case will be evaluated individually to determine the appropriate course of action regarding subject study participation. In any of the situations noted above, data collected up to and including the exit of the subject will be used in data analysis. No data will be collected after the exit of the subject from the study. Study exits are expected and will be taken into consideration during data analysis as described below.

Additionally, subject attrition has been calculated into the study sample size; therefore, all subjects exited from the study will be counted toward the randomization goal and will not be replaced. Investigators must document, in subject medical records, the reasons and circumstances for all subject exits.

Generally, subjects should not be removed from the study due to late identification of eligibility criteria deviations, unless increased subject risk is indicated. In cases where further participation in the study poses potential risk to the subject, study exit should be considered. In addition, to subject safety, consideration should be given to the scientific validity of the primary endpoints when making decisions concerning subject exit.

Study follow-up options and requirements for subjects exited from the study should be determined and applied to all subjects exited for similar reasons. Deviations in subject eligibility, as defined in the protocol, should be considered protocol deviations and reported to the Institutional Review Board (IRB) or Ethics Committee (EC) immediately upon discovery, in accordance with local regulations. Subjects that are randomized, but do not receive a study treatment during the index procedure post-randomization may be exited from the study after completion of the primary endpoint visit assessments (12-month follow-up). Any patient who doesn't receive the assigned randomization treatment will also be excluded from the imaging sub-cohort.

If a subject cannot continue to participate in the study (i.e., attend hospital visits), but the investigator is able to maintain contact with the subject and they have not withdrawn consent to collect further data, then the investigator should collect vital status data from the patient via telephone interview (or other appropriate methods). In this instance the original follow-up schedule should be followed. The investigator must document the reason for moving to vital status only data collection and the justification must be provided to the Sponsor for approval. Provided that the Sponsor approves the reason for vital status only data collection, any additional data collection mandated by the protocol that is unable to be collected will not be considered a protocol deviation. If it is not feasible to obtain vital status information, then the investigator should discontinue the patient.

Subjects have the right to discontinue from the study at any time or be discontinued at the investigator's discretion.

5.5 Subject Withdrawal

Subjects have the right to withdraw from the trial at any time and for any reason without prejudice to their future medical care by the Trial Personnel or Institution. If a subject (or the subject's legal representative) decides to withdraw, all trial tests and procedures will be stopped, and an inquiry will be made about the cause of withdrawal.

The following events are considered sufficient reasons for a subject to be withdrawn from the study:

1. The subject decides to voluntarily withdraw.
2. The PI or Sponsor decides that discontinuing the trial or discontinuing the subject is in the subject's best interest.
3. Noncompliance.
4. The subject is lost to follow-up.

All subjects should be encouraged to remain in the study through five years post-randomization; however, if a subject decides to discontinue study participation, the reason for discontinuation must be recorded in the medical record and submitted via the electronic Case Report Form (eCRF). Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total study subjects.

If a subject is withdrawn or terminated due to medical safety considerations because of an adverse event (AE), the AE must be followed by medical attention to satisfactory resolution and all trial data related to the subject will be reported.

5.6 Subject Lost to Follow-up

Every attempt must be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful.

For each missed visit the following is the minimum effort required to obtain follow-up information:

- Minimum of three attempts to make contact via telephone
- If contact via phone is not successful, a certified letter from the PI must be sent to the subject's last known address

All contact efforts to obtain follow-up must be documented in both the subject's medical records and on the study Case Report Forms (CRFs).

If, the patient has reached 12-month follow-up, has missed 2 consecutive follow-up visits and the above efforts have been made on each occasion, then the patient will be considered lost to follow-up.

If the subject is able to be contacted, all efforts should be made to perform the required study visit and complete the relevant case report forms. However, if a subject is contacted and a study visit cannot be performed, the study site should complete the relevant case report forms with any relevant data obtained from the subject contact.

6 Subject Selection

During the study enrollment phase, patients from the general interventional cardiology population will be screened according to protocol inclusion and exclusion criteria. Subjects should be consented and sign the informed consent prior to initiating any study-specific procedures that are not considered routine SOC clinical assessments. Subjects who have met all clinical inclusion and exclusion criteria and signed the IRB/EC–approved consent form will then be screened for imaging criteria during an index procedure.

Once angiography and intravascular imaging (IVUS or OCT) are complete and the Investigator is satisfied that the study subject has met all of the remaining study eligibility criteria, he/she shall declare his/her intent to enroll the subject. The investigator will declare which SOC treatment option will be used if the patient is randomized to SOC, prior to randomization. The decision regarding SOC treatment will be recorded in the eCRF. Note that there is an overall limit on the number of SOC patients planned to be treated with BA that may be included in the study. A maximum of 20% of SOC patients may be planned for treatment with BA. Once this limit is reached, patients who the investigator intends to treat with BA only should be recorded as screen failures and should not be included in the study. Actual enrollment in the study occurs at the time successful pre-dilation/pre-treatment is completed and the randomization output is generated in the study EDC. Subjects will be considered enrolled in the imaging cohort when: 1.) informed consent, including consent to participation in the imaging cohort, has been documented; 2.) baseline angiographic and OCT imaging has been performed, and 3.) the subject has been randomized.

Each site should maintain a screening log to document the outcome of all subjects who underwent the angiographic screening. The screening log will contain either the enrollment and subject number of subjects who passed the angiographic screen and underwent successful pre-dilation/pre-treatment and randomization, or the reason for non-enrollment of subjects who did not pass screening (either general inclusion/exclusion criteria, angiographic criteria, failure to cross with wire, or unsuccessful pre-dilation/pre-treatment).

6.1 Eligibility Criteria

6.1.1 Inclusion Criteria

6.1.1.1 Clinical 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.

6.1.1.2 Imaging Inclusion Criteria

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.

6.1.2 Exclusion Criteria

6.1.2.1 Clinical Exclusion Criteria

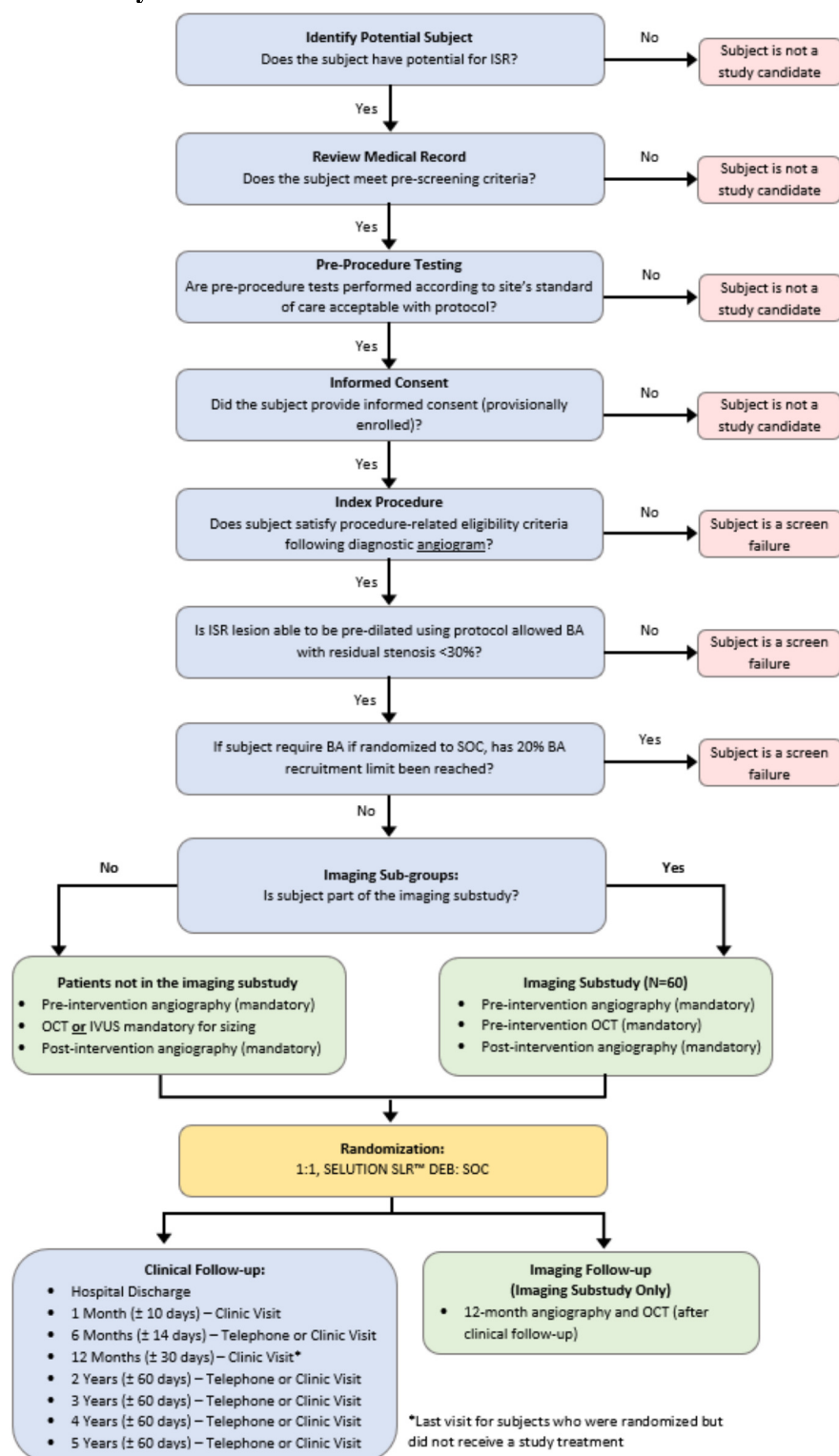
1. Known hypersensitivity or allergy to Sirolimus or other pharmacologic agents required for the procedure.
2. STEMI within 30 days.
3. Planned treatment of additional lesions in the target vessel, or more than two (2) non-target lesions within non-target vessels, during the index procedure.
4. Target 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 $[GFR] \leq 30$ 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.

6.1.2.2 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.

Figure 4. Clinical Study Flowchart



7 Trial Procedures and Assessments

7.1 Schedule of Events

Table 2. Schedule of Events

Events	Screening/Baseline		Index Procedure	Post – Procedure/ Discharge	1 Month ± 10 Days	6 Months ± 14 Days	12 Months ± 30 Days	2,3,4,5 Years ± 60 Days	Unsch. Visit
	Within 7 days Prior to Procedure	Within 24 hours Prior to Procedure			Clinic Visit	Clinic or Telephone Visit	Clinic Visit	Clinic or Telephone Visit	
Informed consent form	X								
Demographic, medical, and cardiac history	X								
Physical examination	X								
Angina status	X			X	X	X	X	X	X
CBC	X								
Creatinine	X								
CKMB or troponin T ¹		X		X					X ⁵
Pregnancy test ²	X								
COVID-19 status ⁶		X		X	X	X	X	X	X
ECG		X		X			X		X ³
Coronary angiography			X				X ³		X ⁵
IVUS/OCT			X						R
OCT (imaging sub-group only)			X				X ^{3,4}		
AE/SAE monitoring			X	X	X	X	X	X	X
Device Deficiency			X						
Concomitant Medication ⁷		X		X	X	X	X	X	X

AE: adverse event; CBC: complete blood count; CKMB: creatine kinase-muscle/brain; ECG: electrocardiogram
IVUS: intravascular ultrasound; OCT: Optical coherence tomography; R: recommended; SAE: serious adverse event.

¹ CKMB or Troponin T preferred (Troponin I is not accepted). Obtain at baseline and 4-24 hours post-procedure; if the biomarker is elevated, then repeat levels at 4-6 hours should be obtained to assess the peak value.

² For women of childbearing potential.

³ Imaging subset only. Required after 12-month clinical follow-up completed. May be performed up to 30 days after clinical follow-up is completed, but not before clinical follow-up. However, patients who undergo clinically indicated angiography after 6 months (180 days), will be considered compliant and do not require repeat 12-month angiography.

⁴ OCT required at time of angiographic follow-up in the imaging subset.

⁵ Obtain for repeat visits where ischemic event is suspected.

⁶ Covid status if available. If not available will not be considered a protocol deviation.

⁷ All cardiovascular and diabetic medications administered should be recorded from 24 hours pre-procedure through the 12-month follow-up assessment. Use of antiplatelet/anticoagulant therapy will be recorded throughout the 5-year follow-up period.

7.2 Screening and Baseline Procedures

Individuals with coronary artery disease (CAD) who qualify for a PCI procedure will be pre-screened by authorized site personnel by reviewing the medical record. At each investigational center, a qualified investigator will approach individual subjects who are potential candidates for participation and will explain the purpose, procedures, device, risks, and benefits, and intent of the study to each potential participant. Interested subjects or legal representatives (if allowed by local IRB/EC) will be invited to join the study and asked to provide written informed consent prior to initiation of any study-related procedure.

The ICF that is used must be approved by the IRB/EC and other local regulatory bodies (as appropriate). The ICF will be translated into appropriate local languages. The subject or legal representative must sign two original copies of the ICF. One original copy of the completed document must be given to the subject; the other original copy must be placed in the hospital chart.

Failure to obtain a signed and hand dated informed consent prior to the procedure constitutes a protocol deviation, which must be reported in accordance to all applicable regulations.

All subjects or legal representatives who sign the ICF and begin the study screening process will be tracked by utilizing a study screening log at each study site. The screening log is used to track the subsequent enrollment or non-enrollment (including the reasons for non-enrollment) on all subjects who signed the consent, met the clinical inclusion criteria and underwent angiographic screening procedures. The screening log documents the screening effort at each site, and the effort to enroll consecutively eligible subjects in this study.

Potential study subjects will proceed with the following SOC procedures to further assess eligibility.

7.2.1 Pre-procedure/Baseline Evaluations

- Physical assessment within 7 days prior to the index procedure, including weight, height and blood pressure.
- Demographics within 7 days prior to the index procedure.
- Medical history within 7 days prior to the index procedure:
 - General medical, cardiac, neurologic and renal history.
 - Cardiovascular history.
 - Risk factors (e.g., dyslipidemia, hypertension, diabetes mellitus, tobacco use).
 - History of peripheral vascular disease, stroke, transient ischemic attack (TIA).
- Ischemic/anginal status assessment (according to Canadian Cardiovascular Society Classification [CCSC]).
- Current cardiovascular and diabetic medications, including anti-platelet/anticoagulant medications within 24 hours prior to the index procedure.
- 12-lead electrocardiogram (ECG) according to each site's SOC to ensure suitability to undergo a PCI procedure, within 24 hours prior to the index procedure.

- Routine laboratory assessments:
 - All subjects must have cardiac enzymes (CKMB is preferred [or troponin T if CKMB is not available, Troponin I is not accepted]), evaluated within 24 hours prior to the index procedure. Baseline cardiac enzyme sample may be obtained from the sheath during the index procedure, prior to randomization.
 - All subjects must have a creatinine blood level assessed within 7 days prior to the index procedure.
 - Women of childbearing potential must have a negative pregnancy (serum and/or urine) test within 7 days prior to index procedure in accordance with the institutional standard. Female subjects who are surgically sterile or post-menopausal are exempt from having a pregnancy test.
 - CBC
- COVID-19 status – patients are not required per protocol to undergo specific testing for COVID-19, however if patients have been tested for COVID-19 then the results will be recorded in the trial EDC.

If any of the pre-procedure/baseline tests specified above are not routine part of standard clinical care or are required to be repeated in order to demonstrate protocol eligibility criteria leading up to the index procedure, then written informed consent must be obtained before these tests are performed or repeated. Subjects are considered provisionally enrolled with the signature on the written ICF, however a subject will only proceed to the baseline evaluations and index procedure if all initial and applicable procedure-related eligibility criteria are met.

7.3 Concomitant Medications

Unless clinically contraindicated, all subjects should receive the recommended medication regimen listed in **Table 3** at the investigator's discretion in accordance with local clinical guidelines. Pre-and post-procedure activated clotting time (ACT) measurements for subjects receiving heparin are strongly recommended but not required if the test is not performed as SOC at the investigational institution. If ACT is not performed, anticoagulation should be in accordance with SOC procedures and applicable guidelines.

All cardiovascular and diabetic medications administered should be recorded in the medical record and reported in the eCRF from 24 hours pre-procedure through the 12-month follow-up assessment.

Use of antiplatelet/anticoagulant therapy will be recorded throughout the 5-year follow-up period.

Table 3. Concomitant Medication Regimen Recommendations

Timing	Medication	Regimen
Prior to Procedure	Aspirin	Minimum 150 mg (within 24 hours prior to procedure)
	Clopidogrel or Ticagrelor/Prasugrel	Loading dose of 600 mg Clopidogrel within 24 hours prior to index procedure or immediately post-procedure (within 30 minutes). Alternatively, a loading dose of 60 mg Prasugrel or 180 mg Ticagrelor. No loading dose is required for subjects on chronic thienopyridine therapy.
During Procedure	Heparin or Bivalirudin	Per routine hospital practice. For Heparin, a bolus of 50-70 units/kg is recommended up to 5000 units. If Heparin is administered, it is recommended to maintain ACT of ≥ 250 seconds (or ≥ 200 seconds if a glycoprotein IIb/IIIa receptor blocker is administered) throughout the interventional portion of the procedure.
	Intracoronary Nitroglycerin	Intracoronary Nitroglycerin 100-200 μ g is required prior to baseline and post-intervention angiograms.
Post-Procedure DAPT	Aspirin* and Clopidogrel or Ticagrelor/Prasugrel	Aspirin minimum 75 mg daily* indefinitely. Same thienopyridine agent for the minimum recommended duration (see text), as follows: Clopidogrel: 75 mg daily. Prasugrel: 10 mg daily; a lower dose of 5 mg daily is allowed for subjects < 60 kg. Ticagrelor: 90 mg twice daily.

ACT: activated clotting time; DAPT: dual antiplatelet therapy.

* Aspirin may be omitted at the discretion of the investigator in subjects with requirement for ongoing oral anticoagulants.

7.4 Index Procedures

Signed written ICF must be obtained for all subjects who are potential study candidates prior to enrollment and completion of index procedure requirements.

7.4.1 Subject Preparation and Baseline Imaging

Subject preparation and percutaneous access should be performed according to standard hospital policy for care of interventional cardiology patients unless otherwise specified in this investigational plan. Both femoral and radial access techniques are acceptable. The procedure begins once percutaneous access has been established, defined as the time of sheath insertion.

Following intracoronary injection of Nitroglycerin, (see **Table 3**) baseline angiography of the vessels(s) will be performed in at least two orthogonal views to characterize the target lesion(s) and to confirm angiographic eligibility criteria. Angiographic imaging should be captured without the presence of a guidewire in the field of view to avoid artifact effects. Assessment of angiographic eligibility criteria is based on visual assessment of the pre-procedure angiogram.

Mehran in-stent restenosis classification system will be used to record the pattern of ISR.

IVUS and/or OCT will be performed in all subjects after determining angiographic eligibility and prior to randomization. IVUS or OCT should document vessel size, previous stent under-expansion, malapposition, or stent fracture, and severity of calcification in the target lesion. Note that for patients who are in the angiographic and OCT imaging cohort, pre-interventional OCT is mandated.

7.4.2 Target Lesion Pre-dilation/Pre-Treatment

After confirming all clinical and target lesion inclusion and exclusion criteria, the selected target lesion must be adequately pre-dilated/pre-treated before randomization. Pre-dilation/pre-treatment may include use of non-compliant angioplasty balloons as well as cutting or scoring balloons, or atherectomy. A visually estimated residual diameter stenosis < 30% with TIMI grade flow > 2 in the target lesion, without dissection greater than NHLBI Type C, must be achieved prior to randomization. Caution must be used to avoid dilating beyond the proximal and distal edge of the target lesion that is planned for stenting or SELUTION SLR 014 DEB treatment (i.e., geographic miss). Use of final non-compliant balloon sized 1.1-1.2 times the RVD is recommended.

7.4.3 SOC treatment decision

Prior to randomization the SOC treatment choice must be declared; either DES or BA. Note that there is a limit of 20% (N=42) of recruited patients who may be treated with BA in the SOC group. If this limit has been reached then patients requiring BA rather than DES should be declared screen failures and should not be randomized.

7.4.4 Randomization

Subjects who have satisfied all clinical and angiographic inclusion and exclusion criteria, after successful pre-dilation/pre-treatment as defined above, will then be randomized in a 1:1 ratio to receive either the SELUTION SLR 014 DEB or SOC (control group of DES or BA). Each subject will receive one (1) unique randomization number associated with a randomization assignment allocated via the SELUTION SLR 014 DEB ISR study electronic data capture (EDC) eCRF (details will be provided in eCRF guidelines). Randomization will be stratified by study center, BMS or DES ISR, and whether there has been previous repeat stenting of the target lesion (1 vs. 2 stent layers). To prevent bias, the blocks and randomization schedules will be predefined prior to the first study enrollment.

The assigned randomized treatments are to be completed as described below. Once randomized the subject is considered enrolled in the trial and included in the ITT population. This includes subjects that are randomized but do not receive the study treatment or receive treatments not in accordance with the randomization assignment. Crossover to the SELUTION SLR 014 DEB at the time of index procedure is not permitted. Bailout use of DES in the SELUTION SLR 014 DEB arm is permitted as described under bailout stenting below.

7.4.5 Study Treatments

SELUTION SLR 014 DEB:

After target lesion pre-dilatation/pre-treatment per 7.4.2, a SELUTION SLR 014 DEB study device should be selected with nominal diameter 1.0-1.1 times the RVD and length that allows approximately 2 mm longer than the proximal and distal edges of the target lesion. In circumstances where the lesion length is longer than the available SELUTION SLR 014 DEB, overlapping balloons may be utilized. The recommended overlap is a minimum of 1 mm. The SELUTION SLR 014 DEB should then be delivered and positioned in the lesion with approximately 2 mm proximal and distal to the lesion and deployed using the pressure recommended in the IFU. The balloon should be inflated for 60 seconds provided that the patient can tolerate this duration. The minimum inflation time is 30 seconds. Where initial balloon inflation time is below the minimum 30 seconds an additional (new/unused) SELUTION SLR 014 DEB should be used following the same inflation guidelines (target 60 seconds, minimum 30 seconds). To maintain clinical effectiveness, no SELUTION SLR 014 DEB, once expanded, should be inflated a second time. The number of balloons used, and the inflation time of each balloon must be recorded in the eCRF. If additional treatment is needed a second SELUTION SLR 014 DEB should be used and not standard POBA.

After inflation, the balloon should then be fully deflated and removed. Final angiography should be performed after intracoronary Nitroglycerin to assess for final quantitative angiography, angiographic complications, and visually estimated % diameter stenosis. IVUS and OCT **should not** be performed after SELUTION SLR 014 DCB, as it may disrupt the drug coating which has been applied to the vessel walls. Note that per the IFU the SELUTION SLR 014 DEB must only be inflated once.

Control Treatment:

For subjects randomized to the control group (SOC) the treating physician may choose to implant a commercially available DES or alternatively may use POBA only to treat the patient. The decision should be based on the treating physicians' assessment of the best treatment option for the individual patient. However, it is expected that patients with one prior stent will receive DES and patients with two prior stents will receive POBA. Treating physicians may deviate from this if it is determined to be in the best interest of the patient, but the justification for the treatment decision must be recorded in eCRF.

Choice of DES is at the treating physician's discretion but is limited to ZES and EES devices (See Section 3.4). The DES should be sized according to the RVD, based on pre-treatment IVUS or OCT. After DES or BA deployment, **Additional balloon inflations should be performed as needed to obtain < 30% residual diameter stenosis and resolve proximal or distal edge dissections greater than or equal to NHLBI grade B.** Repeat IVUS or OCT after stent deployment may be performed at the operator's discretion to confirm stent expansion and apposition. Final angiography should be performed after intracoronary Nitroglycerin to assess for final quantitative angiography, angiographic complications, and visually estimated % diameter stenosis.

Bailout Stenting:

After final angiography, bailout stenting should be considered after SELUTION SLR 014 DEB or control BA group if any of the following are evident:

- Residual diameter stenosis > 50%
- Persistent dissection $\geq$ NHLBI grade C

In these cases, a commercially approved DES should be selected in accordance with length needed to treat residual stenosis or dissection and diameter, preferably based on pre-treatment IVUS or OCT (approximately 1.0 times RVD). Repeat IVUS or OCT are recommended to confirm stent expansion and apposition and for untreated dissection.

After final angiography patients who have received a DES (control patients), who have a residual diameter stenosis > 50% requiring high pressure post-dilation of the stent, will be considered to have received a bailout treatment.

All bailout stent procedures will be captured in procedure CRF. Bailout stenting performed to treat a dissection should be recorded as an AE. If the bailout procedure results in any of the consequences characteristic of serious adverse event (SAE, death, prolonged hospitalization, etc.; see section 9) then an SAE should be reported.

7.4.6 End of Procedure

After completion of all study treatments, final angiography must be performed of the target vessel after administration of intracoronary Nitroglycerin and in the same views that were taken at baseline.

The end of procedure is defined as the time the last guide catheter has been removed from the subject.

Any device deficiencies must be recorded in the eCRF.

7.5 Post-Procedure to Hospital Discharge

7.5.1 Immediately Post-Procedure

Immediately following the procedure:

- Heparin or Bivalirudin should be discontinued.
- ACT should be monitored in accordance with hospital protocol.
- Vascular sheaths should be removed according to standard hospital practice.
- Approved vascular closure devices may be used at the discretion of the investigator in accordance with the manufacturer's instructions.

Clinical assessment of subject's condition and laboratory tests must be performed according to the details below.

The following assessments are to be performed prior to hospital discharge:

7.5.2 Clinical and Laboratory Assessments

Cardiac Biomarkers:

CKMB is the preferred biomarker and should be obtained between 4-24 hours post-procedure. If CKMB is not available, then troponin assay should be performed. For troponin assay, troponin T

is preferred (Troponin I is not permitted). If the biomarker is elevated, then repeat levels at 4-6 hours should be obtained to assess the peak value.

ECG:

12-lead ECG must be performed within 24 hours after the index procedure.

7.5.3 Clinical Endpoints Prior to Discharge

- Angina status will be assessed prior to discharge.
- AE and SAE will be assessed prior to discharge.
- Antiplatelet and anticoagulation medical therapy will be recorded post-procedure.
- Other cardiovascular and diabetic medications will be recorded post procedure.

Prior to discharge, the research coordinator will review the follow-up requirements with the subject to help ensure compliance with the follow-up schedule. Telephone numbers must be obtained from the subject to ensure the ability to contact him/her. The subject's COVID status if available will be collected. If not available, it will not be considered a protocol deviation.

7.6 Antiplatelet/Anticoagulation Regimen

All subjects will receive a minimum of 75 mg aspirin daily indefinitely, unless there is a requirement for concomitant uninterrupted oral anticoagulation.

P2Y12 inhibitor should be prescribed according to the agent selected pre-procedure, as follows (see Table 3):

- Clopidogrel 75 mg daily
- Prasugrel 10 mg daily or 5 mg daily (for weigh < 60 kg).
- Ticagrelor 90 mg twice daily.

Changes in specific P2Y12 inhibitor must be recorded and appropriate loading dose administered in accordance with local practice.

The DAPT administration post-index procedure is recommended for a minimum of 6 months and highly recommended for 12 months for subjects who receive a DES during the index procedure and are not at a high risk of bleeding. For subjects at high risk of bleeding, the duration may be shortened to 3 months or in accordance with local guidelines. For SOC subjects not receiving a DES during the index procedure, DAPT is recommended for a minimum of 1 month. For SELUTION SLR 014 DEB subjects DAPT administration post-index procedure is recommended for minimum of 1 month.

For subjects requiring uninterrupted oral anticoagulation therapy, aspirin may be omitted in favor of single antiplatelet therapy with P2Y12 inhibitor for the minimum duration of recommended DAPT as above. Beyond this minimum recommended duration, either aspirin may be resumed or P2Y12 inhibitor may be continued at investigator discretion.

7.7 Follow-up Assessments

All randomized subjects will be followed through 5 years of follow-up, with assessments performed at 1 month, 6 months, 12 months, and annually thereafter.

COVID-19 status will be recorded for patients at each follow-up visit. Patients are not required per protocol to undergo specific testing for COVID-19, however if patients have been tested as part of their routine medical care, then the results will be recorded in the trial EDC. It will not be a deviation if COVID-19 status is unavailable.

Follow-up clinic visits are required for data collection at 1 month and 12 months. Telephone or clinic visits may be performed for data collection at the 6-month visit and annual visits beginning at 2 years. However, if visits are unable to occur due to COVID-19 factors such as travel restrictions, patient requiring to self-isolate or patient has active infection, then any follow-up may be performed via telephone. When required clinic follow-up is conducted by telephone rather than in the clinic then this should be documented in the EDC and an explanation of the specific COVID-19 or other factors that necessitated this action should be provided. Any patient assessments that cannot be conducted remotely e.g., angiography should be scheduled for the earliest safe opportunity.

7.7.1 One Month Clinical Follow-up (30 ± 10 Days)

Subjects will be evaluated at 1-month post-procedure (± 10 days) during a research clinic visit. The following assessments must be completed:

- Ischemic/angina status.
- AEs and SAEs since discharge.
- Antiplatelet/anticoagulant medical therapy since discharge.
- Other cardiovascular and diabetic medications since discharge.
- Any coronary intervention (e.g., repeat revascularization) that occurred since the post-procedure discharge.
- COVID-19 Status

7.7.2 Six Month Clinical Follow-up (180 ± 14 Days)

Subjects will be evaluated at 6 months post-procedure (180 ± 14 days) during a telephone contact (or optional research clinic visit). The following assessments must be completed:

- Ischemic/angina status.
- AEs and SAEs since last follow-up.
- Antiplatelet/anticoagulant medical therapy since last follow-up.
- Other cardiovascular and diabetic medications since last follow-up.
- Any coronary intervention (e.g., repeat revascularization) that occurred since last follow-up.
- COVID-19 status

7.7.3 Twelve Month Clinic Visit (360 ± 30 days)

Subjects will be evaluated at 12 months post-procedure (360 ± 30 days) during a research clinic visit. The following assessments must be completed:

- Ischemic/angina status.
- AEs and SAEs since last follow-up.
- Anti-platelet/anti-coagulant medical therapy since last follow-up.
- Other cardiovascular and diabetic medications since last follow-up.
- Any coronary intervention (e.g., repeat revascularization) that occurred since last follow-up.
- 12-lead ECG.
- COVID-19 Status

Angiographic and OCT Subset:

After completion of the 12-month clinic visit, subjects in the angiographic/OCT substudy will undergo repeat angiography and OCT imaging. This should be scheduled in advance at discharge or during an earlier follow-up visit. Subjects in the angiographic subset who undergo clinically indicated angiography after 6 months (180 days), will be considered compliant with angiographic follow-up and the clinically indicated angiogram should be submitted as the follow-up angiogram. Please refer to section 7.8 and core lab manual of operations for specific instructions for angiography, and to section 7.9 and core lab manual of operations for specific instructions for OCT.

7.7.4 Long-Term Clinical Follow-Up at Year 2 (720 ± 60 days), 3 ($1,080 \pm 60$ Days), 4 ($1,440 \pm 60$ Days), and 5 ($1,800 \pm 60$ Days) post-procedure

Subjects will be evaluated at 2, 3, 4, and 5 years post-procedure (annually ± 60 days) during a telephone contact (or optional research clinic visit). The following assessments must be completed:

- Ischemic/angina status.
- AEs and SAEs since last follow-up.
Note: After the 12-month follow-up visit, continuing AEs will be followed through to resolution or until event becomes stable and only SAEs, including Major Adverse Cardiac Events (MACE) and clinical study endpoints, will be recorded. All device related events will be recorded until end of trial.
- Antiplatelet/anticoagulant medical therapy since last follow-up.
- Other cardiovascular and diabetic medications since last follow-up.
- Any coronary intervention (e.g., repeat revascularization) that occurred since last follow-up.
- COVID-19 Status

7.7.5 Unscheduled Study Visit

Subjects may present to the clinic outside of the scheduled follow-up windows. Such unscheduled study visits will be reported if the subject has experienced an AE. For an unscheduled study visit, changes in concomitant cardiac medications and data regarding adverse events will be collected as well as ischemic/angina status. COVID-19 status may also be assessed.

Subjects assessed at an unscheduled study visit may require diagnostic testing (e.g., ECG, angiogram, CKMB or troponin levels) and/or a revascularization procedure to further evaluate and treat ischemic symptoms. IVUS/OCT is recommended if an angiogram is conducted. Any repeat procedure must be reported on the relevant case report forms, including any unscheduled visits prior to the repeat procedure and/or AEs associated with the procedure.

7.7.6 Repeat Angiography and Repeat Revascularization

For subjects who require repeat angiography as part of an unscheduled visit assessment, it is important to assess for the presence of ischemia prior to the decision for revascularization and to document full diagnostic images of the target lesion. This assessment must include documentation of angina status. For stable symptoms, pre-procedure functional ischemic testing is strongly recommended. At the time of coronary angiography, the target lesion should be imaged in the same views as the baseline angiogram. For subjects in the angiographic and OCT subset who present at least 180 days from the index procedure, the angiogram will represent the angiographic follow-up study and should comply with angiographic and OCT core lab instructions.

If there is a decision to perform revascularization of the target lesion, please confirm diameter stenosis $> 50\%$ with angina or positive functional ischemia study. For diameter stenosis $< 70\%$, fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), or other validated intracoronary physiologic measure should be used to document ischemia.

Any commercially available devices may be used for revascularization, including stents, BA, cutting balloon, scoring balloon, rotational atherectomy, orbital atherectomy, and laser. Patients in the SOC group who require revascularization may receive a SELUTION SLR 014 DEB if the treating physician believes that it is in the best interest of the patient and if there is no commercially available DEB on the market in the respective country.

Patients in the SELUTION SLR 014 DEB group who require revascularization should receive a commercially available DES as the preferred treatment choice. BA treatment is an acceptable alternative if clinically justified.

Angiographic data collected during any repeat procedure on the target vessel(s) must be made available to the Clinical Events Committee (CEC) for an independent review and assessment. Likewise, the angiographic images must be submitted to the core laboratory for an independent review and assessment of the target lesion and investigational stent.

7.8 Angiographic Core Laboratory

The angiographic core laboratory will provide sites with a written procedural manual describing the acquisition and submission procedures for the baseline and subsequent repeat angiograms. Sites will be requested to obtain and submit a minimum of two (2) orthogonal views at baseline,

which will be repeated post-procedure, and at the time of any clinically indicated or scheduled follow-up repeat angiography. All study angiograms will be performed after administration of intracoronary Nitroglycerin. Baseline and procedural angiograms for all subjects will be sent to the independent angiographic core laboratory for evaluation, as will 12-13 month angiograms from patients in the Angiographic and OCT imaging sub-group. In addition, any coronary angiograms performed during the trial follow-up period due to suspicion of restenosis of the target lesion(s) will be forwarded to the angiographic core laboratory for analysis.

Core laboratory data will be submitted directly to the clinical database for inclusion in study reports and final analyses.

7.9 Optical Coherence Tomography Core Laboratory

The OCT core laboratory will provide sites with a written procedural manual describing the acquisition and submission procedures. For the angiographic and OCT imaging sub-group, baseline and 12-13 month follow-up OCT images will be forwarded to the independent OCT core laboratory for analysis.

Images from any patient who requires re-intervention and has OCT imaging performed at the time of re-intervention may also be forwarded to the OCT core laboratory.

Core laboratory data will be submitted directly to the clinical database for inclusion in study reports and final analyses.

8 Statistical Considerations and Analysis Plan

The SELUTION SLR 014 DEB ISR clinical trial is a prospective, multi-center, randomized, single-blind, controlled, noninferiority clinical study.

A maximum of 418 subjects will be randomized (including 5% to allow for lost to follow-up), stratified by study center, DES or BMS ISR and whether there are currently 1 (first stent restenosis) or 2 (second stent restenosis) implanted stent layers at the target lesion in a 1:1 ratio to receive the SELUTION SLR 014 DEB or standard of care to include a commercially approved DES or BA without stenting.

The trial is designed to assess the noninferiority of the SELUTION SLR 014 DEB compared to the current SOC with respect to the primary endpoint of 12-month TLF, defined as cardiac death, target vessel MI, or clinically-driven TLR. In addition, the study will assess subjects with one layer of stent treated with the SELUTION SLR 014 DEB versus the 12-month TLF rate in subjects with one layer of stent treated with DES.

8.1 Sample Size Determination and Primary Endpoint Analysis

The sample size of 418 subjects is driven from the primary endpoint (12-month TLF) noninferiority analysis. The event rate estimates and the noninferiority margin were calculated based on a meta-analysis (See **Table 4**) of TLF outcomes for clinical trials of ISR treatment and included either DES or BA groups. Depending on study definitions, TLF, TVF or MACE rates were used to match as closely as possible the TLF definition in this study. The estimated rates for DES and BA were assessed separately, given few studies included the direct comparison. The estimated difference for DES versus BA was calculated using a conservative estimate of the

lower 95% confidence interval (CI) of the meta-analytic difference in TLF rate for DES and BA. This difference between the estimated TLF rates for DES and BA of 21% is consistent with network meta-analyses showing a lower bound of 50-75% reduction for DES versus BA^{6,7}. Based on the difference between DES and BA of 21%, a noninferiority margin of 10% maintains at least 50% (actual = 52%) of the absolute risk difference between DES and BA.

Based on historical data from the American College of Cardiology NCDR, we estimate that 80% of patients in the control group will receive DES and 20% will receive BA. The estimated event rate based on weighted average for the control group is 15%. Given the study design, requiring a residual stenosis < 30% and option for DES for unsuccessful BA, we estimate an event rate for the control group of 12%, which is closer to the estimated DES result.

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
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[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The study will assess noninferiority of the 12-month TLF rate in subjects treated with the SELUTION SLR 014 DEB versus the 12-month TLF rate in subjects treated with SOC. The

analysis will be carried out on the PP set (primary) and as a sensitivity analysis it will also be conducted on the ITT data set.

The analysis will be carried out on the PP set and as a sensitivity analysis it will also be conducted on the ITT data set.

Primary Hypothesis

The primary efficacy objective is to demonstrate the non-inferiority of DEB over SOC. This will be assessed through testing the following hypotheses:

$$H_0^1: p_B^{\text{Eff}} - p_S^{\text{Eff}} \geq \delta^{\text{Eff}}$$

$$H_1^1: p_B^{\text{Eff}} - p_S^{\text{Eff}} < \delta^{\text{Eff}}$$

where p_B^{Eff} and p_S^{Eff} are the 12-month TLF rates in the SELUTION SLR 014 DEB group and comparator SOC group, respectively, and $\delta^{\text{Eff}} = 10\%$ is the noninferiority margin.

Statistical Methods

Statistical assessment for the primary hypotheses will be conducted using a statistical test for noninferiority of proportions based on posterior probability. The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of noninferiority being met). In calculating the posterior probability for TLF rates in each group, a uniform prior (Beta(1,1)) will be assumed. The SELUTION SLR 014 DEB group will be declared noninferior to the SOC group if the posterior probability of the alternative hypothesis H_1^1 is large, that is

$$P(H_1^1 | \text{Data}) = P(p_B^{\text{Eff}} - p_S^{\text{Eff}} < \delta^{\text{Eff}} | \text{Data}) > \pi^1$$

The threshold, $\pi^1 = 0.975$, is a pre-specified level of evidence we require to declare the alternative hypothesis true.

The threshold π^1 was selected such that the one-sided type I rate for testing noninferiority is bounded by 2.5%.

Sample Size Assumptions:

- True 12-month TLF rate is 12.0% in both SOC and SELUTION SLR 014 DEB treatment groups (all subjects – i.e., both 1 and 2 previous layers of stent)
- True 12-month TLF rate is 9.0% in DES subjects and SELUTION SLR 014 DEB treatment group in subjects with one layer of previous stent
- 1:1 randomization of SELUTION SLR 014 DEB versus SOC assuming 80% DES use and 20% POBA use
- 10.0% is the absolute noninferiority margin

assuming $\pi^1 = 0.975$ and $\pi^2 = 0.95$, a sample size of 396 (198 randomized to SELUTION SLR 014 DEB group and 198 randomized to SOC group) evaluable subjects will lead to a power level of 84% to reject H_0^1 at the final analysis. Accounting for an assumed 5% lost to follow up, 418 subjects will be randomized in the study.

Hypothesis-driven Secondary Endpoint

In addition, the study will assess subjects with one previous layer of stent treated with the SELUTION SLR™ DEB versus the 12-month TLF rate in subjects with one previous layer of

stent treated with DES. The rationale for the restricted analysis population for this second test is that we plan for control group patients with 2 layers of previous stent to undergo POBA and thus a comparison of all DEB to DES would not be balanced.

This hypothesis will only be tested if the primary hypothesis of non-inferiority H_0^1 is rejected.

This secondary efficacy objective is to demonstrate non-inferiority of DEB over DES in patients with one previous layer of stent. This will be assessed through testing the following hypotheses:

$$H_0^2: p_{B2}^{\text{Eff}} - p_D^{\text{Eff}} \geq \delta^{\text{Eff}}$$

$$H_1^2: p_{B2}^{\text{Eff}} - p_D^{\text{Eff}} < \delta^{\text{Eff}}$$

where p_{B2}^{Eff} and p_D^{Eff} are the 12-month TLF rates in patients with one layer of stent treated with the SELUTION SLR™ DEB and DES, respectively, and $\delta^{\text{Eff}} = 10\%$ is the noninferiority margin.

The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of noninferiority being met). In calculating the posterior probability for TLF rates in each group, a uniform prior (Beta(1,1)) will be assumed. The SELUTION SLR™ DEB group will be declared noninferior to the DES group if the posterior probability of the alternative hypothesis H_1^2 is large, that is

$$P(H_1^2 | \text{Data}) = P(p_{B2}^{\text{Eff}} - p_D^{\text{Eff}} < \delta^{\text{Eff}} | \text{Data}) > \pi^2$$

The threshold, $\pi^2 = 0.95$, is a pre-specified level of evidence we require to declare the alternative hypothesis true. The threshold π^2 was selected such that the overall one-sided type I rate for testing the primary hypotheses of noninferiority is bounded by 5%.

Sample Size Assumptions:

- True 12-month TLF rate is 9.0% in DES subjects and DEB treatment group in subjects with one layer of previous stent
- 10.0% is the absolute noninferiority margin

assuming $\pi^2 = 0.95$ a sample size of 396 (198 randomized to SELUTION SLR™ DEB group and 198 randomized to SOC group) evaluable subjects will lead to a power level of 90% to reject H_0^2 at the final analysis.

If non-inferiority of SELUTION SLR 014 DEB to DES for the hypothesis-driven secondary endpoint has been met, a test of superiority of SELUTION SLR 014 DEB to DES in patients with one previous layer of stent will be conducted.

The superiority of SELUTION SLR 014 DEB over DES in patients with one layer of stent will be assessed through testing the following hypotheses:

$$H_0^3: p_{B2}^{\text{Eff}} - p_D^{\text{Eff}} \geq 0$$

$$H_1^3: p_{B2}^{\text{Eff}} - p_D^{\text{Eff}} < 0$$

where p_{B2}^{Eff} and p_D^{Eff} are the 12-month TLF rates in patients with one layer of stent treated with the SELUTION SLR 014 DEB and DES, respectively.

The SELUTION SLR 014 DEB group will be declared superior in patients with one layer of stent to the DES group if the posterior probability of the alternative hypothesis H_1^3 is large, that is

$$P(H_1^3|Data) = P(p_{B2}^{Eff} - p_D^{Eff} < 0|Data) > \pi^3$$

The threshold, $\pi^3 = 0.95$, is a pre-specified level of evidence we require to declare the alternative hypothesis true.

8.2 Study Populations

Per-protocol (PP): The PP population is defined as all randomized subjects who received the assigned study treatment, have sufficient follow-up data (at least 11 months of follow-up or experienced the primary endpoint) and satisfy all of the major study inclusion and exclusion criteria. Inclusion and exclusion criteria defined as “major” for the purposes of identifying the PP population will be prespecified in the SAP. An analysis will be conducted for SELUTION SLR 014 DEB vs SOC for all patients who meet the PP definition; this is the primary analysis population. An additional analysis will be made for SELUTION SLR 014 DEB vs DES for all patients who had a single layer ISR at the point of recruitment and who meet the PP definition.

Intent-to-treat (ITT): The ITT population is defined as all randomized subjects. Subjects will be analyzed according to the assigned treatment regardless of treatment received. An analysis will be conducted for SELUTION SLR 014 DEB vs SOC (i.e., all trial patients) and additionally for SELUTION SLR 014 DEB vs DES (single layer ISR patients only).

Angiographic and OCT Follow-up Subset: A subset of approximately 60 subjects will be enrolled after index procedure confirmation and undergo planned angiographic and OCT follow-up within 30 days after completion of the 12-month primary endpoint clinical follow up.

8.3 Statistical Analysis and Reporting of Results

Descriptive statistics will be used to summarize and contrast clinically relevant demographic and background characteristic data collected in this study. A comparison will be made of DEB and SOC groups overall, between the DEB group and each subgroup of the SOC group (the DES subgroup and the POBA subgroup), and between the DEB group and the DES subgroup of the SOC group in the subset of subjects with one layer of previous stent.

In general, statistics for continuous variables will include sample sizes, means, medians, standard deviations, inter-quartile ranges, minimum and maximum values. Categorical variables will be described with counts and percentages. Proportions will be calculated using known non-missing values. Unless otherwise indicated, all statistical tests and/or CIs will be performed at $\alpha = 0.05$ (two-sided).

All descriptive statistical analyses will be performed using Statistical Analysis Software (SAS) for Windows (version 9.1 or higher).

8.3.1 Criteria for Study Success

In order to claim study success from a regulatory perspective, the primary endpoint of non-inferiority TLF in SELUTION SLR 014 DEB vs SOC must be successful for SELUTION SLR 014 DEB.

8.3.2 Handling of Missing Data for Primary and Powered Secondary Endpoint

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection. The following analysis strategies will be adopted to handle missing data with results compared for consistency prior to carrying out the above analysis:

- 1) Only subjects who experienced the primary endpoint (TLF at 12 months) or who had appropriate follow-up (at least 330 days post baseline, given the 30-day visit window allowed around the 12-month visit) will be included in the analysis.
- 2) All subjects will be included in the analysis set including data for subjects missing primary endpoint status due to not experiencing the event and not reaching at least 330 days of follow-up. Data for these subjects will be included as 'NA'. Bayesian method will be used for the imputation. A model will be used for the event probabilities:

$$Y[i, k] \sim \text{dbern}(p[i, k])$$

with

$$\text{logit}(p[i, k]) = \text{beta} * X[k] + \text{logit}(p[1]) + \text{beta0}$$

Where, i represents treatment group ($i = 1$ represents SELUTION SLR 014 DEB, and $i = 2$ represents the comparator group), $X[k]$ are predictors values for subject k . A noninformative prior will be assumed on the intercept parameter beta0 and slope parameters beta , and $\text{Beta}(1,1)$ prior for $p[1]$.

The following variables will be included in the model as covariates:

- Age ($> 75, \leq 75$)
 - Gender
 - Diabetes
 - Lesion length
- 3) Time to event analysis using a Bayesian time to first TLF exponential regression analysis.
 - 4) Tipping point analysis. Here, it is assumed that for all SOC subjects with missing primary endpoint (12-month TLF) status, TLF did not occur. For subjects with missing data, it will be first assumed that the primary endpoint of TLF occurred for exactly one such subject; then the primary analyses will be re-run to assess if noninferiority is met under this assumption. Then it will be assumed the primary endpoint occurred for exactly two SELUTION SLR 014 DEB subjects with missing data, and the primary noninferiority analysis will be rerun. The process will continue sequentially in this manner until all SELUTION SLR 014 DEB subjects with missing data are considered to have met the primary endpoint of TLF. Of interest is the “tipping point”, or i.e., the number of imputed SELUTION SLR 014 DEB TLFs where noninferiority is not met in this analysis.

8.3.3 Analysis of Secondary Endpoints

All secondary endpoints will be analyzed using descriptive methods as described above in section 8.3.

Additional sub-analysis of all endpoints will be conducted based on lesion length and separately on vessel diameter. Lesion lengths above and below 25 mm will be sub-analyzed for each endpoint. Similarly, vessel diameter above and below 2.75 mm will also be sub-analyzed. Details of both analyses will be specified in the SAP.

8.4 Region (US/Outside the US) Heterogeneity

The primary endpoints summaries, including point and interval estimates, will also be reported by region (US vs outside the US [OUS]). To assess consistency of treatment effect size across regions (US versus OUS), region and an interaction of region and treatment will be included in the Bayesian model for the study. For the interaction coefficient, we will calculate

$$p_{int} = 2 * \min\{P(\beta_{int} > 0|\text{Data}), p(\beta_{int} < 0|\text{Data})\}$$

as the two-sided posterior probability of observing an interaction value that is more extreme than 0. This value is similar to a traditional p-value. If $p_{int} < 0.15$ we will conclude that heterogeneity across region is significant and the treatment effect will be calculated and tested within region.

8.5 Subgroup Analyses

The following subgroup analyses will be performed for relevant primary and secondary endpoints:

- SELUTION SLR 014 DEB vs SOC
- SELUTION SLR 014 DEB vs POBA (SOC)
- SELUTION SLR 014 DEB vs DES (SOC) Note: this analysis will include all DES patients (i.e., both 1- and 2-layer ISR).
- 2 stent layers ISR vs 1 stent ISR (i.e., number of stent layers present prior to the point of recruitment)
- BMS ISR vs. no BMS ISR
- DES ISR vs. no DES ISR
- Diabetes vs. No Diabetes
- RVD ≤ 2.75 mm vs. >2.75 mm
- Focal vs diffuse lesions
- ISR occurring less than 1 year after stent implant vs ISR occurring > 1 year after stent implant
- COVID-19 positive vs negative

Treatment group difference (SELUTION SLR 014 DEB versus the SOC) in the primary endpoint rate and the two-sided 95% credible interval of the difference will be presented within each subgroup. A test of interaction on the primary endpoint will be performed to formally assess heterogeneity of treatment effect on the primary endpoint across subgroups in the same manner that will be used the assessment of region heterogeneity discussed above. The purpose of this

analysis is not to formally assess noninferiority within each subgroup, but simply to assess consistency of results across the various subgroups. Subjects with an event or with appropriate follow-up will be included in this analysis. Further details of the subgroup analyses will be provided in the SAP.

8.6 Center Heterogeneity

The primary endpoints summaries, including point and interval estimates, will also be reported by study centers with 10 or more subjects. Consistency of treatment effect across centers will be tested. To assess consistency of treatment effect size across study centers, a Bayesian model will be employed for the subject level data. In this evaluation only centers with 10 or more subjects will be included.

Data for individual k will be assumed to follow a Bernoulli distribution:

$$Y[k] \sim \text{dbern}(p[\text{TRT}[k], \text{center}[k]])$$

where $\text{center}[k]$ is an index variable that indicates the center that the individual k was recruited in, and $\text{TRT}[k] = 1$ for SELUTION SLR™ DEB and $=0$ for SOC.

The assumptions are based on a similar model to the model proposed in Legrand et al.²⁶. The event rate is assumed to have an additive effect for center that varies within study:

$$\text{logit}(p[\text{TRT}[k], \text{center}[k]]) = \delta[\text{center}[k]] + \gamma[\text{center}[k]] * \text{TRT}[k]$$

The two random effects can be interpreted as the influence of the center on the overall TLF rate in the study and on the overall treatment effect, respectively. The center effects $\delta[\text{center}[k]]$ and $\gamma[\text{center}[k]]$, are assumed to be exchangeable and a priori to follow a normal distribution with mean μ_{delta} and μ_{gamma} and standard deviation σ_{delta} and σ_{gamma} , respectively. A uniform prior on (0.1, 10) will be assumed on the random effect variances (σ_{delta} and σ_{gamma}) Gelman et al.²⁷. Independent weakly informative $N(0, 100)$ priors will be assumed for μ_{delta} 's and μ_{gamma} 's. The standard deviation of the random effects can be viewed as a measure of heterogeneity across centers and treatment effect. A value of 1 for standard deviation of random effects ‘...corresponds to substantial heterogeneity.’ Spiegelhalter et al.²⁸; therefore, if the posterior probability that $\sigma_{\text{gamma}} > 1$ exceeds 0.85 and the credible intervals discussed above indicate the interaction is qualitative in nature, then this may preclude all sites from being pooled for the primary analysis, in which case the primary analysis may be re-run excluding study centers causing the interaction.

9 Adverse Events

It is the responsibility of the investigator to assess and report to Sponsor every adverse event and observed device deficiency experienced by the study subject. In this study, subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., “How has your health been since the last visit?”). Any time during the study, the subject

may volunteer information that resembles an AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE eCRF.

AEs shall be assessed and documented throughout the course of the trial beginning after the subject has been randomized. All AEs should be recorded on the appropriate subject CRF. Every AE will be followed-up until the event is resolved, resolved with sequelae, the subject exits the study or until study closure, whichever occurs first.

In case an AE is ongoing at time of study completion, the subject will be followed up per SOC.

9.1 Definitions

9.1.1 Adverse Event

An AE is defined as 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.

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

(MDR Article 2(57))

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Note:

- a. This definition includes events that are anticipated as well as unanticipated events
- b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

Abnormal laboratory findings will be considered AEs, only if determined by the investigator to be clinically significant. Any current condition that is recorded as a pre-existing condition either in the medical history or physical examination section, unless there is a change in nature, severity or degree of incidence, is not an AE.

9.1.2 Adverse Device Effect

An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

9.1.3 Serious Adverse Event

For the US an SAE is any untoward medical occurrence that:

- a) results in death,
- b) is life threatening,
- c) required inpatient hospitalization or prolongation of existing hospitalization,
- d) results in persistent or significant disability/incapacity, or
- e) is a congenital anomaly/birth defect.

For study sites outside the United States (OUS), an SAE is any AE that led to any of the following:

- a) Death,
- b) Serious deterioration in the health of the subject that either resulted in:
 - 1. life-threatening illness or injury, or
 - 2. permanent impairment of a body structure or a body function, or
 - 3. in-patient 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.
 - 5. chronic disease
- c) Fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the clinical study plan, without a serious deterioration in health, is not considered to be an SAE.

Data using both definitions (US and OUS) will be collected and reported according to applicable local regulations and requirements.

9.1.4 Serious Adverse Device Effect

A serious adverse device effect (SADE) is an ADE that results in any of the consequences characteristic of an SAE.

9.1.5 Anticipated Adverse Event

Any AE which by its nature, incidence, severity or outcome has been identified in the protocol or associated study documents (e.g., informed consent documents, device instructions for use, or investigator's brochure).

9.1.6 Unanticipated Adverse Device Effect or Unanticipated Serious Adverse Device Effect

An unanticipated adverse device effect (UADE) is defined in 21 Code of Federal Regulations (CFR) 812.3(s) as any SAE 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 protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of a subject.

In the EU and other OUS countries, the term unanticipated serious adverse device effect (USADE) as defined in International Standards Organization (ISO)14155, is any 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.

9.1.7 Device Deficiency

Inadequacy of a medical device with respect to identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, user errors and inadequate labeling.

Note: device deficiencies that did not lead to an adverse event but could have led to a medical occurrence if either

- a) suitable action had not been taken,
- b) intervention had not been made, or
- c) circumstances had been less fortunate,

shall be reported under the same conditions as an SAE.

Investigators are instructed to report all possible device deficiencies observed during the course of the trial. These incidents will be documented in the eCRF.

Where possible any device that is deemed to have a deficiency should be returned to the Sponsor for analysis.

9.2 Documentation

AEs must be listed on the appropriate eCRF. All AEs will be characterized by the following criteria:

- Intensity or severity
- Relatedness to the study device and procedure
- Outcome
- Treatment or action taken

The following categories of the intensity of an adverse event are to be used:

- **Mild:** Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae;

- **Moderate:** Interferes with the subject's usual activity, but the subject is still able to function;
- **Severe:** Events that interrupt a subject's usual daily activity and generally require a systemic drug therapy or other treatment.

9.3 Relatedness

Relatedness will be determined using the following criteria:

- 1) Not related: relationship to the device or procedures can be excluded when:
 - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
 - the event has no temporal relationship with the use of the investigational device or the procedures;
 - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
 - the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
 - the event involves a body-site or an organ not expected to be affected by the device or procedure;
 - the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
 - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
 - harms to the subject are not clearly due to use error;
 - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- 2) Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- 3) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- 4) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
 - the investigational device or procedures are applied to;
 - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

9.4 Reporting of (Serious) Adverse Events and Device Deficiencies

All participating study sites should report SAEs and device deficiencies that might have led to a SADE to MedAlliance or its designee within 24 hours of knowledge of the event, preferably by completing the eCRF.

The investigator should notify MedAlliance or its designee as soon as possible concerning any subject death during the study. The death should be reported in the eCRF. In addition, the precipitating cause of death should be recorded on an AE eCRF, reflecting an outcome of death, once determined. Documentation of the death event should be sent to MedAlliance as soon as it is available and should include the appropriate completed CRFs, a death certificate and a copy of the notification of the death sent to the IRB/EC, as required. If a death certificate is not available, a detailed statement (death report) signed by the investigator should be provided. A copy of the autopsy report (if this was available/performed) should be made available as well.

The death report should include all of the following, if available:

- Date, time and place of death
- Immediate cause of death
- Circumstance surrounding the death

- Relationship to the investigational device and/or any study-related procedures

It is the responsibility of each Investigator to report all SAEs to their reviewing IRB/EC, according to national regulations and IRB/EC requirements. A copy of the IRB/EC report should be forwarded to the Sponsor or its authorized representative.

Additionally, at OUS sites, all SAEs must be reported to MedAlliance within 24 hours in order to comply with Competent Authority reporting.

All other events should be reported by all participating sites to the Sponsor as soon as possible, preferably upon awareness of the event, by completing an AE eCRF.

In case of emergency, contact the Clinical Research Organization (CRO) **and** the Sponsor by e-mail, phone or fax:

CRO:

IQVIA MedTech

Email address: SelutionISR.medtech@iqvia.com

Sponsor:

MedAlliance

Email address: selutionisr@medalliance.com

9.5 Reporting of Unanticipated Adverse Device Effects or Unanticipated Serious Adverse Device Effects

If an adverse event occurs that the investigator believes may be a potential UADE/USADE, the site should immediately contact MedAlliance or its designee to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a patient, the site should immediately notify MedAlliance.

The investigator shall submit to the reviewing IRB a report of any UADE/USADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. In OUS countries any potential USADE shall be reported according to national regulations. All UADEs/USADEs must be documented by the investigator including the date of onset, a complete description of the event, possible reason(s) for the event, severity, duration, actions taken, and outcome. Copies of all supporting documents should be submitted concurrently with the AE eCRF, documenting the UADE/USADE.

In the US a report from the Sponsor will be submitted to the Food and Drug Administration (FDA) and to all reviewing IRBs/ECs and participating investigators within 10 calendar days after the Sponsor first receives notice of the effect. The Sponsor will submit other reports as required by the FDA and other applicable regulatory agencies.

In EU reports from the Sponsor will be submitted to relevant Competent Authorities within 7 calendar days.

The final determination of an event being classified as an unanticipated event will be initially determined by the CRO providing safety monitoring services for the trial and confirmed by MedAlliance.

9.6 Reporting of Study Endpoint Adverse Events

Whenever a clinical event related to a study endpoint is suspected or identified, all available supporting source documents (i.e., progress notes, discharge summaries, catheterization lab reports, angiographic data of repeat procedure on the target vessel, ECGs, lab results, etc.) are required for evaluation of the event by the CEC. Copies of such documentation shall be obtained from the investigator, blinded / de-identified as to the subjects' identity, and provided to the Sponsor or designee as soon as they are available.

9.7 Reporting Responsibilities

Table 5. Investigator Reporting Responsibilities

Type of Report	Investigator Reporting Responsibilities	
	Report Prepared For	Recommended Reporting Time Frame
Unanticipated Adverse Device Effect/ Unanticipated Serious Adverse Device Effect	Sponsor and IRB/EC ¹	As soon as possible, upon awareness of the effect. Written: As soon as possible, but not later than 3 calendar days after the investigation site personnel becomes aware of the effect.
Withdrawal of IRB/EC Approval or other action on part of the IRB/EC that affects the study	Sponsor	Written: Within 5 working days of IRB/EC decision.
Progress Reports	IRB/EC ¹	At regular intervals, but in no event less than yearly.
Significant deviations from investigational plan	Sponsor and IRB/EC ¹	Emergency: As soon as possible but in no event later than 5 working days after the deviation occurs to protect the life or physical well-being of a subject in an emergency. Non-emergency: Prior approval by Sponsor and if deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subject, IRB/EC and FDA as an IDE supplement.
Inappropriate Informed Consent	Sponsor and IRB/EC ¹	Within 5 working days after the use of the device occurs.
Final Report	Sponsor and IRB/EC ¹	Within 3 months after termination or completion of study or termination of site's participation.
(Serious) Adverse Events	Sponsor and IRB/EC ¹	In accordance with the protocol, applicable local regulations, and IRB/EC requirements.
Other	As Required	Upon request by the IRB/EC or FDA or other Competent Authorities, provide accurate,

Type of Report	Investigator Reporting Responsibilities	
	Report Prepared For	Recommended Reporting Time Frame
		complete, and current information about any aspect of the study.

EC: Ethics Committee; FDA: Food and Drug Administration; IDE: Investigational Device Exemption; IRB: Institutional Review Board.

¹ Reporting to IRB/EC only where required by local legal requirement.

Table 6. Sponsor Reporting Responsibilities

Type of Report	Sponsor Reporting Responsibilities	
	Report Prepared For	Recommended Reporting Time Frame
SAEs	Appropriate CA/EC (OUS)	OUS: All reportable SAEs as defined by MDR Art. 80(2) and MDCG 2020-10-1 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it are to be reported immediately, but not later than 2 calendar days after awareness by Sponsor. Any other reportable events are to be reported immediately, but not later than 7 calendar days following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.
Unanticipated Adverse Device Effects/ Unanticipated Serious Adverse Device Effects	FDA, all reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	US: Written -Within 10 calendar ² days from the time the Sponsor first learns of the effect. OUS: Within 7 calendar days
Withdrawal of IRB/EC Approval or other action on part of the IRB/EC that affects the study	FDA, all reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	Written – Within 5 working days.
Withdrawal of FDA approval	Reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	Written – Within 5 working days.
Device Recall	FDA, all reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	US: Written – Within 30 working days. OUS: Within 2 working days
Progress Reports	FDA, all reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	At regular intervals, but in no event less than yearly.

Type of Report	Sponsor Reporting Responsibilities	
	Report Prepared For	Recommended Reporting Time Frame
Current Investigator List	FDA	Names and addresses of participating investigators at 6-month intervals (starting at 6 months after FDA approval)
Study Closure	FDA, all reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	Within 30 working days of the completion or decision to terminate the study.
Final Report	FDA, all reviewing IRBs/ECs ¹ , participating investigators and appropriate CAs ¹ .	Within 6 months of study closure.
Periodic Serious Adverse Effect/Adverse Device Effect Summaries	Reviewing EC ¹ and appropriate CAs ¹ .	In accordance with OUS regulation and/or local legal requirements or upon request.

CA: Competent Authority; EC: Ethics Committee; FDA: Food and Drug Administration; IRB: Institutional Review Board; MDR: Medical Device Regulation.

¹ EC and CA reporting to the extent required by national, local laws and EC-specific requirements.

² FDA requires 10 working days.

9.8 Data Handling and Record Keeping

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the SELUTION SLR 014 DEB or entered as a control in the investigation.

All core laboratories and clinical sites will maintain study records until the Sponsor notifies them and the reviewing regulatory authorities that research is completed or terminated under the clinical investigation in compliance with national law. Record retention dates will be provided to study sites by Sponsor or its designee at the onsite closeout visit. Archiving of study records will be performed in line with national and international requirements.

If the PI at a site withdraws from the study, (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator). Notice of such transfer will be given in writing to CRO.

9.9 Electronic Data Capture

This trial will use an EDC system called *staicy* which will be provided by the trial CRO IQVIA MedTech. The *staicy* EDC will be web based with data stored using a cloud-based system. Details of the system and instructions for using the system will be provided in a separate Data Management Manual.

9.10 Electronic Case Report Form Completion

An EDC system will be built for the study. The EDC system will include eCRFs designed to capture study information, which are completed by trained site staff.

eCRFs documenting SAEs, U(S)ADEs, device failures and device malfunctions should be submitted via the EDC system as soon as possible, preferably with 24 hours after the investigator becomes aware of the event. All other eCRFs should be completed in a timely manner, preferably within 5-10 days of the subject's enrollment of follow-up visit. All angiographic media should be prepared and sent to the angiographic core laboratory, preferably within 7 working days of data collection. All collected study data will be made available and sent in the appropriate format to the Sponsor, if requested, after the study has reached its primary endpoint at 12 months.

Table 7. Timelines for eCRF completion

Type of eCRF	Recommended Time of Notification
Subject Enrollment eCRF	Within 24 hours of enrollment
Baseline eCRFs	Within 48 hours of enrollment
Procedure eCRFs	Within 48 hours of procedure
Hospital Discharge Form eCRF	Within 48 hours of discharge
Clinical Follow-up eCRFs	Within 48 hours of subject visit
Adverse Event eCRF	Within 48 hours of knowledge of event
Serious Adverse Event/UADE eCRF	Within 24 hours of knowledge of event
Major Event eCRFs	Within 48 hours of event occurrence
Study Exit eCRF	Within 48 hours of subject visit

EC: Ethics Committee; eCRF: electronic Case Report Form; CRO: contract research organization; IRB: Institutional Review Board.

9.11 Investigator Records

Investigators are required to maintain on file the following accurate, complete and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB/EC, MedAlliance, a monitor, the FDA (e.g., a letter sent from the investigator to the IRB/EC), or any other regulatory agency.
- All clinical forms and documentation, including:
 - A copy of the signed subject ICF
 - Date and time of exposure to investigational device

- All procedure and follow-up report forms, including supporting documents
- Records of any AE, including supporting documentation
- Records pertaining to subject deaths during the study
- Documentation and rationale for any deviations from the clinical protocol
- Any other records required by MedAlliance

9.12 Sponsor Records

MedAlliance or designee will maintain the following records:

- All correspondence pertaining to study with the investigator(s), IRB/EC and FDA (or any other competent authority)
- Investigational balloon shipment and inventory reconciliation reports (US sites only)
- Investigator agreements, financial disclosures and current curriculum vitae
- Name and address of each investigator and each IRB/EC involved with the study
- AEs and complaints
- ADEs (whether anticipated or unanticipated)
- Completed eCRFs
- Confirmation of completed subject ICFs
- Clinical Investigational Plan (CIP) and report of prior studies
- Screening visit reports
- Monitoring reports
- Clinical progress reports
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.
- Records pertaining to Data Safety Monitoring Board (DSMB) and CEC activities.
- Statement of the extent to which the good manufacturing practice regulation Part 21 CFR 820 will be followed in manufacturing the balloon.

Table 8. Responsibilities for Submitting Reports and Other Data

Type of Notification/Report/Other Data	Submitted to	Recommended Time Window for Submission
Screening Logs	Sponsor via CRO	Submit weekly
Informed consent not obtained from subject	Sponsor via CRO, IRB/EC	Within 5 working days of index procedure
ECG	ECG Core Lab	Within 24 hours of ECG
Angiography	Angiography Core Lab	Within 24 hours of angiography
Device malfunction/ failure	Notify Sponsor via CRO	Within 24 hours
All SAEs	Notify Sponsor via CRO and IRB/EC	Within 1 working day of knowledge of event
Unanticipated adverse device effects	Notify Sponsor via CRO and IRB/EC	Within 1 working day of knowledge of event
Withdrawal of IRB approval	Notify Sponsor via CRO	Within 5 working days of withdrawal
Annual reports	Sponsor, IRB/EC, Regulatory Bodies	Annually
Emergency deviation from the Investigational Plan	Notify Sponsor via CRO and IRB/EC	Within 5 working days of deviation
Final report	Sponsor, IRB/EC	Within 3 months of study completion or termination

EC: Ethics Committee; ECG: electrocardiogram; IRB: Institutional Review Board.

10 Study Committees

10.1 Steering Committee

The Steering Committee is composed by the PI, MedAlliance representative, CRO and core lab representatives, representative site PIs, and other scientific members with relevant study expertise. The Steering Committee will meet periodically to review study progress and conduct and to provide feedback to the Sponsor on an ad hoc basis. Steering Committee membership will be decided by Sponsor.

10.2 Data Safety Monitoring Board

An independent DSMB will have responsibility for monitoring safety and efficacy aspects of the study. Its conduct will be governed by a written charter describing its rules of operation and responsibilities. It will be composed of at least four members with experience in clinical trial research: three (3) physicians from the fields of cardiology and interventional cardiology and one (1) biostatistician who are not directly involved in the conduct of the trial.

The DSMB will review aggregate and individual subject data related to safety, data integrity, and overall conduct of the trial on a periodic basis, to be defined at their first meeting prior to enrollment of the first subject in the study. The DSMB may be unblinded to treatment group assignment.

The primary responsibility of the DSMB will be to provide oversight on safety aspects of the study. The DSMB may make three primary types of recommendations to the steering committee and study Sponsor as a result of its monitoring activities:

- Continuing the study without changes;
- Stopping the study for safety reasons; or,
- Continuing the study with changes to its protocol or conduct.

Any material changes to the study protocol or conduct recommended by the DSMB that affect the collection or evaluation of scientific evidence, or terms and conditions of the IDE approval, and which the Sponsor desires to implement, will be subject to prior review and approval by the FDA, applicable CA and EC/IRBs.

10.3 Clinical Events Committee

The CEC for this study will include at minimum three (3) member physicians, with at least one (1) interventional cardiologist. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the trial.

At the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a study endpoint related clinical event. All members of the CEC will be blinded to the primary results of the trial and to treatment assignments for review of individual events.

Once the specific criteria for clinical events and endpoints are established, the CEC will be responsible for adjudicating all study endpoint-related clinical events when all necessary data are available. The CEC will also review and adjudicate all potential study endpoint related clinical events when the minimum data are not available. For each adjudicated event in patients who have tested positive for COVID-19 the CEC will indicate if the event outcome is likely to have been impacted by COVID-19 infection.

In the case of attribution, target and non-target lesion/vessel events will be determined using one (1) eCRF data and source documentation verification provided by study investigators and two (2) core laboratory reports. In cases where event attribution is unclear, assignment will be made to the target lesion/vessel.

The details of CEC operations are included in a written charter.

11 Ethical and Regulatory Considerations

This study will be conducted in accordance with the principles outlined in the Declaration of Helsinki, FDA regulations (21CFR), ISO 14155, ICH/GCP Guidelines and any other national or local requirements (including any additional requirements imposed by EC/IRB and/or CA/FDA is applicable).

11.1 Role of the Study Sponsor

MedAlliance has the overall responsibility for the conduct of the study, including assurance that the study meets and is conducted within the regulatory requirements specified by each reviewing regulatory authority and the standards prescribed in ISO 14155. In this study, Sponsor will have certain direct responsibilities and will delegate other responsibilities to IQVIA MedTech (CRO) and other designees. Sponsor, IQVIA MedTech (CRO), and other designees will ensure adherence to the Sponsor general duties, selection of investigators, monitoring, supplemental applications, maintaining records, and submitting reports.

11.2 General Duties

MedAlliance's general duties include submitting the application to appropriate regulatory authorities and obtaining overall regulatory approval.

MedAlliance, or designee, is responsible to obtain the approval from the competent authority, if applicable, prior to any site initiation. MedAlliance will report to the competent authorities any new information that may affect the safety of the subjects or the conduct of the clinical investigation, as applicable.

MedAlliance or designees are responsible for ensuring informed consent is obtained, proper clinical site monitoring is performed, providing quality data that satisfies regulations and informing study investigators of unanticipated adverse device effects events and deviations from the protocol, as appropriate.

As the designated data coordinating center, IQVIA MedTech (CRO) will prepare written reports and a final report as directed by the Sponsor and will coordinate data collection and transfer with the Angiography Core Laboratory and other vendors.

11.3 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code (ID number and subject name code) 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 audit performed by regulatory authorities) provided the data are treated as confidential and that the subject's privacy is guaranteed.

"Protected Health Information" will be treated and maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy rule and the General Data Protection Regulation (EU) 2016/679 (GDPR) on the protection of individuals with regard to the processing of personal data.

The duration of the storage time of the personal data at the investigational sites will be in accordance with the national regulations.

11.4 Informed Consent and Institutional Review Boards or Ethics Committee

Prior to the subject's participation in the study, written ICF is required from all subjects in accordance with their IRB/EC. Informed consent should be obtained in accordance with the FDA regulations (21CFR, Part 50), ISO 14155, ICH/GCP Guidelines, the Declaration of Helsinki and any other national or local requirements. A copy of the signed informed consent document will be given to the subject and another retained by the investigator. Any revisions to the approved informed consent must be reviewed and approved by MedAlliance before submission to the IRB/EC.

The investigator is required to inform MedAlliance and the reviewing IRB/EC within five (5) days if any subject has not appropriately consented to participate in the study. MedAlliance is then required to report any failure to obtain subject consent to the FDA within five (5) working days of learning of such an event. In order to assist with the consent process, MedAlliance will provide a subject consent template form to study sites as a basis for adaptation to local requirements and submission to their IRB/ EC for approval.

IRB/EC approval is required from each institution prior to participation in this clinical study. Subject enrollment may not begin until the IRB/EC and MedAlliance have granted approval for the study site. IRB/EC approval is also required throughout the duration of this clinical study. If IRB/EC approval is withdrawn, MedAlliance must be notified within five (5) working days.

11.5 Selection of Investigators

Sponsor and its designees will select qualified investigators, obtain signed study agreements and provide the investigators with the information necessary to conduct the study.

11.6 Initiation of Study Sites

Prior to subject enrollment, a study initiation visit will be completed at each investigational site to ensure the following: IRB/EC approval has been obtained and documented prior to subject screening, the investigators and study personnel are appropriately trained and clearly understand the study, the investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

11.7 Monitoring

Qualified monitors representing the Sponsor will conduct monitoring activities to ensure that all investigators conduct the study in compliance with the protocol and the Investigators' Agreements. A mixture of on-site and remote monitoring will be utilized. The site will receive notification prior to each monitoring visit during the course of the study. It is expected that the investigator and/or sub-investigator and other appropriately trained study staff are available during the monitoring event.

The progress of the study will be monitored by:

- Ensuring the completed eCRF matches the source documents, and resolve any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.

- Periodic on-site visits and if necessary remote monitoring of data.
- Frequent telephone or email communications between the Investigator and assigned study site monitors.

11.8 Visits

Periodic monitoring visits will be made in accordance with the approved monitoring plan at all active study sites throughout the clinical study to assure that the Investigator's obligations are fulfilled and all applicable regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the IRB/EC, device and device inventory are controlled and the Investigator is executing all agreed activities.

IQVIA MedTech (CRO) will perform the monitoring responsibilities according to their standard operating procedures. Protocol deviations and site or PI non-compliance will be closely monitored and a corrective and preventative action will be initiated where needed.

IQVIA MedTech (CRO) will review significant new information, including unanticipated adverse events and ensure that such information is provided to the appropriate regulatory authorities and the investigators. Sites will notify the relevant reviewing IRB/ECs.

On one or more occasions, the study site may be inspected or audited by MedAlliance, its designee, or applicable regulatory authorities. The Investigator will be informed in advance of this visit and is expected to allow access to the original medical records and provide all requested information. A representative or designee of Sponsor may accompany the study site monitor to the site.

11.9 Protocol Compliance

The investigator is required to conduct the study in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify MedAlliance and the reviewing IRB/EC in writing, no later than five (5) working days after any significant deviation from the study plan, to protect the life or physical well-being of a subject in an emergency. Except in such emergency, prior approval by MedAlliance is required for significant deviations from the study plan. MedAlliance categorizes instances of protocol non-compliance as either violations or deviations.

11.10 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 (MedAlliance and IRB/EC) investigator using the investigational balloon for study purposes

- Subject inclusion/exclusion violations and protocol requirement violations that affect the primary endpoints of the study design

In some instances, compliance issues with the consent process may occur. The investigator should seek guidance from the site's IRB/EC to ensure the subject received appropriate information to consider their participation in the study. The investigator is obligated to take any action the IRB/EC feels is necessary, including subject removal from the study.

Deviations in the consent process for subjects that the IRB/EC allows to continue in the study will be considered protocol violations in the analysis of study data. All violations will be reported to FDA in accordance with applicable regulatory timelines.

The study site should report the protocol violation to the reviewing IRB/EC and provide a copy of the notification to MedAlliance. The site should also report the protocol violation to MedAlliance on the applicable CRF.

11.11 Protocol Deviations and Medical Emergencies

Protocol deviations are defined as instances where protocol requirements are not followed in such a manner whereby data is unusable or unavailable. The investigator will not deviate from the protocol without the prior written approval of the Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the viability of the study. In medical emergencies, prior approval for protocol deviations will not be required but the Sponsor personnel must be notified within 24 hours of occurrence. Protocol deviations are less serious in nature and do not require IRB/EC notification, as long as they do not have an effect on the rights, safety or welfare of the study subject. 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. Both protocol deviations and violations will be reported to the FDA in progress reports.

11.12 Study Close-out Visit

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits, all data have been entered into the EDC system, all queries have been resolved, and final electronic signatures have been obtained) a study closeout visit will be performed. All unused study devices, and any unused study materials and equipment will be collected and returned to Sponsor. The study monitor will ensure that the Investigator's regulatory files are current and complete, and that all outstanding issues from previous visits have been resolved. Other issues that will be reviewed with site personnel at this visit include: discussing retention of study files, the possibility of site audits, publication policy, and to ensure that the Investigator will notify the site's IRB/EC regarding study closure.

11.13 Device Accountability and Storage

Tracking of the investigational product used in this study will be consistent with 21 CFR Part 821 and ISO 14155, and in accordance with location-specific requirements.

The site will notify the Sponsor as soon as possible after opening any SELUTION SLR 014 DEB used in this study, including the description, dimensions, and lot number of the device. If a SELUTION SLR 014 DEB is opened, but not implanted, it must be returned to the Sponsor in accordance with the Sponsor's packaging and shipping instructions.

The SELUTION SLR 014 DEB should be stored in its original packaging in a dry and dark location, at room temperature typically 15-25°C (59-77°F).

Subject to availability, the Sponsor will provide the site with replacement consignment inventory of the SELUTION SLR 014 DEB. Additionally, the PI or designee will ensure that an adequate supply of SELUTION SLR 014 DEB is on hand to support uninterrupted enrollment of subjects in the study. Orders for additional devices must originate from the PI or designated study personnel.

11.14 Labeling

The SELUTION SLR 014 DEB and its associated components will have a label that will be visible on the pertinent shipping cartons and storage containers. The required labels or manuals will bear the following information:

- Name, model and lot number of the stent
- Name and addresses of the manufacturer and distributor
- Labeling statement: "CAUTION – Investigational Device. Limited by United States Law to Investigational Use." – applicable for US sites only. For OUS sites, the investigational device statement will be compliant with applicable local regulations.
- Quantity of contents
- All relevant contraindications, hazards, adverse device effects, interfering substances or devices, warnings and precautions
- Expiration date

11.15 Other Institutions and Physicians

The study is not transferable to other institutions attended by the investigator unless prior approval is obtained from MedAlliance, the governing competent authority (if applicable) and the appropriate IRB/EC. Additional sites may be included in this study, but may not exceed the limits set by the FDA. Only approved investigators are authorized to participate in the study; however, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject with an investigational device. In any such situations, the IRB/EC and the investigator must continue to provide oversight for that subject's medical care and rights as a research subject. MedAlliance will ensure that the necessary support is available to any physician providing immediate care for a subject in order to answer questions about the investigational stent and provide guidance in collecting the necessary documentation

required for the clinical study. Documentation obtained will then be forwarded to the approved investigator for review and signature before this data may be used to support the endpoints of the study.

11.16 Subject Insurance

Sponsor will maintain appropriate clinical study liability insurance coverage as required under applicable laws and regulations for the duration of the trial.

11.17 Supplemental Applications

If required, changes in the Investigational Plan will be submitted to the appropriate regulatory authorities and/or IRB/EC to obtain approval before implementation of the changes.

11.18 Medicare Population Statement

This study is evaluating the safety and effectiveness of the SELUTION SLR 014 PTCA DEB in subjects with cardiovascular disease undergoing interventions for in-stent restenotic coronary artery disease. The results of this study are expected to be generally applicable to the populations eligible for Medicare. The prevalence of cardiovascular disease increases with age, and the majority of study subjects are expected to meet Medicare eligibility criteria based on age alone. Subjects with end-stage renal disease are excluded from the study because the outcomes in this population would be expected to excessively confound the overall study results; therefore, the applicability of the study results to this subset of the Medicare population is not guaranteed. Subjects eligible for Medicare due to disability are eligible to participate in the study provided they are willing and able to provide informed consent and comply with study procedures and required follow-up evaluations; therefore, the study results are expected to be applicable to this subset of Medicare beneficiaries. In summary, the study is highly relevant to the population eligible for Medicare and is designed so that the study results are expected to be generally applicable to the Medicare beneficiary population.

12 Risk Analysis

12.1 Potential Risks

Potential risks associated with the SELUTION SLR 014 DEB are those related to conducting percutaneous transluminal coronary angioplasty (PTCA) procedures for the treatment of coronary artery lesions, using the SELUTION SLR 014 DEB as PTCA Balloon Catheter and the administration of Sirolimus. Limited published data is available for the specific risks associated with the use of Sirolimus DEBs and therefore the risk occurrence presented below is based on similar techniques, alternative therapies or competitor products. The relative occurrence data will be updated with new data specific to Sirolimus DEBs as and when data becomes available.

12.1.1 Conducting PTCA Procedures

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

12.1.2 Use of SELUTION SLR 014 DEB Drug Coating or Active Pharmaceutical Ingredient

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.

12.2 Potential Benefits

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with the SELUTION SLR 014 DEB may reduce the potential for added stent layers and provide a noninferior treatment of ISR to SOC.

Moreover, in this clinical investigation, all subjects will have a more intense medical follow-up compared with standard practice, which can be beneficial to the long-term clinical outcome of study participants.

Additionally, information gained from the conduct of this study may be of benefit to others with the same medical condition. Efficacy and safety data collected on the SELUTION SLR 014 DEB will contribute to expanding the knowledge of use of DES in interventional cardiology.

12.3 Risk Mitigation

All subjects will receive chronic daily antiplatelet therapy (or single antiplatelet therapy plus systemic anticoagulation in patients with indications for the latter) for a minimum of 30 days in the experimental group and for a minimum of 3-6 months (depending on bleeding risk) in the SOC group receiving a DES, or a minimum of 1 month in the SOC group receiving BA. Subjects will also receive a minimum of 75 mg aspirin daily, to be taken indefinitely.

To minimize potential risks associated with study procedures, all efforts will be made to select investigators who are experienced and skilled in using interventional devices.

Additionally, at study initiation, all investigators will be trained regarding the IFU and protocol. All enrolling investigators will be instructed on appropriate subject selection in an effort to minimize the risk of recruiting ineligible subjects to the study.

Subjects will be monitored closely throughout the trial duration and will be evaluated at pre-specified time points to assess their clinical status. An independent data monitoring committee will monitor safety of study participants throughout the trial.

At all study sites subject material will be maintained in strict confidence and in accordance with the law. To that end specific guidelines will be followed as they relate to use of subject identifiers, storage of subject information, transmission of data or subject information, disclosure

of data, data access and contact with study subjects. Sites will be monitored for compliance with these standards.

To minimize the risk of the invasive assessment and the study procedure, investigators will be certified based on the following: current medical license, privileges to perform these services at their treatment center, and board certification in Cardiology, or equivalent experience. At study initiation all investigators will be instructed on appropriate methods and the protocol for the procedure. Additionally, all enrolling investigators will be instructed on appropriate subject selection, in an effort to minimize the risk of recruiting subjects to study treatment who are found subsequently to be ineligible for the study. Appropriate angiographic technique and “as low as reasonably practical” principles will be utilized to expose subjects to the least amount of contrast dye and radiation while providing high resolution angiograms.

Risks associated with the SELUTION SLR 014 DEB were identified and evaluated using a failure mode and effects analysis (FMEA) approach in accordance with *EN ISO 14971:2012, Medical Devices – Application of risk management to medical devices*. The risk management analysis was completed by identifying the hazards and estimating the probabilities and severities of risks associated with energy hazards, biological hazards, environmental hazards and hazard arising from functional failure, maintenance, aging and substantial misuse. All efforts have been made to minimize these risks during the development and pre-clinical testing of the SELUTION SLR 014 DEB. Therefore, it is believed that the risks have been reduced to as low as possible for this type of device, without compromising its intended purpose and use.

13 Amendments

Amendments to relevant study documents shall be notified to, or submitted for approval by, the EC/IRB and relevant regulatory authorities (CA in Europe and FDA in US), according to the applicable local regulations and requirements. The version number and date of amendments shall be documented. Changes to the approved clinical Investigation which have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation will not be implemented without notifying or seeking prior approval from the relevant EC/IRB and regulatory authorities.

14 Use of Information and Publication

MedAlliance intends to publish the results of this clinical investigation. MedAlliance reserves the right to include the report of this clinical investigation, or any other datasets generated by the investigation, in any regulatory documentation or submissions or in any informational materials prepared for the medical profession. The ownership of the data shall at all times be held by MedAlliance. MedAlliance further reserves the right to use anonymized data generated by the investigation for the following purposes: future metanalysis; research and development on the trial device (or related devices); support of patent applications.

MedAlliance and the Steering Committee reserve the right for the first publication of the clinical investigation results. MedAlliance 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 from their own site, after the first publication has occurred.

Any prior publication in any way or form is not permitted, without approval by MedAlliance. Institution and Investigator reserve the right to publish the results of data obtained solely at their investigational site for the study. Before publishing, however, the institution and PI shall submit copies of any manuscript proposed for publication to MedAlliance for review at least 30 days in advance of submission for publication or presentation to a publisher or other third party.

The Study National PIs and/or Study Steering Committee reserve the right to review and approve all manuscripts prior to publication. The Sponsor reserves the right to delete any confidential information or other proprietary information (including trade secrets and patent protected materials) that is being utilized and inappropriately released, and to provide input from other investigators in the study regarding the content and conclusions of the publication or presentation. In addition, MedAlliance may extend such review period for another 90 days, if deemed necessary, but will not unreasonably delay review and comment.

All information not previously published concerning the test product and MedAlliance is considered confidential and is the sole property of MedAlliance. Site personnel agree to use this information only in connection with this study and will not use it for other purposes without written permission from MedAlliance.

15 Suspension, Premature Termination or End of the Study

No formal statistical rule for early termination of the trial due to insufficient effectiveness or safety issues has been defined. However, the DSMB may define rules by which an early termination may be recommended.

MedAlliance reserves the right to discontinue the clinical trial at any stage, with suitable written notice to the investigator. Possible reason(s) may include but are not limited to:

- An unanticipated adverse device effect occurs and it presents an unreasonable risk to subjects.
- The DSMB or Steering Committee makes a recommendation for the early termination of the trial.
- Further product development is cancelled.

Should discontinuation of the trial occur, the investigator shall return all clinical trial materials (including devices) to the Sponsor and provide a written statement to the IRB/EC explaining the reasons for premature termination. In the event of a premature termination of the clinical investigation enrolled subjects will be followed up as per the institution's SOC.

MedAlliance, or its designees, retain the right to remove either the Investigator or the investigational site from the study for issues of non-compliance with the protocol or regulatory requirements.

If, for any reason, the Sponsor suspends or prematurely terminates the investigation at an individual investigation site or suspends or terminates the entire investigation then the Sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC/IRB is notified, either by the principal investigator or by the Sponsor. If the suspension or premature termination was in the interest of safety, the Sponsor shall inform all other principal investigators. The principal investigator or authorized designee shall promptly inform the

enrolled subjects at his/her investigation site, if appropriate. For EU member states, in cases of early termination or temporary halt, the summary and the report shall become publicly accessible immediately after submission.

The Clinical Investigation will end after the final study visit has been performed for the last patient. Study end reporting to regulatory authorities will be performed within 15 days of the study end (but 24 hours if based on safety grounds) or according to local requirements (if these are different). In addition, a clinical investigation report will be submitted within one year of the end of the clinical investigation or within three months of the early termination or temporary halt. For EU Member States, the summary and the clinical investigation report shall become publicly accessible in a publicly accessible database, at the latest when the device is registered and before it is placed on the market or within 1 year after it is available, whichever occurs first.

Appendix A: Abbreviations and Acronyms

Abbreviation/Acronym	Complete Term
ABR	Angiographic Binary Restenosis
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
ARC	Academic Research Consortium
ARD	Absolute Risk Difference
AV	Arteriovenous
BA	Balloon Angioplasty
BARC	Bleeding Academic Research Consortium
BMS	Bare-Metal Stent
CA	Competent Authority
CAD	Coronary Artery Disease
CABG	Coronary Artery Bypass Graft
CBC	Complete Blood Count
CCS	Chronic Coronary Syndrome
CCSC	Canadian Cardiovascular Society Classification
CEC	Clinical Events Committee
CI	Confidence Interval
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
CKMB	Creatine Kinase-Muscle/Brain
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
cTn	Cardiac Troponin
DAPT	Dual Antiplatelet Therapy
DCB	Drug-Coated Balloons
DEB	Drug Eluting Balloon
DES	Drug Eluting Stent
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EES	Everolimus-Eluting Stents
EU	European
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
FKBP12	FK506-binding protein 12
FMEA	Failure mode and effects analysis
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation/Acronym	Complete Term
ICF	Informed Consent Form
IDE	Investigational Device Exemption
iFR	Instantaneous Wave-Free Ration
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Standards Organization
ISR	In-Stent Restenosis
ITT	Intention-to-Treat
IVL	Intravascular Lithotripsy
IVUS	Intravascular Ultrasound
IQR	Interquartile Range
kg	Kilogram
LBBB	Left Bundle Branch Block
LLL	Late Lumen Loss
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MAE	Major Adverse Event
MAR	Missing at Random
µg	Microgram
MDR	Medical Device Regulation
mg	Milligram
MI	Myocardial Infarction
MLD	Minimum lumen diameter
mm	Millimeter
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target of Rapamycin
NCDR	National Cardiovascular Data Registry
NHLBI	National Heart, Lung, and Blood Institute
NSTEMI	Non-ST elevation myocardial infarction
OCT	Optical Coherence Tomography
OPC	Objective Performance Criteria
OUS	Outside the United States
PCB	Paclitaxel-Coated Balloons
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PK	Pharmacokinetic
PLGA	Poly (lactic-co-glycolic acid)
POBA	Plain Old Balloon Angioplasty
PP	Per-Protocol
PSVR	Peak Systolic Velocity Ratio
PTA	Percutaneous Transluminal Angioplasty
PTCA	Percutaneous Transluminal Coronary Angioplasty
R	Recommended
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation/Acronym	Complete Term
SAS	Statistical Analysis Software
SCAI	Society for Cardiac Angiography and Intervention
SCB	Sirolimus-Coated Balloon
SD	Standard Deviation
SEM	Scanning Electron Microscope
SLR	Sustained Limus Release
SOC	Standard of Care
STEMI	ST-Elevation Myocardial Infarction
TIA	Transient Ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularization
TVF	Target Vessel Failure
TVR	Target Vessel Revascularization
tx	Treatment
UADE	Unanticipated Adverse Device Effect
UDMI	Universal Definition of Myocardial Infarction
ULN	Upper Limit of Normal
US	United States
USADE	Unanticipated Serious Adverse Device Effect
ZES	Zotarolimus-Eluting Stents

Appendix B: Definitions

Acute Closure:

Occurrence of new (during the procedure) severely reduced flow (Thrombolysis in Myocardial Infarction [TIMI] grade 0–1) within the target vessel that persists and requires rescue by stenting or other treatment, or results in myocardial infarction (MI) or death. Abrupt closure requires proven association with a mechanical dissection of the treatment site or instrumented vessel, coronary thrombus, or severe spasm. Abrupt closure does not mean “no reflow” (due to microvascular flow limitation), in which the epicardial artery is patent but had reduced flow. Abrupt closure also does not mean transient closure with reduced flow in which the index treatment application does reverse the closure.

Subacute Closure:

Abrupt closure that occurs after procedure is completed (and subject left the catheterization laboratory) and before the 1-month follow-up evaluation.

Threatened Acute Closure: Grade-B dissection and $\geq 50\%$ diameter stenosis or any dissection of grade C or higher.

Acute Gain:

Immediate dimensional change in minimum lumen diameter (MLD) (mm) that occurred after the final post-dilatation as compared with the MLD at baseline and measured by quantitative coronary angiography from the average of two orthogonal views.

Adverse Device Effect (ADE):

An adverse device effect (ADE) is a device-related adverse event (AE), i.e., any adverse event for which a causal relationship between the device and the event is at least a reasonable possibility (the relationship cannot be excluded). Note that this definition includes AEs resulting from insufficient or inadequate instructions for use (IFU), deployment, implantation, installation or operation, or any malfunction of the investigational medical device, as well as any event resulting from user error or from intentional misuse of the investigational medical device.

Adverse Event (AE):

An AE is defined as 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.

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

(MDR Article 2(57))

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Note:

- a. This definition includes events that are anticipated as well as unanticipated events
- b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

Abnormal laboratory findings will be considered AEs, only if determined by the investigator to be clinically significant. Any current condition that is recorded as a pre-existing condition either in the medical history or physical examination section, unless there is a change in nature, severity or degree of incidence, is not an AE.

Anticipated Adverse Event (AE):

Any undesirable experience (sign, symptom, illness, abnormal laboratory value or other medical event) occurring to a subject, whether or not considered related to the investigational product(s) or drug regimen prescribed as part of the clinical protocol, that has been predefined in the protocol or associated study documents (e.g., informed consent documents, device instructions for use, or investigator's brochure), that is identified or worsens during a clinical study.

Bleeding:

Bleeding events will be adjudicated from the Bleeding Academic Research Consortium (BARC)²⁵ Type 0 to 5. Type 2 and greater will be considered significant.

Type 0: No bleeding.

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.

Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding that would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional (b) leading to hospitalization or increased level of care, or (c) prompting evaluation.

Type 3:

3a: Overt bleeding plus a hemoglobin drop of 3-5 g/dL (provided hemoglobin drop is related to bleed) or requiring transfusion.

3b: Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed) or cardiac tamponade or bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid).

3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal bleeds) or intraocular bleed compromising vision

Type 4: Coronary artery bypass graft (CABG)-related bleeding, transfusion of ≥ 5 U whole blood or packed red blood cells within 28-hour period, chest tube output of ≥ 2 L within a 24-hour period

Type 5: Fatal bleeding.

5a: Probable fatal bleeding, no autopsy or imaging confirmation but clinically suspicious.

Canadian Cardiovascular Society Classification (CCSC) of Angina:²⁹

Class I: Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity. Angina upon walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold or wind, or under emotional stress, or only during the first hours after awakening. Angina if walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III: Marked limitations of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace.

Class IV: Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.

Cerebrovascular Accident or Stroke:

Cerebrovascular accident is defined as the occurrence of cerebral infarction (ischemic stroke) or intracerebral hemorrhage and atraumatic subarachnoid hemorrhage (hemorrhagic stroke). Stroke is defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria or other focal neurological deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis or rupturing aneurysm that either:

1. Persists > 24 hours or results in death in < 24 hours, or
2. Persists < 24 hours duration if the following treatments were used:
 - a. Pharmacologic, i.e., thrombolytic drug administration, or
 - b. Non-pharmacologic, i.e., neuro-interventional procedure (e.g., intracranial angioplasty)
3. Persists < 24 hours but has neuro-radiological (magnetic resonance imaging [MRI] or computed tomography [CT]) diagnostic changes suggestive of acute tissue injury.

Clinically Driven Target Lesion Revascularization (TLR):

Revascularization at the target lesion (defined as the previous stented segment plus 5.00 mm proximal or distal) associated with ischemic symptoms, or positive functional ischemia study, including invasive fractional flow reserve (FFR), instantaneous wave-free (iFR) or other intracoronary physiologic study and angiographic diameter stenosis $\geq 50\%$; or revascularization

of a target lesion with diameter stenosis $\geq 70\%$ by coronary angiography without either ischemic symptoms or a positive functional study.

Clinically Driven Target Vessel Revascularization (TVR):

Revascularization in the target vessel including sidebranches associated with ischemic symptoms or positive functional ischemia study and an angiographic diameter stenosis $\geq 50\%$ by coronary angiography; or revascularization of a target vessel with diameter stenosis $\geq 70\%$ by coronary angiography without either ischemic symptoms or a positive functional study.

De Novo Lesion:

A native coronary artery lesion not previously treated.

Deaths:

All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Cardiac Death: Death due to immediate cardiac cause (e.g., MI, low output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This also includes all procedure-related deaths, including those related to concomitant treatment.

Vascular Death: Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other vascular cause.

Non-Cardiovascular Death: Death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

Device Success:

Attainment of $< 30\%$ residual stenosis of the target lesion using the assigned study treatment only.

Dissection National Heart, Lung, and Blood Institute (NHLBI) Classification:³⁰

Grade A: Small radiolucent area within vessel lumen disappearing with passage of contrast material.

Grade B: Appearance of contrast medium parallel to vessel lumen disappearing within a few cardiac cycles.

Grade C: Dissection protruding outside vessel lumen persisting after passage of contrast material.

Grade D: Spiral-shaped filling defect with or without delayed run-off of contrast material in antegrade flow.

Grade E: Persistent luminal filling defect with delayed run-off of contrast material in distal lumen.

Grade F: Filling defect accompanied by total coronary occlusion.

Distal Embolization:

New abrupt cut-off or filling defect distal to the treated lesion.

Emergent Bypass Surgery:

Coronary bypass surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure resulting in new ischemia.

In-Segment (or lesion) Measurement:

In-segment will include 5.00 mm proximal and distal to the treated segment.

In-Stent Measurement:

Measurements within boundaries of the stent.

In-Stent Restenosis:

Stenosis of > 50% within a prior coronary stent (not extending > 5.00 mm beyond the proximal or distal stent edge) with associated angina or coronary ischemia by functional stress testing, electrocardiogram (ECG) or laboratory testing.

Intracoronary Thrombus:

Presence of a filling defect within lumen, surrounded by contrast material seen in multiple projections in absence of calcium within the filling defect, or persistence of contrast material within lumen, or a visible embolization of intraluminal material downstream.

Late Loss Index:

Ratio of late loss to acute gain.

Late Lumen Loss (LLL):

Difference between post-procedure MLD and follow-up angiography minimal lumen diameter.

Lesion Class (American College of Cardiology/American Heart Association Class):³¹

Type A: Minimally complex, discrete (length < 10 mm), concentric, readily accessible, non-angulated segment (< 45°), smooth contour, little or no calcification, less than totally occlusive, not ostial in location, no major side branch involvement, absence of thrombus.

Type B: Moderately complex, tubular (length 10–20 mm), eccentric, moderate tortuosity of proximal segment, moderately angulated segment (> 45°, < 90°), irregular contour, moderate or heavy calcification, total occlusions < 3 months old, ostial in location, bifurcation lesions requiring double guide wires, some thrombus present.

Type B1: one adverse characteristic.

Type B2: two or more adverse characteristics.

Type C: Severely complex, diffuse (length > 20 mm), excessive tortuosity of proximal segment, extremely angulated segments > 90°, total occlusions > 3 months old and/or bridging collaterals, inability to protect major side branches, degenerated vein grafts with friable lesions.

Lesion Success:

Attainment of < 30% residual stenosis of target lesion using any percutaneous method.

Major Adverse Cardiac Events (MACE):

All-cause death, MI (Q-wave or non-Q-wave), any clinically-driven target lesion revascularization (TLR).

Minimal Lumen Diameter (MLD):

Average of two orthogonal views (when possible) of the narrowest point within the area of assessment – in lesion, in stent or in segment. Visually estimated during angiography by the investigator and measured during quantitative coronary angiography by the angiographic core laboratory.

Myocardial Infarction (MI):

Note: Regardless of standard definitions, for this study periprocedural myocardial infarction will be adjudicated according to the manufacturer-defined URL, rather than the site laboratory defined ULN, to reduce the variability introduced by arbitrary site ULNs.

Society for Cardiac Angiography and Intervention Definitions:

Peri-procedural myocardial infarction will be defined within the first 48 hours post-procedure according to criteria proposed by the Society for Cardiac Angiography and Intervention³².

- I. If baseline Creatine kinase-muscle/brain (CKMB) (or troponin if CKMB not available) is normal:
The peak CKMB measured within 48 hours of the procedure rises to > 10 times the local laboratory upper limit of normal (ULN), or to > 5 times ULN with new pathologic Q-waves in > 2 contiguous leads or new persistent Left bundle branch block (LBBB), OR in the absence of CKMB measurements and a normal baseline cardiac troponin (cTn), a cTn (I or T) level measured within 48 hours of the PCI rises to > 70 times the local laboratory ULN, or > 35 times ULN with new pathologic Q-waves in > two (2) contiguous leads or new persistent left bundle branch block (LBBB).
- II. If baseline CKMB (or troponin if CKMB is not available) is elevated but values are stable or falling:
The CKMB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
- III. If baseline CKMB (or troponin if CKMB is not available) is elevated but values are not stable or falling:
The CKMB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level, AND there is evidence of new myocardial injury based on new ST elevation or depression and clinical signs of clinically relevant MI.

Academic Research Consortium-2 Definitions:

Peri-procedural myocardial infarction will also be classified using Academic Research Consortium-2 (ARC-2) definitions

Myocardial infarction:

- Absolute rise in cardiac troponin (from baseline) ≥ 35 times upper reference limit
- Plus 1 (or more) of the following criteria
 - New significant* Q waves or equivalent
 - Flow-limiting angiographic complications
 - New “substantial” loss of myocardium on imaging

Significant periprocedural myocardial injury:

- Absolute rise in cardiac troponin (from baseline) ≥ 70 times upper reference limit

Fourth Universal Definition of Type 1 MI:

Spontaneous myocardial infarction will be defined according to the Fourth Universal Definition of Type 1 MI³³:

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

Criteria for PCI-Related MI ≤ 48 Hours After the Index Procedure (Type 4a MI)

Coronary intervention–related MI is arbitrarily defined by an elevation of cTn values >5 times the 99th percentile URL in patients with normal baseline values. In patients with elevated preprocedure cTn in whom the cTn level are stable ($\leq 20\%$ variation) or falling, the postprocedure cTn must rise by $>20\%$. However, the absolute postprocedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required:

New ischemic ECG changes;

Development of new pathological Q waves*;

Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;

Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization. †

*Isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but <5 times the 99th percentile URL.

†Postmortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial hemorrhage meets the type 4a MI criteria.

No Reflow:

Sustained or transient reduction in antegrade flow not associated with an obstructive lesion at treatment site.

Percent Diameter Stenosis:

The value calculated as $100 \times (\text{reference vessel diameter [RVD]} - \text{MLD}) / \text{RVD}$ using the mean values from two orthogonal views (when possible) by quantitative coronary angiography.

Perforation:

Perforations will be classified as follows:

Angiographic Perforation: Perforation detected by clinical site or core laboratory at any point during procedure.

Clinical Perforation: Perforation requiring additional treatment (including efforts to seal perforation or pericardial drainage), or resulting in significant pericardial effusion, acute closure, MI or death.

Pericardial Hemorrhage/Tamponade: Perforation resulting in cardiac tamponade.

Percutaneous Coronary Intervention (PCI):

All interventional cardiology methods for treatment of (CAD).

Procedure Success:

Attainment of < 30% residual stenosis of the target lesion using the assigned study device only without occurrence of in-hospital MACE.

Restenotic Lesion:

Lesion in a vessel segment that has undergone prior percutaneous treatment with or without a stent placement.

Reference Vessel Diameter (RVD):

Average of normal segments within 10 mm proximal and distal to target lesion from two orthogonal views using quantitative coronary angiography.

Serious Adverse Device Effect (SADE):

ADE that results in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE):

For the US an SAE is any untoward medical occurrence that:

- a) results in death,
- b) is life threatening,
- c) required inpatient hospitalization or prolongation of existing hospitalization,
- d) results in persistent or significant disability/incapacity, or

e) is a congenital anomaly/birth defect.

For study sites outside the United States (OUS), an SAE is any AE that led to any of the following:

a) Death,

b) Serious deterioration in the health of the subject that either resulted in:

1. life-threatening illness or injury, or
2. permanent impairment of a body structure or a body function, or
3. in-patient 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.
5. chronic disease

c) Fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

Stent Thrombosis:

Stent thrombosis should be reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the catheterization lab.

Timing

Acute stent thrombosis: 0–24 hours post–stent implantation

Subacute stent thrombosis: > 24 hours–30 days post–stent implantation

Late stent thrombosis: 30 days–1 year post–stent implantation

Very late stent thrombosis: > 1 year post–stent implantation

Categories (Definite, Probable and Possible):

Definite Stent Thrombosis:

Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.

Angiographic Confirmation of Stent Thrombosis:

Presence of an intracoronary that originates in the stent or in the segment 5.00 mm proximal or distal to the stent, and presence of at least one of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest.
- New ischemic ECG changes that suggest acute ischemia.
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI).
- Note: The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

Non-occlusive: Intracoronary thrombus is defined as a spheric, ovoid or irregular non-calcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

Occlusive Thrombus: TIMI 0 or TIMI 1 intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from side branch).

Pathological Confirmation of Stent Thrombosis:

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

Probable Stent Thrombosis:

Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within first 30 days.
- Regardless of time after index procedure, any MI related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
- For studies with ST-elevation MI population, exclusion of unexplained death within 30 days may be considered evidence of probable stent thrombosis.

Possible Stent Thrombosis:

Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

Study Deviation:

Incident in which the investigator or site personnel did not conduct the study according to the clinical protocol or investigator agreement.

Major Deviation: Any deviation from subject inclusion and exclusion criteria or subject informed consent procedures.

Minor Deviation: Deviation from a clinical protocol requirement such as incomplete/inadequate subject testing procedures, non-compliance with study thienopyridine medication regimens, follow-ups performed outside specified time windows, etc.

Target Lesion Failure (TLF):

Cardiac death, target vessel MI or clinically-driven TLR.

Target Lesion Revascularization (TLR):

Repeat percutaneous intervention of target lesion or bypass surgery of target vessel performed for restenosis or other complication of target lesion. Target lesion is defined as the treated segment starting 5.00 mm proximal to the stent and ending 5.00 mm distal to the stent.

Target Vessel Failure (TVF):

Composite endpoint comprised of cardiac death, target vessel MI or clinically-driven TVR.

Target vessel failure will be reported when any of the following events occur:

- Recurrent MI occurs in territory not clearly attributed to a vessel other than target vessel.
- Cardiac death not clearly due to a non-target vessel endpoint.
- TVR is determined.

Target Vessel Myocardial Infarction (MI):

MI that occurs in a territory that cannot be clearly attributed to a vessel other than the target vessel.

Target Vessel Revascularization (TVR):

Repeat percutaneous intervention or surgical bypass of any segment of the target vessel. Target vessel is defined as the entire major coronary vessel proximal and distal to target lesion, including upstream and downstream branches and the target lesion itself.

Thrombolysis in Myocardial Infarction (TIMI) Classification 7:³⁴

TIMI 0: No perfusion.

TIMI 1: Penetration with minimal perfusion. Contrast fails to opacify entire bed distal to stenosis for duration of cine run.

TIMI 2: Partial perfusion. Contrast opacifies entire coronary bed distal to stenosis. However, rate of entry and/or clearance is slower in coronary bed distal to obstruction than in comparable areas not perfused by dilated vessel.

TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

Total Occlusion:

Lesion with no flow (TIMI 0). Total occlusions are usually classified as persisting less than or more than 3 months (chronic total occlusion).

Transient Ischemic Attack (TIA):

Focal neurological abnormality of sudden onset and brief duration (lasting less than 24 hours) that reflects dysfunction in the distribution of the affected artery. Transient ischemic attacks (TIAs) include transient monocular blindness (e.g., amaurosis fugax, defined as a transient episode of monocular blindness, or partial blindness, lasting 10 minutes or less) and transient hemispheric attacks.

Unanticipated Adverse Device Effect (UADE) or Unanticipated Serious Adverse Device Effect (USADE):

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect 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 protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of a subject. In the OUS countries, the term unanticipated serious adverse device effect (USADE) is used for serious

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

Unstable Angina:

Per the American College of Cardiology/American Heart Association 2002 Guideline Update for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction (NSTEMI), there are three [3] principal presentations of unstable angina:³⁵

1. *Rest Angina*: Angina occurring at rest, and prolonged, usually > 20 minutes.
2. *New-Onset Angina*: New-onset angina of at least CCS class III severity.
3. *Increasing Angina*: Previously diagnosed angina that has become distinctly more frequent, longer in duration or lower in threshold (i.e., increased by greater than or equal to one CCS class to at least CCS class III severity).

Vascular Complications:

Vascular complications may include the following:

1. Pseudoaneurysm.
2. Arteriovenous fistula.
3. Peripheral ischemia/nerve injury.
4. Vascular event requiring transfusion or surgical repair.

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