STATISTICAL ANALYSIS PLAN

ProspectIve, SingLe-Arm, Global MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery and/or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon and In-Stent Restenosis

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Statistical Analysis Plan Version 6.0
06JAN2021

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1 INTRODUCTION

This statistical analysis plan (SAP) outlines the data and procedures used for assessing the safety and performance in Protocol CP-1005, Cohort 2, (which is equivalent to Protocol CP-1005-B): prospective, single-arm, global multi-center study to evaluate treatment of obstructive superficial femoral artery (SFA) and/or popliteal lesions with a novel paclitaxel-coated percutaneous angioplasty balloon and in-stent restenosis (ISR).

This SAP has been developed to align with the following protocols:

PROTOCOL NUMBER CP-1005

- Version 11.0 – Australia, Belgium, Italy and New-Zealand
- Version 8.0 – Germany, Spain and UK and sites from Australia, Belgium, Italy sites not participating in ISR cohorts
- Version 8.1 - France only

PROTOCOL NUMBER CP-1005-B

- Version 2.0 – Austria and Poland
- Version 3.1 - Germany only

Subjects enrolled in Protocol CP-1005, Cohort 2, (which is equivalent to Protocol CP-1005 B), the ISR population, are to be followed for three years. Any further changes to the protocol may necessitate changes to this plan. For any details where the SAP differs from the clinical study protocol, the methods and details described in the SAP will supersede the protocol. Changes from planned analyses will be documented with rationale in Section 13.

2 STUDY OBJECTIVES

The objective of this study is to assess the safety and efficacy of the Stellarex 0.035" OTW drug-coated angioplasty balloon (Stellarex 035 DCB) for treatment of in-stent restenosis (ISR) in the superficial femoral (SFA) and/or popliteal arteries.

3 STUDY DESIGN

The study is a prospective, multi-center, non-randomized, single-arm trial to demonstrate efficacy and safety of the Stellarex 035 DCB by comparison to pre-defined performance goals for the treatment of ISR in the SFA and/or popliteal arteries. Up to 130 subjects with ISR were planned for enrollment. At the time of this revision, the study completed enrollment with 129 subjects.

4 DISCUSSION OF STUDY DESIGN

This is a prospective, international, multi-center, single-arm study. All subjects will be treated with the Stellarex 035 DCB. Subjects meeting the definition of Rutherford Clinical Category (RCC) 2, 3 or 4 with atherosclerotic lesion(s) ≤20 cm located in the SFA and/or popliteal artery are eligible for enrollment.

A second cohort (Cohort 2-ISR) has been added to the study to evaluate patients with ISR. Subjects meeting the definition of RCC 2, 3 or 4 with in-stent restenosis in the SFA and/or popliteal artery are eligible for enrollment.

The study was initially planned with the interim 6-month and final 12-month analyses in a Bayesian framework. However, prior to the 6-month interim analysis the statistical design was revised based on regulatory feedback to a frequentist analysis with study endpoints evaluated at the single fixed time point of 12 months. The interim and final analysis in the Bayesian framework was removed.

5 STUDY HYPOTHESES

There are two co-primary endpoints in the statistical design of this study. The Stellarex 035 DCB will be evaluated by comparison to efficacy and safety performance goals, PGe, and PGs, respectively. The two endpoints and their corresponding statistical hypotheses are:

- Primary Efficacy: Primary patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from clinically driven target lesion revascularization (CD-TLR).

  $H_0: \pi_e \leq PGe$

  $H_1: \pi_e > PGe$

  Where π_e is the proportion of subjects experiencing primary patency at 12 months post-procedure and PGe is the efficacy performance goal.

- Primary Safety: Freedom from device and procedure-related death through 30 days post procedure and freedom from target limb major amputation and CD-TLR through 12-months post procedure, which is called 'freedom from safety composite events' in the following text.

  $H_0: \pi_s \leq PGs$

  $H_1: \pi_s > PGs$

  Where π_s is the proportion of subjects experiencing freedom from safety composite events and PGs is the safety performance goal.

- Secondary Efficacy: Freedom from TLR through 12-months post procedure.

  $H0: \pi es \leq PGes$

  $H1: \pi es > PGes$

  Where π_{es} is the proportion of subjects experiencing freedom from TLR at 12 months post-procedure and PGes is the secondary efficacy performance goal.

6 RATIONALE AND JUSTIFICATION FOR PERFORMANCE GOALS

The FDA written feedback dated June 9, 2016 for Q160693 recommended inclusion of a secondary assessment for effectiveness using a performance goal (PG) based on literature values which should be met for study success. The EXCITE PTA historical control that was originally planned for primary analysis of this study was removed in Version 5. The primary analysis for the study will use a PG for efficacy (PGe) and safety (PGs).

To develop performance goals for efficacy and safety, Philips conducted a literature search and review of clinical publications specific to the treatment of femoropopliteal-ISR. Eight (8) ISR trials, including 5 randomized controlled trials (RCTs), 2 PMA supplements and one prospective "all comers" study, with minimal one-year follow-up were identified and reviewed.

A random-effect-model meta-analysis was performed by using Comprehensive Meta Analysis (CMA) software that combines the results of the multiple studies described above to estimate the weighted average of treatment effects for efficacy and safety separately. Meta-analytic results were considered to make recommendations for the PGe, as well as the PGs.

Selection of Efficacy Performance Goal (PGe)

The primary efficacy endpoint is primary patency at 12 months, defined as the absence of target lesion restenosis per duplex ultrasound (peak systolic velocity ratio [PSVR] ≤ 2.5) and freedom from CD-TLR. A systolic velocity ratio >2.5 suggests >50% diameter restenosis.

The performance of Percutaneous Transluminal Angioplasty (PTA) from seven ISR studies (5 RCTs, one PMA Supplement and one prospective "all comers" study) is shown below in Table 6.1. Table 6.1 provides a meta-analysis of reported efficacy outcomes for 244 PTA subjects. The weighted average rate of 12-month primary patency is 32.2% (95% CI=23.4%, 42.4%).

Table 6.1. Meta-Analysis 12-month Primary Patency Rates (PPR) in PTA Subjects[1-7]

Model	Study	Study Design	PP(n)/N	Statistics for each study			Weight (Random)
				PPR	Lower Limit	Upper Limit	Relative Weight
	Lutonix ISR (PMA SSED)[1]	RCT	8/16	0.496	0.270	0.724	11.15
	FAIR/Krankenberg[2]	RCT	15/40	0.375	0.240	0.532	16.36
	PACUBA/Kinstner[3]	RCT	4/32	0.134	0.053	0.300	10.70
	Orchid DCB/Liao[4]	RCT	16/31	0.516	0.345	0.683	15.24
	DEBATE ISR/Liistro[5]	Prospective all-comers	11/39	0.282	0.164	0.441	15.36
	RELINE/Bosiers[6]	RCT	12/44	0.280	0.168	0.429	16.04
	EXCITE ISR (K140775)[7]	RCT	10/42	0.238	0.133	0.389	15.15
Random			76/244	0.322	0.234	0.424	

The Vascular InterVentional Advances (VIVA) Physicians, Inc. (Rocha-Singh, et al., 2007)[8], published an analysis of the safety and performance goals for prospective single-arm trials of bare nitinol stents to treat patients with debilitating claudication associated with femoropopliteal (FP) atherosclerotic lesions. VIVA Physicians analyzed the subject-level data of the PTA control arm from three FDA submitted, RCTs conducted by industry. The analysis identified 116 patients in the PTA control arm with a 12-month FP patency of 28%. A similar cohort of 191 patients was identified from the medical literature in which the 12-month vessel patency equaled 37%. From these combined patient cohorts, an expected vessel patency for PTA was estimated to equal 33%. VIVA Physicians concluded that the bare nitinol stent 12-month efficacy performance goal should be set to equal twice this rate to establish superiority of nitinol stenting over PTA.

Employing VIVA's method in determining the Stellarex 035 DCB 12-month efficacy performance goal (PGe), a PGe of 64% (2*32.2%) is proposed as being clinically reasonable,

relevant and meaningful to demonstrate superiority of the Stellarex DCB over PTA in treating ISR.

Selection of Safety Performance Goal (PGs)

The primary safety endpoint is defined as freedom from device and procedure-related death through 30 days post procedure and freedom from target limb major amputation and CD-TLR through 12-months post procedure, which is referred to as 'freedom from safety composite events' hereafter and reported under the "Event Free" column in Table 6.2 and Table 6.3.

Table 6.2 provides a meta-analysis of reported primary safety outcomes for 437 PTA subjects. The weighted average rate of 12-month freedom from safety composite events for PTA subjects is 50.1% (95% CI=38.7%, 61.5%).

Table 6.2. Meta-Analysis Primary Safety (Freedom from Safety Composite Events) in PTA Subjects[1-7,9]

Model	Study	Study Design	Event Free(n)/N	Statistics for each study			Weight (Random)
				Event Free Rate	Lower Limit	Upper Limit	Relative Weight
	Lutonix ISR (PMA SSED)[1]	RCT	17/28	0.610	0.423	0.770	11.26
	FAIR/Krankenberg[2]	RCT	18/44	0.410	0.276	0.559	12.70
	PACUBA/Kinstner[3]	RCT	9/39	0.230	0.124	0.386	11.38
	Orchid DCB/Liao[4]	RCT	20/31	0.645	0.465	0.791	11.48
	DEBATE ISR/Liistro[5]	Prospective all-comers	28/42	0.667	0.513	0.792	12.33
	RELINE/Bosiers[6]	RCT	18/44	0.410	0.276	0.559	12.70
	EXCITE ISR (K140775)[7]	RCT	22/56	0.390	0.272	0.522	13.26
	IN.PACT Admiral ISR (PMA SSED)[9]	Single arm	99/153	0.647	0.568	0.719	14.90
Random			231/437	0.501	0.387	0.615	

Evaluating the study-level data from six ISR studies involving 375 DCB subjects, we are presenting the associated data for freedom from safety composite events at 12 months under the "Event Free" column in Table 6.3. The weighted average rate of freedom from safety composite events is 82.4% (95% CI=67.8%, 91.2%).

Table 6.3. Meta-Analysis Primary Safety (freedom from Safety Composite Events) in DCB Subjects[1-5,9]

Model	Study	Study Design	Event Free(n)/N	Statistics for each study			Weight (Random)
				Event Free Rate	Lower Limit	Upper Limit	Relative Weight
	Lutonix ISR (PMA SSED)[1]	RCT	38/52	0.731	0.596	0.834	18.15
	FAIR/Krankenberg[2]	RCT	41/47	0.872	0.743	0.941	16.48
	PACUBA/Kinstner[3]	RCT	17/35	0.490	0.331	0.651	17.83
	Orchid DCB/Liao[4]	RCT	31/33	0.939	0.787	0.985	12.34
	DEBATE ISR/Liistro[5]	Prospective all-comers	38/44	0.864	0.728	0.938	16.43
	IN.PACT Admiral ISR (PMA SSED)[9]	Single arm	147/164	0.899	0.842	0.936	18.78
Random			312/375	0.824	0.678	0.912	

In Philips' Stellarex Vascular e-registry (SAVER), the Stellarex 035 DCB was used to treat 212 patients with in-stent restenosis. The rate of freedom from CD-TLR (a driver of the safety composite events) at 12 months is 84%.

The proposed PGs is 65%. This PGs weights the response of PTA subjects from Table 6.2 (50.1%) with the response of DCB subjects from Table 6.3 (82.4%), and the response of Stellarex 035 DCB ISR subjects in the SAVER registry (84%).

Selection of Secondary Efficacy Performance Goal (PGes)

The Secondary Efficacy endpoint is the Freedom from TLR through 12-months post procedure. Meta-analysis (Table 6.4) includes the studies recommended by FDA (SAVER, In.Pact Admiral and Lutonix) and the FAIR and Orchid DCB RCTs (i.e., Level 1 evidence). The PACUBA study was excluded due to the outlier outcomes and DEBATE-ISR study was excluded as well due to the small sample size and non-RCT study. Given that not all studies reported both CD-TLR and TLR and CD-TLR is a clinically more meaningful endpoint, the CD-TLR rate was priorly selected when both CD-TLR and TLR reported in the same study and the TLR rate was used when the CD-TLR rate was not available. The meta-analytic result for 12-month freedom from CD-TLR/TLR rate in DCB subjects is 86.6% (95% CI = 81.2%, 90.6%) as shown in Table 6.4. The freedom from CD-TLR/TLR rate after DCB treatment of ISR is expected to equal the weighted average rate from the meta-analysis, i.e. 86.6%.

Table 6.4 Meta-Analysis for 12-month Freedom from (TLR or CD-TLR) in DCB Subjects

Model	Study	Study Design	Event Free(n)/N	Parameter	Statistics for each study			Weight (Random)
					Event Free Rate	Lower Limit	Upper Limit	Relative Weight
	SAVER registry[10]	Single arm	178 / 212	CD-TLR	0.84	0.784	0.883	34.14
	IN.PACT Admiral ISR (PMA SSED)[9]	Single arm	139 / 155	TLR	0.899	0.840	0.937	26.35
	Lutonix ISR (PMA SSED)[1]	RCT	41 / 52	CD-TLR	0.784	0.652	0.875	20.72
	FAIR/Krankenberg[2]	RCT	40 / 44	TLR	0.908	0.780	0.965	11.55
	Orchid DCB/Liao[4]	RCT	31 / 33	CD-TLR	0.933	0.780	0.982	7.24
Random			429/496		0.866	0.812	0.906	

The proposed performance goal of freedom from CD-TLR or TLR is 76%, which is set at 10% below the meta-analysis result.

On November 17, 2020, SPNC/Philips had a teleconference with the FDA (Q160693/S005). FDA discussed their concern over the mix and match of TLR and CD-TLR with the different studies for determination of the performance goal and asked if the use of a performance goal of CD-TLR is less strict. SPNC/Philips stated that not all of the studies collected TLR rates, and for this reason the approach was taken to include reported CD-TLR rates alongside TLR rates. Additionally, CD-TLR indicates a more urgent need to re-vascularize based on objective, pre-defined criteria. SPNC/Philips agreed that while using any TLR may be more stringent, it is unlikely that the difference between TLR and CD-TLR would be that different. The meta analysis results for rate of freedom from TLR from four ISR studies involving 497 DCB subjects are

presented in Table 6.5. The weighted average rate of freedom from 12-month TLR is 87.9% (95% CI=83.2%, 91.5%) which is a 1.3% difference compared to the 86.6% weighted average rate of freedom from CD-TLR or TLR shown in Table 6.4.

Table 6.5 Meta-Analysis Secondary Efficacy (12-month freedom from TLR) in DCB Subjects

Model	Study	Study Design	Event Free(n)/N	Statistics for each study			Weight (Random)
				Event Free Rate	Lower Limit	Upper Limit	Relative Weight
	SAVER registry[10]	Single arm	177 / 212	0.834	0.778	0.878	39.98
	IN.PACT Admiral ISR (PMA SSED)[9]	Single arm	139 / 155	0.899	0.841	0.938	29.00
	LUTONIX ISR (PMA SSED)[1]	Single arm	78/86	0.907	0.825	0.953	19.38
	FAIR/Krankenberg[2]	RCT	40/44	0.908	0.780	0.965	11.63
Random			434/497	0.879	0.832	0.915	

In addition, Philips has reviewed PTA TLR data from four peripheral arterial disease (PAD) ISR studies (three RCTs, one single arm study) per FDA comments.

Table 6.6 provides a meta-analysis of reported secondary efficacy outcomes for 319 PTA subjects. The weighted average rate of 12-month freedom from TLR is 50.7% (95% CI=38.34%, 63.13%).

Table 6.6 Meta-Analysis Secondary Efficacy (12-month freedom from TLR) in PTA Subjects

Model	Study	Study Design	Event Free(n)/N	Statistics for each study			Weight (Random)
				Event Free Rate	Lower Limit	Upper Limit	Relative Weight
	FAIR/Krankenberg[2]	RCT	21/40	0.525	0.373	0.673	22.08
	IN.PACT Admiral ISR (PMA SSED)[9]	Single arm	98/153	0.641	0.562	0.713	28.90
	RELINE/Bosiers[6]	RCT	19/44	0.422	0.286	0.570	22.60
	EXCITE ISR (K140775)[7]	RCT	34/82	0.417	0.316	0.526	26.42
Random			172/319	0.507	0.383	0.6313	

The Stellarex DCB PGes of 76% proposed is 49.9% higher than the 50.7% PTA freedom from TLR rate, which indicates a 51.3% relative reduction in TLR rate. This 76% PGes is clinically meaningful as experts in the treatment of PAD have stated that a DCB with 20%-50% less TLR rate than non-drug therapies would be clinically acceptable.[11]

Based on the specification in section 11.2, all secondary endpoints will be evaluated in the MITT analysis set and will be based on non-missing data. SPNC/Philips is blinded to the results of 12 month freedom of TLR, except for the known information of 121 subjects with 12 month data

available for this study. For example, the secondary endpoint would be achieved with 121 subjects of no-missing data if there are 102 or more free TLR, the observed rate would be 84% (102/121) (95% CI = 76.5%, 90.3%).

7 DETERMINATION OF SAMPLE SIZE

The performance of the Stellarex 035 DCB will be assessed by comparison to the performance goals established as stated above.

At the time of this revision, the study enrollment has been completed. The actual sample size is 129 in which 121 subjects have completed 12-month follow-up. The aim is to evaluate whether the sample size of 129 is an adequate sample size to yield sufficient power for demonstrating statistical significance for the primary hypotheses.

Primary Efficacy Endpoint

Available meta-analytic results for 12-month primary patency rate in DCB subjects is 70.2% (95% CI = 53.8%, 82.7%) as shown in Table 7.1, which serves as the reference rate for what is expected to be observed for this study.

Table 7.1. Meta-Analysis 12-month Primary Patency Rates in DCB Subjects[1-5]

Model	Study	Study Design	PP(n)/N	Statistics for each study			Weight (Random)
				PPR	Lower Limit	Upper Limit	Relative Weight
	Lutonix ISR (PMA SSED)[1]	RCT	32/49	0.662	0.520	0.780	21.81
	FAIR/Krankenberg[2]	RCT	31/44	0.705	0.556	0.820	21.17
	PACUBA/Kinstner[3]	RCT	14/35	0.407	0.259	0.574	20.86
	Orchid DCB/Liao[4]	RCT	29/33	0.879	0.718	0.954	16.46
	DEBATE ISR/Liistro[5]	Prospective all-comers	33/41	0.805	0.656	0.899	19.69
Random			139/202	0.702	0.538	0.827	

The sample size estimate was determined by using PASS 14.0.15 software with the following assumptions:

- The expected 12-month patency rate in the Stellarex 035 DCB subjects is 78.0%, which is higher than meta-analytic estimates, and equal to the upper confidence limit (UCL) of the PPR from the Lutonix ISR (PMA) trial.
- The Efficacy Performance Goal (PGe) is 64%.
- The Type 1 error, $\alpha = 0.025$ (one-sided).
- Power = 85%

A sample size of 100 evaluable subjects is required to achieve 86.1% power to detect a difference (P1-P0) of 0.14 using a one-sided exact test with a target significance level of 0.025. The actual significance level achieved by this test is 0.022. These results assume that the population proportion under the null hypothesis (P0) is 0.64. Allowing for up to 15% of subjects with missing 12-month efficacy endpoint data, the required enrolled sample size is 118 DCB subjects.

Primary Safety Endpoint

Available meta-analytic result for freedom from safety composite events rate in DCB subjects is 82.4% (95% CI = 67.8%, 91.2%) as shown in the above Table 6.3. It is therefore assumed that freedom from safety composite events rate after DCB treatment of ISR equals the weighted average rate from the meta-analysis.

The sample size estimate by using PASS 14.0.15 software assumed the following:

- The expected 12-month proportion of freedom from safety composite events in DCB subjects is 82.4%.
- The Safety Performance Goal (PGs) is 65%.
- The Type 1 error, $\alpha = 0.025$ (one-sided).
- Power = 85%.

Regarding the safety endpoint, with 118 sample size the power of the test will achieve 98.8% to detect a difference (P1-P0) of 0.1740 using a one-sided exact test with a target significance level of 0.025. These results assume a proportion under the null hypothesis (P0) of 0.6500.

Secondary Efficacy Endpoint:

- The expected 12-month proportion of freedom from TLR in DCB subjects is 86.6%.
- The Secondary Efficacy Performance Goal (PGes) is 76%.
- The Type 1 error, $\alpha = 0.05$ (two-sided).
- Power = 80%.

Regarding the secondary efficacy endpoint, with 118 sample size the power of the test will achieve 84.098% power to detect a difference (P1-P0) of 0.1060 using a two-sided exact test with a target significance level of 0.0500. These results assume that the proportion under the null hypothesis (P0) is 0.7600.

Overall Study Power

Taking into consideration both the co-primary efficacy and safety endpoints, with required 118 DCB subjects, the overall study power is 86.1%*98.8%=85%. Given actual sample size of 129 for this study is thereby determined to be adequate for primary hypotheses.

8 INTERIM ANALYSIS

The study was initially planned to perform an interim analysis when all subjects had the opportunity to complete the 6-month follow-up. However, the interim analysis was not completed and the statistical design was revised to analyze the endpoints at the single fixed time point of 12 months. The decision to not perform the interim analysis was made while blinded to study results and was based on regulatory input and statistical considerations.

9 ANALYSIS POPULATIONS

The primary analyses for efficacy and safety will be based on a modified intention-to-treat principle, whereby all subjects enrolled who did not receive a bailout stent will be analyzed regardless of treatment received. The intention-to-treat and the per-protocol analysis sets are designated as supportive.

9.1 Intention-to-Treat

The Intention-to-Treat (ITT) population will be comprised of all subjects who successfully complete the preliminary qualification procedures and were subsequently enrolled to receive the Stellarex DCB.

9.2 Modified Intention-to-Treat

The Modified Intention-to-Treat (MITT) will be comprised of all subjects in the ITT population who did not receive a bailout stent and did not receive provisional treatment for >50% residual stenosis post all assigned treatment or bailout stenting. The primary analysis will be based on the MITT population.

9.3 Per-Protocol

The Per-Protocol (PP) population will consist of ITT subjects who had no bail-out stenting and no major protocol deviations defined by the study management team. All trial endpoints will be analyzed using both the Intention-to-Treat and Per-Protocol populations, with the MITT analysis a priori designated as primary.

Exclusions due to major protocol deviations will be defined prior to evaluation of outcomes and reasons for exclusion will be provided.

10 GENERAL STATISTICAL CONSIDERATIONS

The following general comments apply to all statistical analyses and data presentations.

10.1 Descriptive Statistics

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarized using frequency counts and percentages.

For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories.

For categorical and ordinal variables, percentages will be calculated based on non-missing data.

10.2 p-values

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "< 0.001." If a p-value is greater than 0.999 it will be reported as ">0.999".

10.3 Duration Variables

Study Day 0 is the day of the index procedure. Study day is calculated relative to day 0 and will be calculated as:

Study Day = (Date of Event – Date of Study Device Deployment)

Duration variables will be calculated using the general formula: [(end date – start date)]

10.4 Kaplan-Meier Analysis

For endpoints analyzed with Kaplan-Meier time-to-event methods, analysis time points corresponding to 1, 6, 12, 24, and 36 months will be presented at 30, 180, 365, 730, and 1095 days, respectively. Unless otherwise specified, if a subject is event-free, their date of censoring will be considered as the date of last contact in the study. For Kaplan-Meier estimates presented with the corresponding 95% log-log confidence interval ($L_{\hat{S}}, U_{\hat{S}}$), Greenwood's estimate of the standard error will be used. The Kaplan-Meier estimate of the event rate, $\hat{F}$, may be computed as $1 - \hat{S}$ and the corresponding 95% log-log confidence interval is as follows:

$$L_{\hat{F}} = 1 - U_{\hat{S}}$$
$$U_{\hat{F}} = 1 - L_{\hat{S}}.$$

10.5 Partial Dates

In the case of partial dates, the dates of the event will be imputed. Imputation of partial dates is subject to the condition that the imputed date occurs on or after the procedure date and on or before the subject's last contact date. In the case of adverse events with partial start and stop dates, the imputed dates are subject to the additional condition that the start date must occur on or before the stop date of the event.

	Valid Portion	**Missing Portion**	**Imputed Value for Missing Portion[1]**
Start Date	Month, Year	Day	Set day to 15th day of the known month and year
	Year	Day, Month	Set date to June 30th of the known year
	None	Day, Month, Year	Date of procedure
Stop Date[2]	Month, Year	Day	Set day to 15th day of the known month and year
	Year	Day, Month	Set date to June 30th of the known year
	None	Day, Month, Year	None

[1]Imputed date must occur on or after the procedure date. For adverse events and concomitant medications, the start date must occur on or before the stop date.
[2]Date of death will be imputed per the imputation rules for a stop date.

10.6 Visit Windows and Visit Definitions

For the purposes of analysis, a visit will be considered in-window if it occurs within the intervals detailed below as specified in the protocol, and out-of-window if otherwise.

Study Visit	**Window**	**Target**
Baseline	Any CRF entered in the Baseline visit Labs within 7 days	Any CRF entered in the Baseline visit
Discharge	Any follow-up CRF entered in the Discharge visit	Any follow-up CRF entered in the Discharge visit
1 Month	15-45 Days	30 Days
6 Month	150-210 Days	180 Days
12 Month	335-395 Days	365 Days
24 Month	670-790 Days	730 Days
36 Month	1035-1155 Days	1095 Days

Baseline is defined as the last measurement for the outcome of interest obtained before exposure to the study device.

For endpoints that are measured continuously but reported with frequency counts and percentages at discrete time points (e.g. 12 month MAE, death), the presence of a valid data point implies knowledge of the subject's event status through the analysis time point (e.g. 12 months). Specifically, a subject is assumed to be event-free until the first event or up to the latest data point reported. Events occurring through the end of the visit window will be included in the event count. Subjects that do not have an event but have follow-up through the start of the visit window will be included in the denominator.

For the purposes of this document, the in-hospital event rate and the discharge event rate may be interchangeable.

In-hospital event rates will be estimated as the number and percentage of subjects with an event on or before the discharge visit date. The denominator will include subjects with an event and those that had a discharge visit date. If the discharge date is missing and the subject had an event, the event will be included in the calculation of the in-hospital event rate.

10.7 Duplex Ultrasound Assessments (DUS)

In the case that multiple DUS (e.g., a duplex ultrasound was non-diagnostic, requiring a repeat ultrasound) of the target lesion are performed within the visit window, the first diagnostic DUS will be used as the basis for determining restenosis.

Absence of target lesion restenosis as determined by duplex ultrasound (Peak Systolic Velocity Ratio (PSVR) ≤ 2.5) will be based on the core lab assessment of patent, stenosed, or occluded. If the core lab cannot determine the PSVR and in cases where PSVR alone is insufficient to assess stenosis (e.g. low cardiac output, or inflow stenosis), the core lab will make an assessment as to whether the lesion is patent, 50-99% stenosis or occluded in the target lesion stenosis field. In all other circumstances where PSVR is measurable and is alone sufficient to assess stenosis, the core lab will make an assessment of patent or 50-99% stenosis in the target lesion stenosis field based on a strict PSVR ≤ 2.5.

11 ANALYSIS OF STUDY ENDPOINTS

11.1 Primary Safety and Efficacy Endpoints

The primary safety endpoint is defined as freedom from device and procedure related death through 30 days post-procedure and freedom from target limb major amputation and CD-TLR through 12 months post-procedure.

Device and procedure related deaths within 30 days post-procedure will be considered toward primary safety endpoint failures. Target limb major amputation events and CD-TLR occurring through 12 months will be considered toward primary safety endpoint failures.

The primary efficacy endpoint is defined as patency at 12 months post-procedure, defined as absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from CD-TLR.

The first occurrence of duplex assessed restenosis prior to the end of the 12-month window (395 days), will be considered toward the target lesion restenosis component of the endpoint. Time to event will be calculated as the time to CD-TLR or first duplex restenosis, whichever occurs first. Subjects without a CD-TLR and without duplex restenosis, will be censored at the date of the last duplex assessment through the close of the 12-month window showing no restenosis or study exit,

whichever comes first. If a subject is free from CD-TLR and has no available duplex assessment showing restenosis or absence of restenosis (all duplex assessments are missing or non-diagnostic), the subject will be censored on their procedure date.

11.1.1 Primary Analysis of the Primary Safety and Efficacy Endpoints

The primary analysis will be performed on the MITT analysis set. The primary efficacy and safety endpoints will be analyzed as dichotomous (success/failure) endpoints.

In a complete case analysis whereby only subjects with complete endpoint data will be included, both endpoints analyses will be performed by constructing one-sided 97.5% confidence intervals about the estimates of the percentage of subjects experiencing the freedom from safety composite events through 12 months and the percentage of subjects with primary patency at 12 months post-procedure using the exact binomial method.

If missing data related to the primary endpoints occurs, the multiple imputation (MI) as detailed in Appendix A will be applied.

The primary efficacy and safety endpoints will also be supportively analyzed using Kaplan-Meier survival analysis as described in Section 10.4.

11.1.1.1 Primary Safety Endpoint

The primary safety endpoint is freedom from device and procedure related death through 30 days post-procedure and freedom from target limb major amputation and CD-TLR through 12 months post-procedure, which is called 'freedom from safety composite events' in the following text:

$H_0: \pi s \leq 0.65$

$H_1: \pi s > 0.65$

where πs is the proportion of subjects experiencing freedom from safety composite events and 0.65 is the PGs.

Subjects failing any component of the primary safety endpoint will be considered safety failures, and subjects who remain event free through 12 months will be considered safety successes. If the subject died between 30 days and 12 months but had a major amputation or CD-TLR before the death occurred, the subject would be considered a failure of the primary endpoint. Otherwise, if the subject did not have a major amputation or CD-TLR up until the time of death the subject would be considered to have missing outcome status and will be imputed by MI.

Primary safety endpoint is met when the lower confidence limit (LCL) of point estimate is above 65%.

11.1.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from CD-TLR. The endpoint is evaluated under the following hypothesis:

$H_0: \pi e \leq 0.64$

$H_1: \pi e > 0.64$

where π_e is the proportion of subjects experiencing primary patency at 12 months post-procedure and 0.64 is the PGe.

Subjects failing any component of the primary efficacy endpoint will be considered efficacy failures, and subjects who meet all efficacy events through 12 months will be considered efficacy successes.

Primary efficacy endpoint is met when the lower confidence limit (LCL) of point estimate is above 64%.

11.1.2 Sensitivity Analyses of the Primary Safety and Efficacy Endpoints

11.1.2.1 Supportive Analyses on the ITT and the PP Analysis Sets

The primary analysis methods will be performed on the ITT and the PP analysis sets as supportive analyses.

The evaluation of the endpoint on the ITT set will include subjects receiving a bailout stent and will serve as an assessment of the impact of exclusion of these subjects receiving a bailout stent from the primary analysis set (MITT). Additionally, safety event rates will be provided separately for subjects receiving a bailout stent vs. subjects not receiving a bailout stent.

11.1.2.2 Missing Data

Missing data for the primary endpoints will be imputed using multiple imputation as described in Appendix A. To assess the impact of missing data on the results the following sensitivity analyses will be performed:

- A complete case analysis whereby only subjects with complete endpoint data will be included in the analysis
- A tipping point and worst-case analysis

11.1.3 Subgroup/Poolability Analyses of the Primary Safety and Efficacy Endpoints

Subgroup analyses will be performed separately for subgroups defined by the following baseline characteristics:

- Sex
- Race,
- Age (< 65 versus ≥ 65),
- Lesion length < 100 mm, 100-200 mm, > 200 mm, < 150 mm versus ≥ 150 mm, < 180 mm versus ≥ 180 mm, < 200 mm versus ≥ 200 mm
- Reference vessel diameter (< 4 mm, 4 up to 5 mm, 5 mm up to 6 mm, and ≥ 6 mm).

Subgroup analyses will be descriptive in nature.

To assess if there is heterogeneity among the sites, and to determine if pooling of the data is reasonable, the percentage of patients with 12-month primary patency within each site will be determined and a Pearson chi-square statistic will be used to determine if there are differences between sites. If the p-value of the Pearson chi-square statistic is greater than 0.10 then the sites will be considered poolable.

11.1.4 Analysis of Primary Safety Endpoint under Other Common Definitions

As a supportive analysis, to assess the primary safety endpoint under other common definitions the endpoint will be evaluated such that any CD-TLR or non CD-TLR will be considered as a failure of the safety composite.

11.2 Secondary Endpoints

The secondary efficacy endpoint is freedom from TLR through 12 months post-procedure:

$H_0: \pi s \leq 0.76$

$H_1: \pi s > 0.76$

where πs is the proportion of subjects experiencing freedom from TLR and 0.76 is the PGes.

The secondary efficacy endpoint of 12-month freedom from TLR rate in DCB subjects will be based on non-missing data and assessed by constructing two-sided 95% confidence intervals about the estimates of the 12-month freedom from TLR rate using the exact binomial method. If the LCL of the point estimate is above the performance goal of 76%, the null hypothesis is rejected and the endpoint is met.

All secondary endpoints will be analyzed descriptively. For time-to-event variables, Kaplan-Meier time-to-event methods will be used as described in Section 10.4. For binary outcomes counts, percentages, and exact 95% confidence intervals using the exact binomial method will be presented, unless otherwise noted. Continuous data will be presented descriptively with n, mean, standard deviation, median, minimum, maximum and 95% confidence interval. Hypothesis testing will not be performed to pursue labeling goals or claims.

All secondary endpoints will be evaluated in the MITT analysis set and will be based on non-missing data.

11.2.1 Major Adverse Event (MAE) Rate

MAE rate and at 1, 6, 12, 24, and 36 months post procedure is defined as a composite rate of cardiovascular death, major target limb amputation and CD-TLR.

The overall MAE rate at each time point will be based on the date of the first component event. The event rate at each time point will be estimated from a Kaplan-Meier analysis according to Section 10.4.

11.2.2 Rate of Adverse Events

Rate of adverse events in hospital and at 1, 6, 12, 24, and 36 months.

The overall adverse event rate at each time point will be determined by the adverse event start date of the first event for a subject. The event rate at each time point will be presented as counts and percentages.

11.2.3 Rate of Clinically-Driven Target Lesion Revascularization (CD-TLR)

Rate of CD-TLR at 6, 12, 24, and 36 months.

The rate at each time point will be based on the date of the first CD-TLR. The event rate at each time point will be estimated from a Kaplan-Meier analysis according to Section 10.4.

11.2.4 Rate of Clinically-Driven Target Vessel Revascularization (CD-TVR)

Rate of CD-TVR at 6, 12, 24, and 36 months.

The rate at each time point will be based on the date of the first CD-TVR. The event rate at each time point will be estimated from a Kaplan-Meier analysis according to Section 10.4.

11.2.5 Rate of Major Amputation of the Target Limb

Rate of major amputation of the target limb at 6, 12, 24, and 36 months.

The rate at each time point will be based on the date of the first major amputation on the target limb. The event rate at each time point will be estimated from a Kaplan-Meier analysis according to Section 10.4.

11.2.6 Mortality Rate

Mortality rate at 6, 12, 24, and 36 months.

The date of death will be used to estimate the event rate at each time point. The rate at 6, 12, 24, and 36 months will be estimated as a proportion according to Section 10.4.

11.2.7 Arterial Thrombosis in the Treated Segment

Rate of occurrence of arterial thrombosis of the treated segment at 1, 6, 12, 24, and 36 months.

The rate at each time point will be based on the date of the first event meeting the criteria for arterial thrombosis in the treated segment. The rate at 1, 6, 12, 24, and 36 months will be estimated as a proportion according to Section 10.4.

11.2.8 Ipsilateral Embolic Events of the Study Limb

Rate of ipsilateral embolic events of the study limb within 30 days post-procedure.

The overall rate through 30 days will be summarized as the number of subjects enrolled with at least one embolic event on the study limb.

11.2.9 Primary Patency Rate

Primary patency rate at 6, 24, and 36 months, defined as the absence of target lesion restenosis determined by duplex ultrasound peak systolic velocity ratio (PSVR) of ≤ 2.5 and freedom from CD-TLR.

Subjects having a CD-TLR prior to the close of the analysis window as defined in Section 10.6 will be considered a failure of the secondary patency endpoint. Subjects having any duplex ultrasound that is stenosed or occluded prior to the analysis window will be considered a failure of the endpoint. To be considered a success for the absence of target lesion restenosis component of patency rate, a lesion must have an in-window diagnostic duplex ultrasound with a patent target lesion stenosis assessment from the core laboratory and be free from CD-TLR through the end of the window or through last study contact, whichever comes first.

The rate at 6, 24, and 36 months will be estimated as a proportion according to Section 10.6.

As a secondary analysis, a Kaplan-Meier analysis of freedom from loss of patency at 6, 24, and 36 months will be performed according to Section 10.4. The date of the first failure (CD-TLR or duplex assessment of restenosis or occlusion) will be used as the basis for the failure time. All other subjects (subjects free from CD-TLR and with either patent or missing duplex assessment) will be censored at their last patent duplex or time of last contact, whichever occurs first.

11.2.10 Alternative Patency Rate

Alternative patency rate at 6, 12, 24, and 36 months, defined as the absence of target lesion restenosis determined by duplex ultrasound peak systolic velocity ratio (PSVR) of < 2.4 and freedom from CD-TLR.

Subjects having a CD-TLR prior to the close of the analysis window as defined in Section 10.6 will be considered a failure of the secondary patency endpoint. Subjects having any duplex ultrasound prior to the close of the analysis window with PSVR greater than or equal to 2.4 or for which the assessment of patency is occluded will be considered a failure of the endpoint. To be considered a success for the absence of target lesion restenosis component of patency rate, a lesion must have an in-window diagnostic duplex ultrasound with PSVR<2.4 from the core laboratory and be free from CD-TLR through the end of the window or through last study contact,

whichever comes first. Subjects for which PSVR is not available (lesion is also not occluded) will have missing data for the alternative patency rate.

The rate at 6, 24, and 36 months will be estimated as a proportion according to Section 10.6.

As a secondary analysis, a Kaplan-Meier analysis of freedom from loss of patency at 6, 24, and 36 months will be performed according to Section 10.4. The date of the first failure (CD-TLR or post-procedure duplex assessment of restenosis based on PSVR 2.4 or occlusion) will be used as the basis for the failure time. All other subjects (subjects free from CD-TLR and with either patent or missing duplex assessment) will be censored at their last patent duplex or time of last contact, whichever occurs first.

These analyses will be repeated using PSVR criteria of <2.0.

11.2.11 Lesion Succes

Lesion success is defined as achievement of a final in-lesion residual diameter stenosis of ≤ 50% after using the study device. This will be captured after post-dilatation if post-dilatation is performed; otherwise it will be captured post-study treatment. This will be reported as a binary endpoint with the denominator including all lesions with evaluable data at the completion of the procedure.

11.2.12 Technical Success

Technical success, defined as achievement of a final in-lesion residual diameter stenosis of ≤50% (as determined by the angiographic core laboratory), using the Stellarex DCB without a device malfunction. This will be captured after post-dilatation if post-dilatation is performed; otherwise it will be captured post-study treatment. This will be reported as a binary endpoint with the denominator including all lesions with evaluable data at the completion of the procedure and without pre-dilatation stenting.

11.2.13 Clinical Success

Clinical success (per subject) defined as technical success without the occurrence of major adverse events during procedure. Major adverse events are defined as in Section 11.2.1, and MAEs occurring on the same day as the procedure will be assumed to have occurred during the procedure. This will be reported as a binary endpoint with the denominator including all subjects with evaluable angiographic data at the completion of the procedure and without pre-dilatation stenting.

11.2.14 Procedural Success

Procedural success (per subject) defined as lesion success without the occurrence of major adverse events during procedure. Major adverse events are defined as in Section 11.2.1, and MAEs occurring on the same day as the procedure will be assumed to have occurred during the procedure. This will be reported as a binary endpoint with the denominator including all subjects with evaluable data at the completion of the procedure.

11.2.15 Change in Ankle-Brachial Index (ABI)

Change in ABI from pre-procedure to 6, 12, 24, and 36 months.

The endpoint will be analyzed at all time points. The endpoint will be summarized among those with compressible arteries and for subjects with non-compressible arteries, toe-brachial index (TBI) will be analyzed if available. Continuous summaries for ABI and TBI will be presented separately. Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects a deterioration and a positive change signifies an improvement.

Summaries of improved/same/worsened based on ABI or TBI, so long as the same measurement is taken at both baseline and follow-up, will be provided along with continuous summaries.

11.2.16 Change in Walking Impairment Questionnaire (WIQ)

Change in WIQ from pre-intervention to 6, 12, 24, and 36 months.

Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects a deterioration and a positive change signifies an improvement. Summaries of improved/same/worsened will be provided along with the continuous summaries.

11.2.17 Change in Rutherford-Becker Clinical Classification (RCC)

Change in RCC from pre-intervention to 6, 12, 24, and 36 months.

Within-subject changes will be calculated as visit value minus baseline value such that a negative change reflects an improvement and a positive change signifies a deterioration. Summaries of improved/same/worsened will be provided alongside the ordinal summaries.

11.2.18 Change in EQ-5D

Change in EQ-5D from pre-intervention to 6, 12, 24, and 36 months.

Within-subject changes will be calculated as visit value minus baseline value such that a positive change reflects an improvement and a negative change signifies a deterioration. Summaries of improved/same/worsened will be provided alongside the ordinal summaries.

11.3 Additional Analyses

11.3.1 Patient Disposition

The number and percentage of subjects in each of the analysis sets will be provided.

Subject accountability and study discontinuation will be summarized for the MITT set. Subject accountability at each protocol required visit will be summarized as the number of subjects with complete visits, missed visits, or study discontinuations prior to the visit.

All subjects who do not complete the study will be tabulated by reason for discontinuation. Additional variables summarized may include total study duration, study completion status, and the primary reason for study discontinuation.

11.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the MITT Set. Variables include age, sex, race, ethnicity, ABI/TBI, and RCC. Additional baseline variables may be included. Medical history will be summarized for the MITT set. Baseline lesion characteristics will also be summarized. For category variables, the summary will be presented with frequencies, and percentages, unless otherwise noted. Continuous data will be presented descriptively with n, mean, standard deviation, median, minimum, and maximum.

11.3.3 Adverse Events

For adverse events, the primary analysis will be based upon patient counts, not event counts. In data summaries, both patient counts and event counts will be presented.

An overall summary of adverse events will be presented and will include the number and percentage of patients who report at least one adverse event and the total number of adverse events. For all adverse event tables, a patient reporting the same adverse event more than once will be counted once when calculating the number and percentage of patients with that particular event.

The frequencies and percentages of adverse events will be presented by event term for all adverse events, serious adverse events, procedural related events, device related events, and procedure or device related events. Unanticipated adverse device effects will be provided in a listing. Complete patient listings of all site-reported adverse events will also be provided.

11.4 Changes in Planned Analyses

The study was designed with an interim analysis at 6 months and final endpoint analysis at 12 months within a Bayesian framework. However, the interim analysis was not performed and the analysis of the study endpoints was revised to a frequentist analysis for the single fixed time point at 12 months prior to performing the interim analysis. Revision of the analysis plan was made while remaining blinded to 6 and 12 month results to reduce the potential for operational bias and further, endpoint analysis will not be conducted until all subjects have the opportunity to complete the 12 month visit, endpoint data monitored and cleaned, and the data considered frozen for the endpoint assessment. All details for the planned methodology for the primary safety and efficacy endpoints are detailed in Section 11.1.

Other deviations or changes from this SAP deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the study report with justification and rationale.

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13 Revision History

Version	Date	Author	Description
1.0	14APR2016	Sarah Verdoliva, NAMSA	Initial Release
2.0	12AUG2016	Feiyi Jia, NAMSA	Plan updated to align with protocol CP-1005 version 9.0
3.0	13AUG2019	Feiyi Jia, NAMSA	Update to include Cohort 2 propsensity Analysis. Revision on Bayesian Analysis with dichotomous endpoints
4.0	19MAR2020	Sarah Verdoliva, NAMSA	Removed interim (6 month) and final analysis in Bayesian framework; updated statistical design to frequentist analysis with single 12 month time point
5.0	18Sep2020	Nancy Jin Philips	Update to evaluate the safety and efficacy of the Stellarex 0.035" OTW drug-coated angioplasty balloon (DCB) by comparison to efficacy and safety performance goals.
6.0	06Jan2021	Nancy Jin Philips	Update to remove non-inferiority margin of 5% and Farrington-Manning non-inferiority test (per feedback to Q160693/S005 Question 4) and evaluate secondary efficacy by setting performance goal (per feedback to Question 3).

APPENDIX A MULTIPLE IMPUTATION PLAN

A.1 Introduction

This multiple imputation plan outlines the data and procedures used for conducting multiple imputation analyses of the primary efficacy and primary safety endpoints for Protocol CP-1005 (Cohort 2, which is equivalent to Protocol CP-1005-B): prospective, single-arm, global multi-center study to evaluate treatment of obstructive superficial *femoral artery and/or popliteal lesions with a novel paclitaxel-coated percutaneous angioplasty balloon and in-stent restenosis.* This version of the multiple imputation plan has been developed with respect to the SAP version 5.0. Any further changes to the SAP, protocol or CRFs may necessitate updates to the multiple imputation plan.

A.2 Multiple Imputation Analysis

Primary analyses of key outcomes will be performed using multiple imputation (MI), whereby each missing datum is replaced by multiple values in multiple datasets. The datasets are conventionally analyzed and the multiple results are combined to yield statistically valid inferences with estimated uncertainty. In the current study, the outcomes of interest for imputation are the primary safety and efficacy endpoints.

Multiple imputation will be conducted using data from the full ITT population. Generally, the steps will be performed as follows:

- Step1: Data will be imputed by using PROC MI with a NIMPUTE=0 option to initially examine the existing missing data pattern falling exactly into a monotonic pattern or an arbitrary missing data pattern.
- Step 2: In PROC MI, missing variables will be imputed by the fully conditional specification (FCS) method with regression, discriminant, or logistic method according to each variable type and missing pattern.
- Step 3: Each of the *M* imputed datasets is analyzed separately using the appropriate procedure SAS, e.g., PROC LIFETEST, or PROC FREQ for binary outcomes.
- Step 4: Analysis results from *M* imputed datasets obtained from step 3 are combined into one overall result. This step can be carried out using SAS PROC MIANALYZE.
- Step 5. All estimates for the endpoints (e.g. proportion of responders, confidence interval) will be presented from the estimates using Rubin's rules for combining across imputed datasets.

Covariates to include in the multiple imputation model will be as follows:

- Pre-exposure: Age, Sex, previous treatment for ISR in target limb (yes/no), diabetes, smoking, body mass index, hypertension, target lesion length, percent diameter stenosis, total occlusion, reference vessel diameter, Tosaka class, TASC D lesion, calcification, RCC, ABI
- Post-exposure: Post-procedure/1 Month duplex ultrasound assessment of target lesion stenosis, 6 month duplex ultrasound assessment of target lesion stenosis, last measured value of CD-TLR/ value of non CD-TLR.
- Endpoint: Safety (yes/no) at 12 Months, Efficacy (yes/no) at 12 Months.

Multiple imputation will be executed in PROC MI with covariates listed in the order as specified above to create 100 imputation datasets. Imputation will be performed for each primary endpoint separately. Explorations to omit predictors may be conducted if the multiple imputation model will not converge.