



SELUTION SLR™ 014 ISR

STATISTICAL ANALYSIS PLAN (SAP)

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

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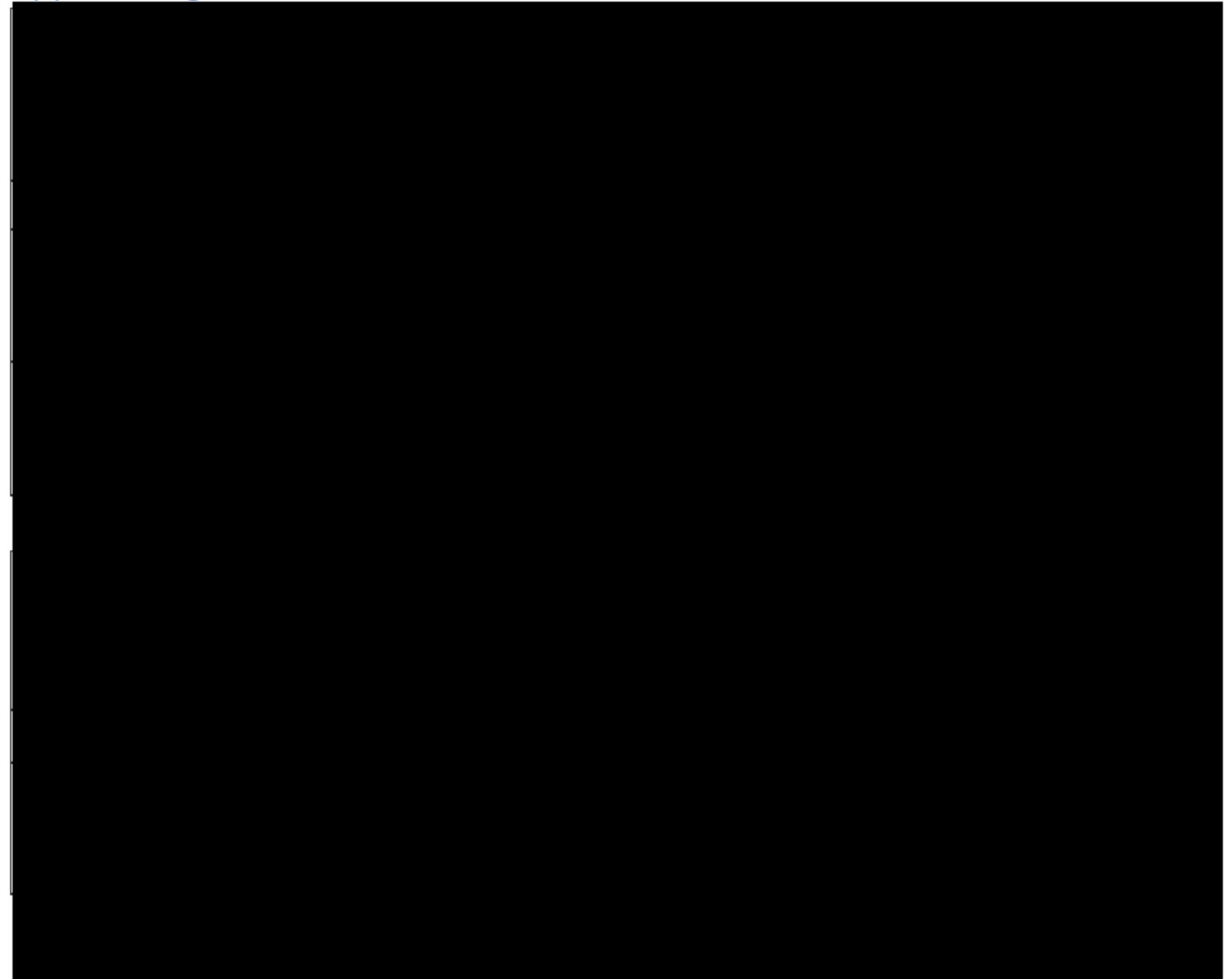
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Approval Signatures



Document History

Revision	Author	Date Reviewed/Revised	Changes	Reason for Changes
Version 1.0		29February2024	New Document	N/A
Version 2.0		17September2024	Clarifying Statistical Methods	Revised in accordance with US FDA Study Design Considerations
Version 3.0		01April2025	<p>Title Page: Restoring proper CIP Rev # & date, as well as adding a SAP Rev # & date to title page</p> <p>Section 2: Clarification on CEC adjudication of endpoint events, Primary endpoint analysis revised to include ARC-2 definition if minimal requirements for SCAI are not met, as well as numbering adjustments</p> <p>Section 3: Added wording to include mPP and mITT analysis sets</p> <p>Section 3.4.1: deletion of header to combine paragraphs with previous section</p> <p>Section 4: Added modified PP and modified ITT</p>	Clarifications and to address concerns about missing cardiac enzymes/biomarker data

			<p>populations for additional sensitivity analyses</p> <p>Section 5.2: Including the mITT analysis set sensitivity analysis</p>	
Version 3.1		15April2025	<p>Administrative revisions due to changes from V3.0 not being fully incorporated and final executed in error (never released).</p> <p>Section 2.1: Broken out to specify edits previously presented under Section 2.</p> <p>Section 2.4: Broken out to specify edits previously presented under Section 2.</p> <p>Section 2.4: Replaced “Primary” with “Secondary” (relating to the endpoint) to clarify previous edit made in error on Version 3.0.</p> <p>Section 4: Included “definitions for” (related to wording) to clarify previous edits in Version 3.0.</p>	<p>Addressing concerns about previous tracked changes and final versions containing formatting issues.</p> <p>Providing additional clarity as a result.</p>

1 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.

For control subjects, the choice of DES is open to the treating investigator but must be either a zotarolimus-eluting stent (ZES) or an everolimus-eluting stent (EES); balloon angioplasty (BA) is an acceptable alternative if clinically justified. Investigators are required to declare which SOC treatment option (DES or BA) 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. The study center has the option to perform the 6 months, 2 year, 3 year, 4 year, and 5 year follow-up visits by phone. 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. More trial design details are available in the clinical investigation plan. 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.

2 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.

2.1 Adjudication of Endpoint Events

A Clinical Events Committee (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. Hence, the CEC will use all information available and its members' best judgment to adjudicate all potential endpoint events irrespective of whether all desired information about the event (e.g., biomarkers, narrative information) are available, and no potential endpoint event will go unadjudicated.

2.2 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.

2.3 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

If this hypothesis-driven secondary endpoint is met, then this endpoint will also be tested for superiority.

2.4 Non-hypothesis-driven Secondary Endpoints

An additional analysis of TLF at 12 months will be done comparing SELUTION SLR 014 DEB versus DES among subjects with one or two previous layers of stent. This analysis will mirror the analysis of the hypothesis-driven secondary endpoint, except it will also include patients treated with DES with two previous stent layers instead of just one previous stent layer.

Other non-hypothesis-driven secondary clinical/performance/imaging endpoints listed below will be conducted comparing SELUTION SLR 014 DEB versus SOC regardless of previous layers of stent.

2.4.1 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.
- Composite efficacy endpoint at 12 months: TLF defined as the patient-oriented composite of any death, myocardial infarction (MI) (spontaneous using Universal Definition of Myocardial Infarction [UDMI] and peri-procedural using Academic Research Consortium [ARC]-2), 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])
- MI (spontaneous MI using the 4th Universal Definition of Myocardial Infarction [UDMI]; peri-procedural MI using 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 thrombosis¹
- Bleeding according to Bleeding Academic Research Consortium (BARC) classification 2-5 (assessed to 12 months).
- 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)

2.4.2 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

2.4.3 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

3 Primary Endpoint Analysis

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, mPP, and mITT analysis sets.

3.1 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:

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

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

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 $\delta^{Eff} = 10\%$ is the noninferiority margin.

3.2 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

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

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 error rate for testing noninferiority is bounded by 2.5%.

3.3 Sample Size Assumptions

See section 8.1 in clinical investigation plan for justification of 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.

3.4 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:

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

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

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 $\delta^{Eff} = 10\%$ 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

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

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 one-sided type I error rate for testing the primary and secondary hypotheses of noninferiority is bounded by 5%.

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:

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

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

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™ DEB and DES, respectively.

The criterion for success is based on the posterior probability of the alternative hypothesis (i.e., of superiority 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 superior 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. The threshold, π^3 was selected such that the one-sided type I error rate for testing the primary, secondary, and tertiary hypotheses is bounded by 5%.

4 Study Populations

The primary analysis population will be the per-protocol population. The intent-to-treat, modified per-protocol, and modified intent-to-treat populations will be used for sensitivity analyses for assessing the impact of protocol deviations on the results.

4.1 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 major study inclusion and exclusion criteria. 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.

Major inclusion and exclusion criteria are defined as below.

- Major Clinical Inclusion Criteria

- Subject is willing and able to provide informed consent and comply with study procedures and required follow-up evaluations.
- Major Imaging Inclusion Criteria
 - Target lesion is within a native coronary artery or major branch.
 - 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.
 - 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.
- Major Clinical Exclusion Criteria
 - ST-elevation myocardial infarction (STEMI) within 30 days.
 - 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).
- Major Imaging Exclusion Criteria
 - Target lesion has >30% residual stenosis by visual estimate or dissection greater than NHLBI type C after pre-dilation/pre-treatment.

4.2 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.

4.3 Modified Per-protocol (mPP)

The modified per-protocol population is defined as a subset of the per-protocol analysis set with non-missing pre-discharge cardiac enzymes / biomarker data for determination of MI or who otherwise have sufficient follow-up data to conclusively determine primary endpoint status (i.e., experienced a primary endpoint event within 1 year).

4.4 Modified Intent-to-treat (mITT)

The mITT population is defined as a subset of the ITT analysis set with non-missing pre-discharge cardiac enzymes / biomarker data for determination of MI or who otherwise have sufficient follow-up data to conclusively determine primary endpoint status (i.e., experienced a primary endpoint event within 1 year).

4.5 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. This population will be used for the analysis of the secondary imaging endpoints.

5 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. These characteristics will be compared between the SELUTION SLR 014 DEB arm and SOC arm in addition to the DES and POBA subgroups of the SOC arm. Special attention will be paid to the following baseline covariates for assessing the comparability of the SELUTION SLR 014 DEB arm with the overall SOC arm, the DES subgroup, and the POBA subgroup:

- Age ($> 75, \leq 75$)
- Gender
- Diabetes
- Lesion length ($>26\text{mm}, \leq 26\text{mm}$)

The relative frequency of these baseline covariates in the DEB arm will be compared against those of the overall SOC arm, the DES subgroup, and the POBA subgroup. Comparisons will report Pearson Chi-Square tests to obtain two-sided p-values which will be compared with an $\alpha = 0.15$.

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 confidence intervals will be performed at $\alpha = 0.05$ (two-sided) unless otherwise stated. P-values will only be calculated for primary, secondary, and exploratory endpoints and the baseline covariates of interest. All Bayesian analyses will report treatment effect estimates with two-sided 95% credible intervals. All descriptive statistical analyses will be performed using Statistical Analysis Software (SAS) for Windows version 9.4 or later. Bayesian analyses will be performed using the open-source program Just Another Gibbs Sampler (JAGS) version 4.3.1 or later.

5.1 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.

5.2 Handling of Missing Data for Primary and Hypothesis-driven Secondary Endpoints

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 in the ITT and MITT analysis sets for sensitivity analyses 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. In each treatment group, a separate logistic model will be used for the event probabilities:

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

$$\text{logit}(p[k]) = \beta * X[k] + \beta_0$$

Where $X[k]$ are predictor values for subject k . Noninformative priors will be assumed on the slope parameters β and intercept β_0 . Ten thousand (10,000) completed data sets will be generated and the posterior probability of non-inferiority will be calculated in each completed data. The probability of non-inferiority after accounting for missing data is the average of these calculated posterior probabilities for each imputed data. This SAP-defined model supersedes the model specified in the protocol and will be the sole prespecified analysis method for this analysis.

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

- Age ($> 75, \leq 75$)
 - Gender
 - Diabetes
 - Lesion length ($> 26\text{mm}, \leq 26\text{mm}$)
3. Time to event analysis using a Bayesian time to first TLF exponential regression analysis. Each group's time to TLF will be assumed to follow an exponential distribution with the following exponential model:

$$Y_{DEB}[k] \sim \text{exponential}(\lambda_{DEB}) \text{ and } Y_{SOC}[k] \sim \text{exponential}(\lambda_{SOC})$$

Where λ_{DEB} and λ_{SOC} are the hazards for TLF for the SELUTION SLR 014 DEB group and SOC group respectively. Priors will be assigned for each hazard.

$$\lambda_{DEB} \sim \text{gamma}(0.1, 0.1) \text{ and } \lambda_{SOC} \sim \text{gamma}(0.1, 0.1)$$

The posterior distributions for the hazards will be used to inform the posterior distribution for 1-year TLF rates:

$$\pi_{DEB} = 1 - \exp(-\lambda_{DEB}) \text{ and } \pi_{SOC} = 1 - \exp(-\lambda_{SOC})$$

The posterior distributions for π_{DEB} and π_{SOC} will be used to compute posterior probabilities of non-inferiority.

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.

5.3 Region 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

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

as the two-sided posterior probability of observing an interaction value that is more extreme than 0. The coefficient β_{int} will be computed using a logistic model including treatment, region, and their interaction.

$$\text{logit}(p[k]) = \beta_0 + \beta_T * TRT[k] + \beta_R * region[k] + \beta_{int} * TRT[k] * region[k]$$

Where $TRT[k]$ and $region[k]$ are indicator variables for treatment and region respectively. Noninformative priors will be applied on all the β parameters.

The value p_{int} 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. Subjects with an event or with appropriate follow-up will be included in this analysis.

5.4 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:

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

Where $TRT[k] = 1$ is an indicator variable for SELUTION SLR 014 DEB and $= 0$ for SOC, and $center[k]$ is an index variable indicating which center that subject k was recruited in.

The assumptions are based on a similar model to the model proposed in Legrand et al.² The event rate is assumed to have an additive effect for center that varies within study:

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

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 $\delta(center[k])$ and $\gamma(center[k])$, are assumed to be exchangeable and a priori to follow a normal distribution with means μ_δ and μ_γ and standard deviations σ_δ and σ_γ respectively. A uniform prior on (0.1, 10) will be assumed on the random effect variances σ_δ and σ_γ . Gelman et al.³ Independent weakly informative $N(0, 100)$ priors will be assumed for μ_δ and μ_γ . 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.⁴; therefore, if the

posterior probability that $\sigma_Y > 1$ 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.

5.5 Analysis of Adverse Events and Device Deficiency/Malfunctions

Adverse events will be summarized using descriptive statistics.

- Site-reported U(S)ADE presented by system organ class and preferred term.
- Site-reported AE presented by system organ class and preferred term.
- Site-reported SAE presented by system organ class and preferred term.
- Site-reported intervention-related AEs presented by system organ class and preferred term.
- Site-reported device deficiency/malfunction categories.

Posterior probability calculations comparing the treatment groups will only be presented for AEs, SAEs, and deficiency/malfunction categories whose frequency exceeds 10. If p_{DEB} and p_{SOC} are the probability of the AE/deficiency/malfunction with the DEB and SOC groups respectively, we will report the posterior distribution that $p_{DEB} > p_{SOC}$, that is, the posterior probability that the probability of the AE/deficiency/malfunction is larger with DEB than SOC. Non-informative independent priors Beta (1, 1) will be assumed on p_{DEB} and p_{SOC} , respectively.

5.6 Analysis of Non-hypothesis-driven Secondary Endpoints

All non-hypothesis-driven secondary endpoints will be analyzed using Bayesian methods similar to those of the primary and hypothesis-driven secondary endpoints.

The comparison of 12 month TLF rates between SELUTION SLR 014 DEB and DES in one and two layers of previous stents will be done in a manner identical to the hypothesis-driven secondary endpoint as detailed in section 3.4, reporting a posterior probability for non-inferiority.

5.6.1 Analysis of Secondary Clinical/Performance/Imaging Endpoints

For categorical secondary clinical/performance/imaging endpoints, the parameters p_B and p_S are the rates in each treatment group. Beta(1,1) priors will be fit on each of the parameters to develop a one-sided posterior probability of a difference between the two groups:

$$p_{diff} = P(p_B^{Sec} - p_S^{Sec} < 0 | Data)$$

For continuous secondary clinical/performance/imaging endpoints, the parameters μ_B and μ_S are the means in each treatment group. Noninformative priors will be fit on each of the parameters to develop a one-sided posterior probability of a difference between the two groups:

$$p_{diff} = P(\mu_B^{Sec} - \mu_S^{Sec} < 0 | Data)$$

5.7 Subgroup Analysis

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

- 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
- Lesion length ≤ 26 mm vs. > 26 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 in the primary and hypothesis-driven secondary endpoints and the respective two-sided 95% credible interval of the differences will be presented within each subgroup. A test of interaction on each primary and hypothesis-driven secondary endpoint will be performed to formally assess heterogeneity of treatment effect on the primary and hypothesis-driven secondary endpoints across subgroups in the same manner that will be used in the assessment of region heterogeneity discussed above.

$$\text{logit}(p_s[k]) = \beta_0 + \beta_T * TRT[k] + \beta_R * subgroup[k] + \beta_{int} * TRT[k] * subgroup[k]$$

Where $p_s[k]$ is the probability of the endpoint of interest, $TRT[k]$ is an indicator for treatment, and $subgroup[k]$ is an indicator for the subgroup of interest. A two-sided posterior probability for the interaction being more extreme than 0 will be calculated as:

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

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.

Treatment group differences in the non-hypothesis-driven secondary endpoints and 95% credible intervals will also be reported within each subgroup. Categorical non-hypothesis-driven secondary endpoints will have their subgroup interactions assessed in the same manner as what will be used in the assessment of region heterogeneity discussed above.

$$\text{logit}(p_s[k]) = \beta_0 + \beta_T * TRT[k] + \beta_R * subgroup[k] + \beta_{int} * TRT[k] * subgroup[k]$$

Where $p_s[k]$ is the probability of the secondary endpoint of interest, $TRT[k]$ is an indicator for treatment, and $subgroup[k]$ is an indicator for the subgroup of interest. A two-sided posterior probability for the interaction being more extreme than 0 will be calculated as:

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

Continuous non-hypothesis-driven secondary endpoints will have their subgroup interactions assessed using a similar scheme, but with a normal linear regression model.

$$y_s[k] = \beta_0 + \beta_T * TRT[k] + \beta_R * subgroup[k] + \beta_{int} * TRT[k] * subgroup[k]$$

Where $y_s[k]$ is the secondary endpoint of interest. A two-sided posterior probability for the interaction being more extreme than 0 will once again be calculated as:

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

Noninformative priors will be applied on all the β parameters.

6 References

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