Spectranetics Always Reaching Farther	**Statistical Analysis Plan Signature Approval**
	Protocol Title: ProspectIve, Randomized, SingLe-Blind, U.S. MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon IDE #G120270 **Version: TP-1499-D**

Prepared By:

Sarah Verdoliva, Medical Research Biostatistician, NAMSA — Date: 01Sep2016

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June Eckhardt, Director of Clinical Affairs — Date

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STATISTICAL ANALYSIS PLAN

ProspectIve, Randomized, SingLe-Blind, U.S. MuLti-Center Study to EvalUate TreatMent of Obstructive SupErficial Femoral Artery or Popliteal LesioNs With A Novel PacliTaxel-CoatEd Percutaneous Angioplasty Balloon

ILLUMENATE Pivotal

Spectranetics, Corp. – United Stated (US) Randomized Clinical Trial (RCT)

PROTOCOL NUMBER: TP 1397-E

Spectranetics Corp.
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TP 1499-D

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1 INTRODUCTION

This statistical analysis plan (SAP) outlines the data and procedures used for assessing the efficacy and safety endpoints of Protocol TP 1397: *Prospective, Randomized, Single-Blind, U.S. Multi-Center Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With A Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon.* This version of the plan has been developed with respect to the protocol version E and E.1. Any further changes to the protocol or CRFs may necessitate updates to the SAP.

2 STUDY SUCCESS CRITERIA

Study success will be declared if both primary efficacy and primary safety endpoints are met.

3 STUDY DESIGN

The ILLUMENATE Pivotal study is a prospective, randomized, multi-center, single-blind study that will include up to 360 subjects in up to forty -five (45) sites across the United States and Europe. It is designed to evaluate the CVI Paclitaxel-coated PTA Catheter (CVI) compared to the bare percutaneous transluminal angioplasty balloon catheter (Bare Balloon Catheter [BBC]) for the treatment of de-novo or post-PTA occluded/stenotic or reoccluded/restenotic (except for in-stent) SFA and/or popliteal arteries.

The study will randomize 300 subjects. The randomization for this trial is blocked with a 2:1 ratio (CVI:BBC) and stratified by site.

4 INTERIM ANALYSES

No formal interim analyses are planned. Early stopping of the trial for effectiveness will not be permitted.

5 DETERMINATION OF SAMPLE SIZE

The recruited sample size was determined to be up to 360 based on the likelihood that approximately 20% of the subjects will be excluded from randomization after the pre-dilation procedure. Statistical sample size estimation for the two co-primary endpoints are as follows:

Effectiveness:

- Superiority design
- 2:1 treatment assignment ratio
- 90% power
- 1-tailed alpha = 0.025

- Treatment effect = 44% improvement over PTA (e.g. CVI Paclitaxel-coated PTA Catheter success rate of 65% vs. Bare Balloon Catheter success rate of 45%)
- Therefore N = 288 subjects (= 192 + 96)

Safety:

- Non-inferiority design
- 2:1 randomization ratio
- 90% power
- 1-tailed 0.025
- Non-inferiority margin (NIM) = 5%
- CVI Paclitaxel-coated PTA Catheter success rate = 60% vs. Bare Balloon Catheter success rate = 40%
- Therefore N' = 185 subjects (=123 + 62)

The study sample size (n=360 enrolled, n=288 randomized) is driven by effectiveness since N > N'.

A 5% NIM, as stringent as it may appear in comparison to 10% used in other cardiovascular studies, drives the sample size estimate to a point that is still lower than the parameters for superiority on the effectiveness side. Using 10% as the NIM would simply reduce the number of required subjects even further.

6 ANALYSIS POPULATIONS

All trial endpoints will be analyzed using both the Intention-to-Treat (ITT) and Per Protocol (PP) populations, with the ITT analysis *a priori* designated as the primary analysis and PP designated as supportive. If the safety set differs from the ITT set, sensitivity analyses may be conducted on the primary efficacy endpoint and all safety endpoints using the safety set.

6.1 Intention-to-Treat Analysis Set

The Intention-to-Treat (ITT) population will be comprised of all subjects who successfully complete the preliminary qualification procedures and are subsequently randomized to receive either the investigational device (CVI Paclitaxel-coated PTA Catheter) or the control device (Bare Balloon Catheter).

6.2 Per-Protocol Analysis Set

The Per-Protocol (PP) population will consist of ITT subjects who had no bail-out stenting and no major protocol deviations. The data for each subject will be reviewed by the blinded angiographic core laboratory.

Bail-out stenting is defined as stent placement any time after randomization. Major protocol deviations will be identified by the clinical team and include inclusion/exclusion violations that

impact the ability to assess the safety and/or efficacy of the study device in the intended population, or procedural violations that change the intended treatment. Exclusions due to major protocol deviations will be defined prior to evaluation of outcomes and reasons for exclusion will be provided.

6.3 Safety Analysis Set

In the unlikely case where a subject is randomized but the procedure is prematurely halted and no balloon is deployed, said subject will be included in the ITT set but excluded from the safety set since the subject was not exposed to the study device. The safety set will be comprised of only those subjects in whom a study device was used, and will include the subjects as they are treated in the case where a subject is treated with a device that differs from their randomization assignment.

7 STATISTICAL ANALYSES

7.1 General Statistical Considerations

7.1.1 Software

Version 9.2 or higher of SAS® statistical software package or other validated statistical software will be used to provide all summaries, listings, graphs, and statistical analyses.

7.1.2 Descriptive Statistics

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation or standard error, median, minimum and maximum. The decision to use either standard deviation or standard error will be based upon the objective of the presentation: standard deviation will be used when the interest is the natural variability of the data; standard error will be used when comparing two or more means. Continuous variables that are recorded using approximate values (e.g., < or >) will be replaced by the closest exact value for the calculation of summary statistics.

Categorical variables will be summarized using frequency counts and percentages. When count data are presented, the percentage for zero counts may be suppressed in order to draw attention to the non-zero counts.

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.

7.1.3 p-values

Unless otherwise specified statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. 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." No adjustments for multiplicity are planned.

7.1.4 Duration Variables

Study Day 0 is the day of study device deployment (index procedure).

Study day is calculated relative to day 0 and will appear in the listings where applicable.

Study day 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)]

7.1.5 Kaplan-Meier Analysis

For endpoints analyzed with Kaplan-Meier time to event methods, analysis time points corresponding to 1, 6, 12, 24, 36, 48, and 60 months will be presented at 30, 180, 365, 730, 1095, 1460, and 1825 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:

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

7.1.6 Missing Data

In the primary efficacy and safety analyses of the intent-to-treat cohort, missing data will be handled by multiple imputation (MI), whereby each missing datum is replaced by multiple values in multiple datasets. See Appendix A and Sections 7.2.1.1 and 7.2.2.1 for more information related to the handling of missing data for the primary endpoints.

Tipping point methods will be employed to assess sensitivity of the primary efficacy and safety endpoints to data imputations for the ITT cohort.

Subjects having missing values of primary patency at 12 months can be imputed as described in Section 7.2.1.1 For all other assessments, techniques will not be used to impute missing data. If a subject is missing a data point for any reason, that subject will not be included in the data summary for which the subject has missing information. The number of data values available for each analysis will be reported so that the reader can assess the potential impact of missing data.

7.1.7 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 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 start date.

	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 start date.

7.1.8 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 otherwise.

Study Visit	Window	Target
Baseline	Any CRF entered in the Baseline visit Labs within 30 days	Any CRF entered in the Baseline visit
Discharge[1]	Any follow-up CRF entered in the Discharge visit	Any follow-up CRF entered in the Discharge visit
1 Month[1]	15-45 Days	30 Days
Post-procedure[2]	Within 45 days post-procedure	45 days post-procedure
6 Month	150-210 Days	180 Days
12 Month	320-410 Days	365 Days
24 Month	685-775 Days	730 Days
36 Month	1050-1140 Days	1095 Days
48 Month	1415-1505 Days	1460 Days
60 Month	1780-1870 Days	1825 Days

[1]Excludes duplex ultrasound assessment, ABI, and Rutherford.
[2]Duplex ultrasound assessment, ABI, and Rutherford Classification only.

Baseline is defined as the last measurement for the outcome of interest obtained before the 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 visit date is missing and the subject had an event, the event will be included in the calculation of the event rate.

7.1.9 Duplex Ultrasound Assessments

In the case that multiple duplex assessments (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 duplex assessment will be used as the basis for analysis.
Patency is defined as the absence of target lesion restenosis as determined by duplex ultrasound (Peak Systolic Velocity Ratio (PSVR) ≤ 2.5) and freedom from clinically-driven target lesion revascularization. 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. Thus absence of target lesion restenosis will be based on the target lesion stenosis field in the duplex ultrasound core lab case report form.

The target lesion will be considered not restenosed if the target lesion restenosis category assessment is marked as patent; it will be considered restenosed if the target lesion stenosis category is marked as 50-99% Stenosed or Occluded. It will be considered missing if the target lesion restenosis category is marked as Unknown or NA or if a duplex ultrasound assessment is not available.

In the occasion where angiography data are available within a protocol-defined window, and duplex ultrasound assessment is not available, the target lesion will be considered not restenosed

if angiography shows that the diameter stenosis is ≤ 50%, and restenosed if the diameter stenosis is greater than 50%. Percent diameter stenosis will be calculated according to the equation provided by the angiographic core lab.

7.2 Primary Endpoints

7.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is patency at 12 months post-procedure. Patency is defined as the absence of target lesion restenosis as determined by duplex ultrasound [Peak Systolic Velocity Ratio (PSVR) ≤ 2.5] and freedom from clinically-driven target lesion revascularization. Duplex ultrasound results will be interpreted as described in Section 7.1.9. Details on deriving the primary effectiveness endpoint are as follows:

1. To be considered a success for the freedom from clinically-driven target lesion revascularization component of primary efficacy, a subject must remain free from a clinically-driven TLR at their in-window 12 month visit or through the end of the 12 month window [410 days]. To be considered a success for the absence of target lesion restenosis component of primary efficacy, a subject must have an in-window 12 month diagnostic duplex ultrasound with a patent target lesion stenosis assessment from the core laboratory.

    a. In the occasion where angiography data are available within a protocol-defined window, and duplex ultrasound assessment is not available, target lesion restenosis will be assessed as described in Section 7.1.9.

2. If a subject fails either component of the primary efficacy endpoint, they will be considered a patency failure; otherwise if they are considered a success for both components of patency, they will be considered a patency success.
3. If a subject does not have follow-up during the 12 month visit window and does not have a clinically-driven TLR event prior to that time, they will be considered to have a missing value for the primary effectiveness endpoint.

    a. Subjects with a missing value for the primary effectiveness endpoint will have failures carried forward, if applicable. If a diagnostic duplex ultrasound showing target lesion restenosis or angiographic data showing restenosis is available anytime post-procedure (0) to just before the opening of the 12 month visit window (319 days), that subject will be assumed to be a patency failure at 12 months in a clinical (non-statistical) imputation.

    b. Subjects with a missing value for the primary effectiveness endpoint will have successes carried backward, if applicable. If a diagnostic duplex ultrasound showing absence of target lesion restenosis or angiographic data showing absence of restenosis, without having a target lesion revascularization (TLR), is available any time after the closing of the 12 month visit window (411 days) to the closing

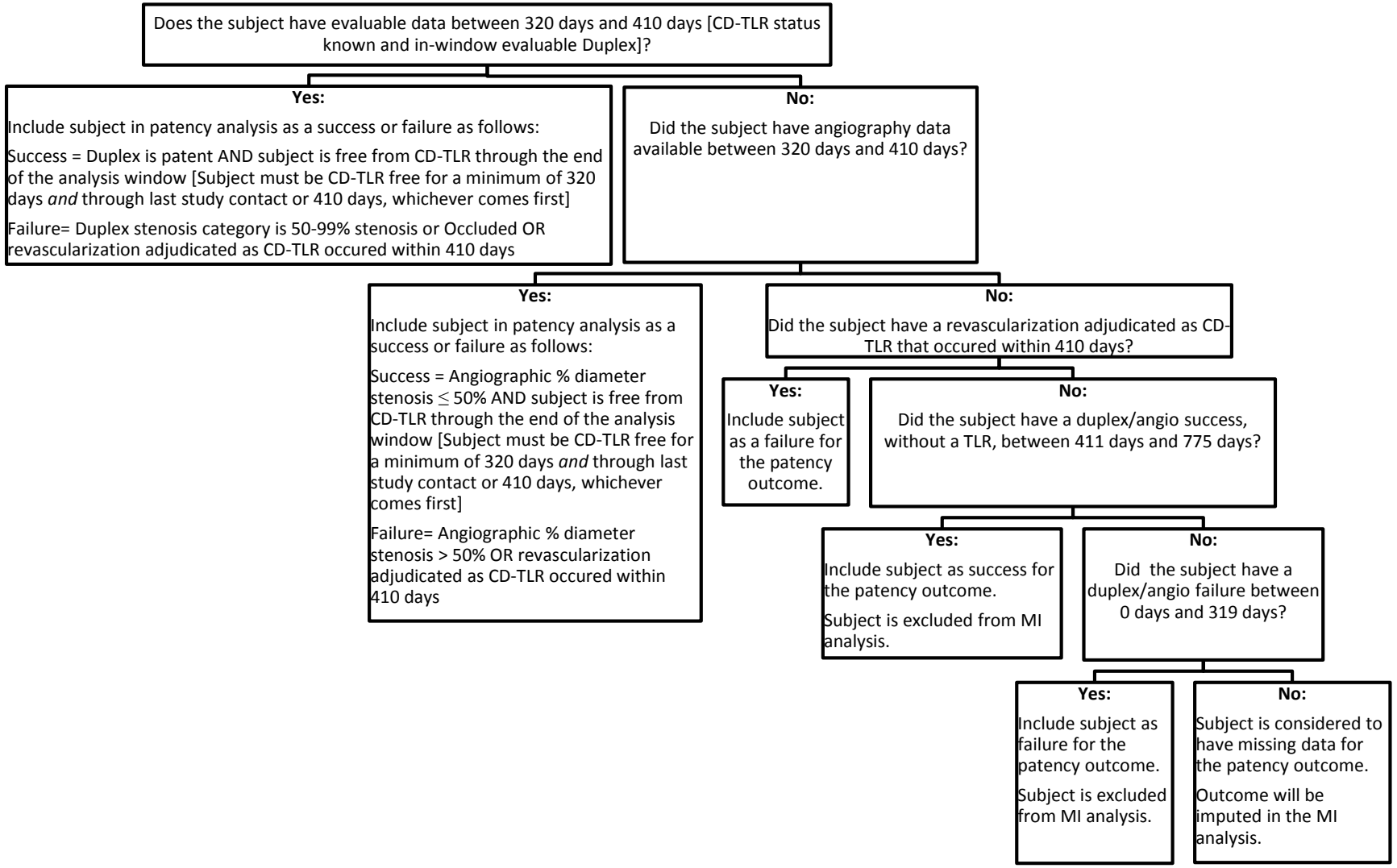
of the 24 month visit window (775 days), that subject will be assumed to be a patency success at 12 months in a clinical (non-statistical) imputation.

c. In the circumstance where a subject is not evaluable for primary patency at 12 months, and is eligible for both the failures carried forward and successes carried backward clinical imputations, the successes carried backward method will be used, and the subject will be counted as a success for the secondary Kaplan-Meier analysis of the primary efficacy endpoint described in Section 7.2.1.2.

d. Subjects having missing 12 month patency outcomes will be imputed using multiple imputation (MI) in the primary analysis, or using tipping point methods in the missing data analysis. Subjects who are clinically imputed as failures or successes will not be included in the MI analysis because the same predictive relationship between covariates and outcomes will not exist for these subjects as it does for other subjects.

A graphical depiction of the process for deriving the primary efficacy endpoint is listed in Figure 1.

Figure 1.Primary Efficacy Endpoint Decision Tree



The primary analysis will be performed using the ITT set, and missing data analyses will be performed according to Section 7.2.1.6. The working hypotheses are that the CVI arm will be superior in effectiveness to the BBC arm. The corresponding statistical hypothesis is:

- Superior Effectiveness: Patency at 12 months post-procedure, defined as the absence of target lesion restenosis determined by duplex ultrasound PSVR ≤ 2.5 and freedom from target lesion revascularization.
    - H_0: $\pi_{CVI} \leq \pi_{BBC}$
    - H_1: $\pi_{CVI} > \pi_{BBC}$

7.2.1.1 Primary Analysis of the Primary Efficacy Endpoint

The primary analysis of the primary efficacy endpoint will be performed using multiple imputation (MI). Details of the MI analysis for the primary efficacy endpoint are included in Appendix A of the SAP. The primary analysis will be performed on the ITT analysis set.

7.2.1.2 Secondary Analysis of the Primary Efficacy Endpoint

As a secondary analysis, freedom from loss of patency estimates using Kaplan-Meier (KM) survival analysis methods and 95% confidence intervals at 365 days will be presented for both the ITT and Per-Protocol analysis sets. The difference between treatment arms at day 365 and the 95% confidence interval for the difference will be presented. The endpoint will be derived as described in steps 1 through 3c in Section 7.2.1. Subjects who have 12 month follow-up but no analyzable DUS data, and no CD-TLR, will be censored at the day of last follow-up. Differences between treatment groups will be assessed with a log-rank test.

7.2.1.3 Sensitivity Analysis of the Primary Efficacy Endpoint

Several sensitivity analyses of the primary efficacy endpoint will be conducted on the ITT analysis set, including:

1. Binary event rates without imputation [complete case]
    - This will also be reported for the Per-Protocol and Safety analysis sets.
    - Success rates for the two treatment arms will be compared using chi-square contingency table methods, corrected for continuity. In the unlikely event that Cochran's Rule is violated [the smallest expected frequency is less than five], then Fisher's Exact tests will be employed.
2. An analysis in which bail-out stenting is deemed a failure of patency
3. An analysis using all TLR (clinically-driven and non-clinically driven)

4. PSVR based sensitivity analysis: Using PSVR ≤2.0 as the threshold for absence of target lesion restenosis based on the target lesion PSVR field

- Total occlusions will be counted as a patency failures for this sensitivity analysis despite having PSVR=0

The primary efficacy endpoint will be derived as described in steps 1 through 3c in Section 7.2.1.

7.2.1.4 Poolability of the Primary Efficacy Endpoint

Response rates across sites will be assessed for homogeneity and poolability at an α-level of 0.15. Should the sites not be poolable, Cochran-Mantel-Haenszel (CMH) will be employed with the dimensions of outcome (success/failure), treatment (CVI/BBC), and site. Those sites with a total number of treated patients of 5 or fewer will be combined into two quasi-sites. For the purpose of this analysis, the relevant statistical test will be a Breslow-Day test of homogeneity of treatment effect across sites (including the quasi-sites as specified above). This analysis will be conducted on the ITT analysis set for the complete case binary endpoint, and the endpoint will be derived as described in steps 1 through 3c in Section 7.2.1.

The quasi-sites will be divided by North/South geography within the United States. The first quasi-site will contain all sites in Oregon, Colorado, South Dakota, Iowa, Wisconsin, Illinois, Indiana, Ohio, Pennsylvania, New Jersey, Virginia, and West Virginia, and will contain 38 subjects. The second quasi-site will contain all sites in California, Oklahoma, Texas, Tennessee, North Carolina, Georgia, and Florida, and will contain 34 subjects. No OUS sites had 5 or fewer enrolled subjects.

In addition to the poolability by site assessment, an assessment will be done to examine homogeneity and poolability by country (US/OUS).

7.2.1.5 Subgroup Analysis of Primary Efficacy Endpoint

Subgroup analyses will be conducted to examine the possible influence of baseline characteristics on patency. A logistic regression model for patency (success/failure) will be run that includes treatment arm, subgroup, and a subgroup by treatment group interaction term. This analysis will be conducted on the ITT analysis set for the complete case binary endpoint, and the endpoint will be derived as described in steps 1 through 3c in Section 7.2.1.

Subgroups of interest will include smoking status (smokers vs. non-smokers), sex (male vs. female), age (below median vs. above median), race, and medication status. Medication status will be assessed as compliance to the protocol-required antiplatelet and anticoagulation regimen.

7.2.1.6 Missing Data Analysis for Primary Efficacy Endpoint

In addition to the primary analysis that uses multiple imputation methods to account for missing data, a tipping point analysis will be employed to assess sensitivity to missing data imputation. This analysis will be conducted on the ITT analysis set.

7.2.2 Primary Safety Endpoint

The primary safety endpoint for this study is freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through the end of the 12 month visit window [410 days]. Subjects failing any component of the primary safety endpoint will be considered a safety failure, and subjects who remain event free through 12 months will be considered safety successes. If a subject does not have follow-up in the 12 month visit window and also does not have a safety event prior to that time, they will be considered to have a missing value for the primary safety endpoint. Their outcomes will be imputed using MI in the primary analysis, or using tipping point methods in the missing data analysis.

The primary analysis will be performed using the ITT set. The working hypothesis is that the CVI arm will be non-inferior in safety to the BBC arm. The corresponding statistical hypothesis is:

Non-inferior Safety: Freedom from device and procedure related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months post-procedure.

- H_0: $\pi_{CVI} \leq \pi_{BBC} - \delta$
- H_1: $\pi_{CVI} > \pi_{BBC} - \delta$

where π is the population proportion for the corresponding treatment group and δ is the non-inferiority margin (5%).

If the test for non-inferiority is met, a test for superiority will be conducted as follows:

- H_0: $\pi_{CVI} \leq \pi_{BBC}$
- H_1: $\pi_{CVI} > \pi_{BBC}$

7.2.2.1 Primary Analysis of the Primary Safety Endpoint

The primary analysis of the primary safety endpoint will be performed using multiple imputation (MI). Details of the MI analysis for the primary safety endpoint are included in Appendix A of the SAP. The primary analysis will be performed on the ITT analysis set.

7.2.2.2 Secondary Analysis of the Primary Safety Endpoint

As a secondary analysis, freedom from loss of primary safety using Kaplan-Meier (KM) survival analysis methods and 95% confidence intervals at 365 days will be presented for the ITT, safety, and per-protocol analysis sets as detailed in Section 7.1.5. The primary safety endpoint will be derived as described in Section 7.2.2. Differences between treatment groups will be assessed with a log-rank test.

7.2.2.3 Sensitivity Analysis of the Primary Safety Endpoint

Sensitivity analyses of the primary safety endpoint will be conducted, including:

1. Binary event rates without imputation [complete case]
    - This will also be reported for the Per-Protocol and Safety analysis sets.
    - Non-inferiority of safety event rates in the CVI arm compared to the BBC arm will be assessed by use of Farrington-Manning non-inferiority exact tests.
2. An analysis using all TLR (clinically-driven and non-clinically driven)

7.2.2.4 Poolability of the Primary Safety Endpoint

Response rates across sites will be similarly assessed for homogeneity and poolability at an α-level of 0.15. Should the sites not be poolable, Cochran-Mantel-Haenszel (CMH) will be employed with the dimensions of outcome (success/failure), treatment (CVI/BBC), and site. Those sites with a total number of treated subjects of 5 or fewer will be combined into two quasi-sites as specified in Section 7.2.1.4. For the purpose of this analysis, the relevant statistical test will be a Breslow-Day test of homogeneity of treatment effect across sites (including the quasi-sites as specified above). This analysis will be conducted on the ITT set for the complete case binary endpoint.

In addition to the poolability by site assessment, an assessment will be done to examine homogeneity and poolability by country (US/OUS).

7.2.2.5 Subgroup Analysis of the Primary Safety Endpoint

A subgroup analysis will be conducted to examine the influence of select baseline characteristics on the primary safety endpoint. A logistic regression model for safety (success/failure) will be run that includes treatment arm, subgroup, and a subgroup by treatment group interaction term. This analysis will be conducted on the ITT analysis set for the complete case binary endpoint.

Subgroups of interest will include smoking status (smokers vs. non-smokers), sex (male vs. female), age (below median vs. above median), race, and medication status. Medication status will be assessed as compliance to the protocol-required antiplatelet and anticoagulation regimen.

7.2.2.6 Missing Data Analysis of the Primary Safety Endpoint

In addition to the primary analysis that uses MI methods to account for missing data, a tipping point analysis will be employed to assess sensitivity to missing data imputation. This analysis will be conducted on the ITT set.

7.3 Secondary Endpoints

All secondary endpoints will be analyzed descriptively, without hypothesis-testing.

For binary variables such as MAE or technical success, counts, percentages and exact 95% confidence intervals using Clopper-Pearson's method will be calculated. For continuous variables, means, standard deviations and 95% confidence intervals will be calculated. These analyses will be conducted on the ITT analysis set.

The following endpoints will be also evaluated as secondary endpoints:

7.3.1 Major Adverse Event Rate

Major Adverse Event (MAE) rate in the hospital, and at 1, 6, 12, 24, 36, 48 and 60 months post procedure is defined as a composite rate of cardiovascular death, target limb major amputation and clinically-driven target lesion revascularization (TLR).

MAE components will be adjudicated by the clinical events committee (CEC). An event will meet the criteria for this endpoint if at least one of the following criteria on the CEC case report form is met:

- "Cardiovascular death" = Yes
- "Index limb amputation" = Yes and "If Yes, is this a major amputation" = Yes
- "Clinically-driven Target Lesion Revascularization" = Yes

The date of cardiovascular death will be determined by the date of death on the exit form corresponding to the site-reported adverse event that the CEC adjudicated as a cardiovascular death.

The date of target limb major amputation will be determined as described in Section 7.3.6.

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 as a proportion according to Section 7.1.8.

As a secondary analysis, a Kaplan-Meier analysis of freedom from MAE and freedom from each component of MAE at 1 month, 6 months, 12 months, and annually thereafter will be performed according to Section 7.1.5.

7.3.2 Rate of Vascular Access and Bleeding Complications

Rate of vascular access and bleeding complications in the hospital and at 1, 6, 12 and 24 months.

The event rate at each time point will be determined by the adverse event start date of the first event meeting the criteria for each vascular access and bleeding complication. Vascular access and bleeding complications will be classified by an independent medical reviewer following final CEC adjudication and reported separately by MedDRA class. The rate at each time point will be estimated as a proportion according to Section 7.1.7.

7.3.3 Rate of Clinically-Driven Target Lesion Revascularization

Rate of clinically-driven target lesion revascularization (CD-TLR) at 6, 12, 24, 36, 48, and 60 months.

Clinically-driven TLR will be adjudicated by the CEC. The date of the clinically-driven TLR will be determined from the revascularization date reported on the site-reported target vessel revascularization form corresponding to the site-reported adverse event that the CEC adjudicated as a clinically-driven TLR. The rate at 6, 12, 24, 36, 48 and 60 months will be estimated as a proportion according to Section 7.1.8.

As a secondary analysis, a Kaplan-Meier analysis of freedom from CD-TLR at 6 months, 12 months, and annually thereafter will be performed according to Section 7.1.5.

7.3.4 Rate of Target Lesion Revascularization

Rate of target lesion revascularization at 6, 12, 24, 36, 48 and 60 months.

Target lesion revascularization will be adjudicated by the CEC. The TLR rate at each time point will be determined by the date of the first event. The rate at 6, 12, 24, 36, 48 and 60 months will be estimated as a proportion according to Section 7.1.8.

As a secondary analysis, a Kaplan-Meier analysis of freedom from TLR at 6 months, 12 months, and annually thereafter will be performed according to Section 7.1.5.

7.3.5 Rate of Clinically-Driven Target Vessel Revascularization

Rate of clinically-driven target vessel revascularization (CD-TVR) at 6, 12, 24 and 36 months.

Events categorized as a clinically-driven TVR by the CEC will meet the criteria for this endpoint. The date of the clinically-driven TVR will be determined from the revascularization date reported on the site-reported target vessel revascularization form corresponding to the site-reported adverse event. The rate at 6, 12, 24, and 36 months will be estimated as a proportion according to Section 7.1.8.

As a secondary analysis, a Kaplan-Meier analysis of freedom from CD-TVR at 6, 12, 24, and 36 months will be performed according to Section 7.1.5.

The protocol definition of clinically-driven TVR excludes any revascularization at the target lesion site. As a secondary analysis, this endpoint will be analyzed with clinically-driven target lesion revascularizations included. Events categorized as clinically-driven TVR or clinically-driven TLR by the CEC will meet the criteria for this secondary analysis definition. The analysis at each time point will be performed as described above.

7.3.6 Rate of Target Limb Major Amputation

Rate of target limb major amputation at 1, 6, 12, 24, 36, 48 and 60 months.

Target limb major amputation will be adjudicated by the CEC. Any event categorized as an index limb major amputation by the CEC will meet the criteria for this endpoint. The date of target limb major amputation will be determined based on source documentation of amputation date and stored in a controlled, locked, and approved spreadsheet that is separate from the database as the date of amputation is not recorded systematically in the database. The rate at 1, 6, 12, 24, 36, 48 and 60 months will be estimated as a proportion according to Section 7.1.8.

As a secondary analysis, a Kaplan-Meier analysis of freedom from target limb major amputation at 1 month, 6 months, 12 months, and annually thereafter will be performed according to Section 7.1.5.

7.3.7 Mortality Rate

Mortality rate at 6, 12, 24, 36, 48 and 60 months.

All subject deaths reported by the site will meet the criteria for this endpoint. The date of death on the study exit form will be used to estimate the event rate at each time point. The rate at 6, 12, 24, 36, 48 and 60 months will be estimated as a proportion according to Section 7.1.8.

A listing of all subject deaths will also be provided. The adverse event corresponding to the death will be reported on the exit form and the corresponding event adjudication from the CEC will be used to categorize the event.

7.3.8 Rate of Arterial Thrombosis in the Treated Segment

Rate of occurrence of arterial thrombosis of the treated segment at 1, 6, 12, 24, 36, 48 and 60 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. Arterial thrombosis will be classified by an independent medical reviewer following final CEC adjudication. The rate at 1, 6, 12, 24, 36, 48 and 60 months will be estimated as a proportion according to Section 7.1.8.

7.3.9 Rate of Ipsilateral Embolic Events of the Target Limb

Rate of ipsilateral embolic events of the target limb.

Embolic events will be classified by an independent medical reviewer following final CEC adjudication.

The overall rate will be summarized as the number of subjects out of those enrolled with at least one embolic event on the study limb. The total number of events reported in the study will also be provided. The rate at 1, 6, 12, 24, 36, 48 and 60 months will be estimated as a proportion according to Section 7.1.8.

7.3.10 Patency Rate

Patency rate defined as the absence of target lesion restenosis as determined by duplex ultrasound (PSVR ≤ 2.5) and freedom from clinically-driven TLR at 6, 24 and 36 months.

Patency is defined as the absence of target lesion restenosis as determined by duplex ultrasound and freedom from clinically-driven target lesion revascularization. To be considered a success for the absence of target lesion restenosis component of patency rate, a subject must have an in-window diagnostic duplex ultrasound with a patent target lesion stenosis assessment from the core laboratory. If ultrasound images are not available at a follow-up or analysis time point, and if an angiogram evaluation is available, the angiogram will be used to determine patency. A result of ≤ 50% residual stenosis will be considered patent. CD-TLR is defined as described in Section 7.3.3.

The rate at 6, 24, and 36 months will be estimated as a proportion according to Section 7.1.8. As a secondary analysis, a Kaplan-Meier analysis of freedom from loss of patency at 24 and 36 months will be performed according to Section 7.2.1.2.

7.3.11 Lesion Success

Lesion success, defined as achievement of a final in-lesion residual diameter stenosis of ≤50% (as determined by the angiographic core laboratory), using any device after wire passage through the lesion.

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 angiographic data at the completion of the procedure.

7.3.12 Technical Success

Technical success, defined as achievement of a final in-lesion residual diameter stenosis of ≤50% (as determined by the angiographic core lab), using the CVI Paclitaxel-coated PTA Catheter or Bare Balloon Catheter without a device malfunction after wire passage through the

lesion. 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 angiographic data at the completion of the procedure and without pre-dilatation stenting.

7.3.13 Clinical Success

Clinical success (per subject) defined as technical success without the occurrence of major adverse events during the procedure. Major adverse events are defined as in Section 7.3.1, 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.

7.3.14 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 7.3.1, 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.

7.3.15 Change in Ankle-Brachial Index

Change in ankle-brachial index (ABI) from pre-procedure 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. Outcomes measured after any revascularization will be included in all summaries. Readings with non-compressible arteries at the time of assessment will be considered as missing data for the change in ABI calculation. Summaries of improved/same/worsened will be provided along with continuous summaries.

7.3.16 Change in Walking Impairment Questionnaire

Change in walking impairment questionnaire (WIQ) from pre-procedure 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. Outcomes measured after any revascularization will be included in all summaries.

7.3.17 Change in Walking Distance

Change in walking distance from pre-procedure 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 continuous summaries. Outcomes measured after any revascularization will be included in all summaries.

7.3.18 Change in Rutherford Classification

Change in Rutherford-Becker classification from pre-procedure 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. Outcomes measured after any revascularization will be included in all summaries.

7.3.19 Change in EQ-5D

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

The EQ-5D index and EQ-5D visual analog scale (VAS) will be summarized for this endpoint. 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. Outcomes measured after any revascularization will be included in all summaries.

7.4 Safety Analyses

7.4.1 Study Discontinuation Due to Adverse Event

Subjects who experienced adverse events leading to discontinuation from the study will be summarized in a tabular form. The following information will be presented for each subject: treatment group, termination date, date of last visit, duration in study (in days), onset and stop dates of the adverse event resulting in treatment discontinuation, severity grade, MedDRA SOC and PT and relationship to study procedure or treatment.

7.4.2 Adverse Events

Adverse events (AEs) will be tabulated with the number of events and subjects with events by MedDRA SOC and PT. All procedure-related, device-related, and procedure or device-related events will be summarized by SOC and PT. SAEs, UADEs, and USADEs will also be

summarized by MedDRA SOC and PT. CEC adjudicated events will be used for the AE analyses; site reported events will be provided in listings.

Complete listings of all adverse events by subject will be provided. For each adverse event the following will be specified: treatment group, start and stop dates, severity grade, MedDRA SOC and PT, relationship to study treatment, action taken, outcome of the adverse event and seriousness (yes/no).

MedDRA Version 17.0 will be used for coding of all adverse events.

7.4.3 Serious Adverse Events

All serious adverse events will be included in listings and will be summarized in tables by treatment arm.

7.4.4 Clinical Laboratory Evaluations

All laboratory values (serum chemistries and hematology) collected from baseline through the Month 12 visit will be summarized by visit and treatment group.

7.5 Other Analyses

7.5.1 Screening Failures

Those patients who fail screening and/or receive a stent following predilatation ("pre-randomization bail-out") will be tabulated within the text of the Clinical Study Report (CSR) with their reason for screening failure. This ensures that the protocol did not systematically and inadvertently bias the resultant patient population sets.

7.5.2 Changes in Planned Analyses

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 with justification and rationale.

7.5.3 Eligibility Criteria

Inclusion and exclusion criteria will be summarized by subject for the ITT set. A summary of any pre-approved inclusion and exclusion criteria waivers will be presented.

7.5.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the ITT set. Demographic variables include age, sex, race, and ethnicity. Baseline characteristics include height, weight, blood pressure, Ankle Brachial Index (ABI), Rutherford stage, and functional walking assessment.

7.5.5 Medical History

Medical history will be summarized by treatment group for the ITT set.

7.5.6 Subject Disposition

The number and percentage of subjects in the safety set and per protocol set will be summarized by treatment group. For all enrolled subjects (ITT 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.

7.5.7 Concomitant Medication

Compliance to the protocol-required antiplatelet and anticoagulation regimen will be summarized for the ITT set.

All protocol-required medications taken from the screening date up to the angioplasty procedure and after the randomized treatment procedure through the last study visit will be summarized.

8 APPENDICES

- Appendix A: Multiple Imputation Plan
- Appendix B: ILLUMENATE SFA Integrated Statistical Analysis Plan

APPENDIX A: ILLUMENATE MULTIPLE IMPUTATION ANALYSIS PLAN

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 of Protocol TP 1397: *Prospective, Randomized, Single-Blind, U.S. Multi-Center Study to Evaluate Treatment of Obstructive Superficial Femoral Artery or Popliteal Lesions With A Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon.* This version of the multiple imputation plan has been developed with respect to the SAP version C. Any further changes to the SAP, protocol or CRFs may necessitate updates to the multiple imputation plan.

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 endpoints, which are defined as follows:

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

- Primary Safety Endpoint: freedom from device and procedure-related death through 30 days post-procedure and freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months post-procedure.

Accordingly, multiple imputation will be implemented in the following fashion:

- A separate imputation model will be built for each primary endpoint for a total of two separate models, one each for the primary efficacy and primary safety endpoints.

- Predictors for the imputation models will include, but may not be limited to, pre-randomization and post-randomization variables as follows:

- Pre-randomization: age, sex, body mass index, lesion length, smoking status, history of diabetes mellitus, hyperlipidemia, history of hypertension, calcification, lesion type (de novo, restenotic), baseline stenosis vs. occlusion of the target lesion, ankle-brachial index and Rutherford clinical category.
- Post-randomization: randomized assignment, 6 month duplex ultrasound assessment of target lesion stenosis, last measured value of non-clinically driven target lesion restenosis, ankle-brachial index, Rutherford clinical category, medication status as defined in Section 7.2.1.5 of the SAP, mode of exit, and study related death.

Explorations to omit predictors may be conducted if the primary safety or efficacy multiple imputation models will not converge.

All subjects will be included in the primary safety endpoint imputation model; all subjects except those who have failures carried forward or successes carried backward as described in Section 7.2.1 will be included in the primary efficacy endpoint imputation model.

Since each of the primary outcomes of interest is binary in nature, logistic regression will be used to produce imputed datasets. Predictor variables which themselves have missing values will also be imputed, using Markov chain Monte Carlo methods.

In practice, 3-5 imputations have been shown to produce valid inference for most purposes, but since the only cost of more imputations is in computing time, 10 imputed datasets will be created for each of the models. The imputed datasets will then be combined for inference using standard methods such as those available in SAS PROC MIANALYZE or other valid statistical software.

3 REFERENCES

1. Little, R.J.A. and Rubin, D.B. (1987) *Statistical Analysis with Missing Data*. J. Wiley & Sons, New York. (2002) Second edition.

2. Rubin, D.B. (1987) *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley and Sons. (2004) Classic edition.

3. Schafer, J.L. (1997) *Analysis of Incomplete Multivariate Data*. Chapman & Hall, London.

APPENDIX B: ILLUMENATE INTEGRATED STATISTICAL ANALYSIS PLAN

1 PURPOSE

Appendix B of the ILLUMENATE Pivotal statistical analysis plan (SAP) outlines the analyses planned for the integrated summary of safety and efficacy. The integrated summary of safety and efficacy will include combined results from the ILLUMENATE Pivotal, ILLUMENATE PK, ILLUMENATE Global, ILLUMENATE European Randomized Clinical Trial (EU RCT), and ILLUMENATE First in Human (FIH) studies in support of the pre-market approval application submission. This version of the integrated statistical analysis plan has been developed with respect to the SAP version C. Any further changes to the SAP, protocol or CRFs may necessitate updates to this plan.

2 STUDY DESIGN

2.1 ILLUMENATE Pivotal

The ILLUMENATE Pivotal study is a prospective, randomized, multi-center, single-blind study that will include up to 360 subjects in up to forty-five (45) sites across the United States and Europe. It is designed to evaluate the CVI Paclitaxel-coated PTA Catheter (CVI) compared to the bare percutaneous transluminal angioplasty balloon catheter (Bare Balloon Catheter [BBC]) for the treatment of de-novo or post-PTA occluded/stenotic or reoccluded/restenotic (except for in-stent) SFA and/or popliteal arteries.

The study randomized 300 subjects (200 CVI:100 BBC) at 43 sites. The randomization for this trial is blocked with a 2:1 ratio (CVI:BBC) and stratified by site.

2.2 ILLUMENATE PK

The ILLUMENATE PK Trial is a prospective, non-randomized, single-arm, multi-center, study to describe the pharmacokinetics of paclitaxel in the blood delivered from the CVI Paclitaxel-coated PTA Catheter in the treatment of de novo or restenotic lesion(s) in the superficial femoral (SFA) and/or popliteal arteries. Twenty-five subjects were planned for enrollment at up to 3 investigational sites in New Zealand. At the end of the enrollment phase, 25 subjects were enrolled at 2 sites. Each subject will be followed for two years.

2.3 ILLUMENATE Global

The ILLUMENATE Global study is a prospective, international, multi-center, single-arm study to assess the safety and performance of the CVI Paclitaxel-Coated PTA Balloon Catheter in the treatment of de novo or restenotic lesions in the superficial femoral (SFA) and/or popliteal arteries. Up to 500 subjects were planned for enrollment at up to 65 sites globally. At the end of

the enrollment phase, 371 subjects were enrolled at 37 sites. Each subject will be followed for five years.

2.4 ILLUMENATE European Randomized Clinical Trial

The ILLUMENATE EU RCT study is a prospective, randomized, multi-center, single-blind study to evaluate the CVI Paclitaxel-coated PTA Balloon Catheter compared to Bare Balloon Catheter (EverCross™ balloon catheter) in the treatment of de novo or restenotic lesions in the superficial femoral and/or popliteal arteries. Approximately 360 subjects were planned for enrollment at up to 30 sites in Europe. Of the planned enrollments, approximately 280 subjects will be randomized in a 3:1 randomization ratio (CVI Paclitaxel-coated PTA catheter: Bare Balloon Catheter) and up to 50 subjects were planned for enrollment into the single-arm stent cohort. At the end of the enrollment phase, 328 subjects total were enrolled; 223 in the CVI arm; 72 in the PTA arm and 33 in the stent cohort at 18 sites in Austria and Germany.

2.5 ILLUMENATE First in Human

The ILLUMENATE FIH Study was a non-randomized, multicenter, single-arm clinical study conducted in subjects requiring treatment of lesions in the SFA/popliteal artery due to occlusion/restenosis. The original protocol allowed for enrollment of 50 subjects treated with the CVI Paclitaxel-coated Catheter after pre-dilatation of the target lesion (Cohort 1). During the study, a protocol amendment was approved to allow enrollment of up to 30 additional subjects (Cohort 2) with direct treatment of the target lesion with the CVI Paclitaxel-coated catheter (without pre-dilatation).

Eighty subjects were enrolled in the study at 3 sites. The first 50 subjects were enrolled in Cohort 1 with pre-dilatation and the last 30 subjects were enrolled in Cohort 2 without pre-dilatation.

3 ANALYSIS POPULATIONS

All endpoints analyzed for the purposes of the integrated summary report will be analyzed using the drug-coated balloon analysis set or the drug-coated balloon safety set; pooled analyses including subjects from the control group of the randomized studies is not planned.

3.1.1 Drug-Coated Balloon Analysis Set

The Drug-Coated Balloon (DCB) analysis set will be comprised of all subjects randomized to the investigational device (CVI Paclitaxel-coated PTA Catheter) for randomized studies (ILLUMENATE Pivotal and ILLUMENATE EU RCT Randomized Cohort) or all subjects enrolled in the single-arm studies (ILLUMENATE PK, ILLUMENATE Global, ILLUMENATE FIH, and ILLUMENATE EU RCT Stent Cohort). The randomized DCB analysis set is a subset of the DCB analysis set and includes only subjects randomized to the investigational device.

3.1.2 Safety Analysis Set

In the case where a subject is randomized but the procedure is prematurely halted and no balloon is deployed, said subject will be excluded from the safety set since the subject was not exposed to the study device. The safety set will be comprised of those subjects in whom a study device was used, including subjects treated with the investigational device despite being randomized to the control group. The DCB safety set would thus be comprised of all subjects defined in the DCB analysis set in whom an investigational device was used, whether inflated or not, and all subjects randomized to the control group and who received the investigational device (DCB).

4 STATISTICAL ANALYSIS

Unless otherwise specified, all statistical analyses will follow the methods and procedures described in the main document of the ILLUMENATE Pivotal statistical analysis plan (SAP), which from this point forward will be referenced as the ILLUMENATE Pivotal SAP. Data from all studies will be pooled, where appropriate, to generate a combined summary of each outcome and data analysis in the integrated safety and effectiveness report. For each outcome and/or data point analyzed, in addition to the pooled result, results will be presented for each study contributing to the combined result. Differences in study design and/or protocol definitions that may impact the combined summary will be clearly described in the report. Any analyses performed for the purpose of the integrated summary report that would be considered post-hoc analyses for any particular study or studies will be described with the results if possible.

4.1 Missing Data

Unless otherwise specified, no statistical techniques will be used to impute missing data. If a subject is missing a data point for any reason, that subject will not be included in that data summary. The number of data values available for each analysis will be reported so that the reader can assess the potential impact of missing data.

The multiple imputation analysis described for the primary analysis of the primary efficacy and primary safety endpoints in the ILLUMENATE Pivotal study will not be performed to impute missing data in the integrated summary of safety and effectiveness.

4.2 ILLUMENATE Visit Windows and Visit Definitions

Study Visit	**Analysis Windows**				
	Pivotal	**PK**	**Global**	**EU RCT**	**FIH**
Baseline	Any CRF entered in the Baseline visit Labs within 30 days.	Any CRF entered in the Baseline visit. Labs within 14 days.	Any CRF entered in the Baseline visit Labs within 7 days.	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	Any follow-up CRF entered in the Discharge visit	Any follow-up CRF entered in the Discharge visit[1]	Any follow-up CRF entered in the Discharge visit	Any follow-up CRF entered in the Discharge visit

Study Visit	Analysis Windows				
	Pivotal	**PK**	**Global**	**EU RCT**	**FIH**
	Discharge visit[1]				
1 Month	15-45 Days[1]	15-45 Days[1]	15-45 Days[1]	15-45 Days	23-37 Days
Post-procedure	Within 45 days post-procedure[2]	N/A	Within 45 days post-procedure[2]	N/A	N/A
6 Month	150-210 Days	150-210 Days	150-210 Days	150-210 Days	150-210 Days
12 Month	320-410 Days	335-395 Days	335-395 Days	335-395 Days	335-395 Days
24 Month	685-775 Days	685-775 Days	670-790 Days	670-790 Days	700-760 Days
36 Month	1050-1140 Days	N/A	1035-1155 Days	1035-1155 Days	N/A
48 Month	1415-1505 Days	N/A	N/A	1400-1520 Days	N/A
60 Month	1780-1870 Days	N/A	N/A	1765-1885 Days	N/A
[1]Excludes duplex ultrasound assessment, ABI, and Rutherford. [2]Duplex ultrasound assessment, ABI, and Rutherford Classification only.					

4.3 Primary Endpoints

4.3.1 Analysis of Patency at 12 Months

Patency at 12 months will be defined for each study according to the definition in the ILLUMENATE Pivotal SAP with any deviations described in the following sections.

For studies in which up to two lesions may be treated with the study device during the index procedure (ILLUMENATE PK, ILLUMENATE Global, ILLUMENATE EU RCT, and ILLUMENATE FIH), the endpoint will be summarized on a per-lesion basis. For the ILLUMENATE Pivotal study, the lesion-based analysis will be the same as the subject-based analysis.

Since the duplex component of patency is a visit driven assessment, the determination of an in-window duplex at each visit will proceed according to the protocol required visit windows defined for each individual study as outlined in Section 4.2 for each study. In subjects with multiple lesions, results of duplex assessments will be considered separately by lesion. Similarly, a clinically-driven target lesion revascularization (CD-TLR) will be considered a failure of patency at 12 months if the revascularization occurs on the lesion prior to the close of the 12 month analysis window as defined in Section 4.2 for each study.

Lesions with missing 12-month data for the patency endpoint will have successes carried backward or failures carried forward as described in the ILLUMENATE Pivotal SAP. Eligibility to impute known successes or failures under these methods will be based on the study-specific analysis windows as defined in Section 4.2.

Lesions without an evaluable duplex to define patency success or failure at 12 months and without a revascularization of the lesion adjudicated as a CD-TLR prior to the end of the 12 months analysis window will be considered to have a missing patency outcome at 12 months.

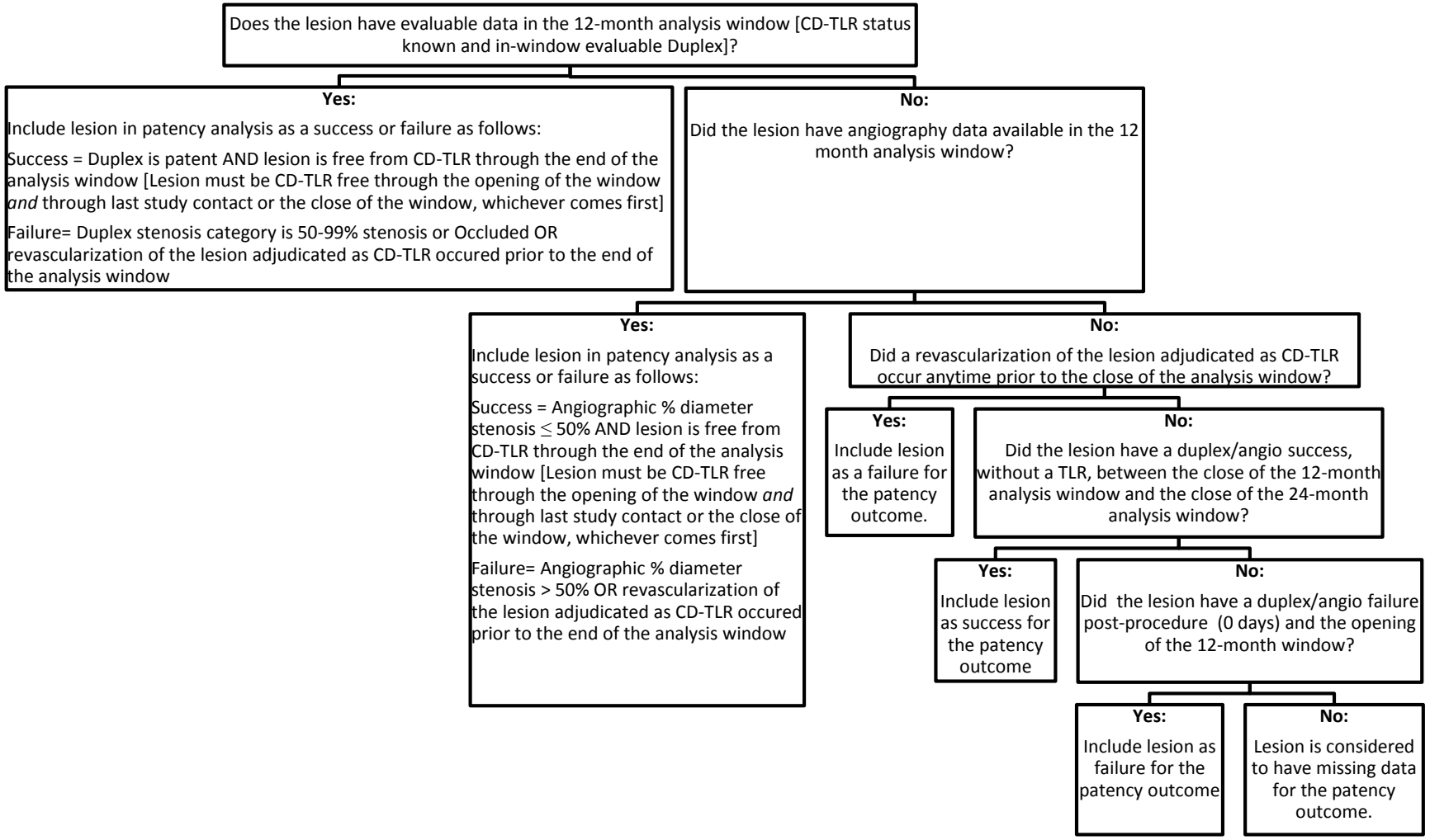
The patency outcome for all studies will be combined to obtain the pooled result.

Details for deriving the 12 month patency endpoint for each lesion are provided in Figure 1. Patency Endpoint Decision .

Analysis of patency at 12 months will be performed on the DCB analysis set. Multiple imputation methods will not be performed for the integrated 12 month patency analysis. The endpoint, pooled and by study, will be summarized as a proportion where the numerator will be the number of lesions considered a patency success and the denominator will be the number of lesions considered a patency success or failure at 12 months. The two-sided exact 95% confidence interval of the proportion will also be presented.

Sensitivity analyses of the primary efficacy endpoint are not planned for the pooled analysis.

Figure 1. Patency Endpoint Decision Tree



4.3.2 Analysis of the Primary Safety Endpoint

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 clinically-driven target lesion revascularization through 12 months. The analysis will be performed per subject on the DCB safety analysis set.

Subjects failing any component of the primary safety endpoint through the end of the 12 month analysis window as defined in Section 4.2 by study will be considered a safety failure, and subjects who remain event free through 12 months will be considered safety successes. If a subject does not have study contact on or after the opening of the 12 month visit window as defined in Section 4.2 and also does not have a safety event prior to the last study contact, they will be considered to have a missing value for the primary safety endpoint. The safety outcome for all studies will be combined to obtain the pooled result.

Multiple imputation methods will not be performed in the integrated analysis of the primary safety endpoint. The composite safety endpoint, pooled and by study, will be summarized as a proportion where the numerator will be the number of subjects considered a safety success and the denominator will be the number of subjects considered a safety success or failure at 12 months. The two-sided exact 95% confidence interval of the proportion will also be presented. Components of the composite safety endpoint may be summarized individually.

Sensitivity analyses of the primary safety endpoint are not planned for the pooled analysis.

4.3.3 Subgroup analysis

Subgroup group analyses are not planned for the integrated summary report. Subgroup analyses using the methods described in the ILLUMENATE Pivotal SAP may be provided as supportive analyses where necessary.

4.4 Secondary Endpoints

All secondary endpoints defined in the ILLUMENATE Pivotal study will be analyzed descriptively for the integrated summary report for the ITT analysis set.

For binary variables such as MAE or technical success, counts, percentages and exact 95% confidence intervals using Clopper-Pearson's method will be calculated. For continuous variables, means, standard deviations and 95% confidence intervals will be calculated. Secondary analysis with Kaplan-Meier time-to-event methods will not be performed except when specified otherwise in this integrated statistical analysis plan.

The following secondary endpoints will be performed in the DCB analysis set and analyzed per lesion or per subject as specified below:

- Patency rate at 6 and 24 months (Per lesion)
- Lesion success (Per lesion)
- Technical success (Per lesion)
- Clinical success (Per subject)
- Procedural success (Per subject)

- Change in ABI, WIQ, Walking Distance, Rutherford-Becker Classification, and EQ-5D (Per subject)

The following secondary endpoints will be performed in the DCB safety analysis set and will be analyzed per subject:

- Major adverse event rate (MAE)
- Rate of vascular access and bleeding complications
- Rate of clinically-driven target lesion revascularization
- Rate of target lesion revascularization
- Rate of clinically-driven target vessel revascularization
- Rate of target limb major amputation
- Mortality rate
- Rate of ipsilateral embolic events of the target limb

Kaplan-Meier analysis may be performed for the following endpoints:

- Major adverse event rate (MAE)
- Rate of clinically-driven target lesion revascularization
- Rate of clinically-driven target vessel revascularization
- Rate of target limb major amputation

Additional details for secondary endpoints with deviations from the methods and procedures defined in the ILLUMENATE Pivotal SAP are defined in the following sections by endpoint.

Due to differences in requirements for data collection on the ILLUMENATE FIH CRFs, the ILLUMENATE FIH study will be excluded from the combined summary for all of the following secondary endpoints:

- Change in WIQ
- Change in Rutherford-Becker Classification
- Change in EQ-5D
- Change in Walking Distance
- Rate of clinically-driven target vessel revascularization
- Rate of vascular access and bleeding complications
- Rate of occurrence of arterial thrombosis of the treated segment
- Rate of ipsilateral embolic events of the target limb

4.4.1 Rate of Clinically-Driven Target Lesion Revascularization

Rate of clinically-driven target lesion revascularization (CD-TLR) will be summarized as detailed in the ILLUMENATE Pivotal SAP. However, since the CD-TLR definition in the ILLUMENATE FIH study was different from all other ILLUMENATE studies, a sensitivity analysis will be provided that includes a retrospective application of the new CD-TLR definition to the ILLUMENATE FIH study patients.

4.4.2 Change in Walking Impairment Questionnaire

Outcomes from the Walking Impairment Questionnaire (WIQ) will be summarized as detailed in the ILLUMENATE Pivotal SAP. For the ILLUMENATE EU RCT study, a version of the WIQ was used that did not capture the complete sub-domains and complete scale. Data from this version will be excluded from the analysis due to the missing data fields. The new version of the WIQ was implemented later in the study, these data will be included in the analysis.

The combined results of change in Walking Impairment Questionnaire will be summarized with data from the ILLUMENATE Pivotal, ILLUMENATE PK, ILLUMENATE Global, and ILLUMENATE EU RCT studies.

4.4.3 Change in walking distance

The ILLUMENATE EU RCT study protocol permits the treadmill test or the 6 minute hall walk as a follow-up assessment of walking distance. As such, change in walking distance will be summarized from the treadmill test or the six-minute hall walk depending on the assessment performed at each individual subject follow-up. For the purposes of the integrated summary report, changes in walking distance in ILLUMENATE EU RCT will be included only when the same assessment was used to evaluate walking distance at each time point.

The combined results of change in walking distance will be summarized with data from the ILLUMENATE Pivotal, ILLUMENATE PK, ILLUMENATE Global, and ILLUMENATE EU RCT studies. Due to the difference in protocol requirements in the ILLUMENATE EU RCT study, the combined result will also be presented including data from the ILLUMENATE Pivotal, ILLUMENATE PK, and ILLUMENATE Global studies only (ILLUMENATE EU RCT will be excluded from the second pooled result).

4.4.4 Change in EQ-5D

The ILLUMENATE PK and ILLUMENATE EU RCT studies do not collect the EQ-5D and will be excluded from summary of EQ-5D in the integrated summary report. The combined summary of change in EQ-5D will be performed in a subset of the DCB analysis set with subjects from the ILLUMENATE Pivotal and ILLUMENATE Global studies according to the details outlined in the ILLUMENATE Pivotal SAP.

4.5 Safety Analyses

Analysis of adverse events and serious adverse events will be performed as described in the ILLUMENATE Pivotal SAP on the DCB safety set. Rare adverse events (defined as ≤2% incidence in the drug-coated balloon group) will be analyzed in a tabular format. Adverse events from the ILLUMENATE FIH study may be excluded from the combined summary of adverse events unless MedDRA coding is performed and pooling of adverse events is deemed appropriate. Reasons for exclusion of the ILLUMENATE FIH adverse events from the pooled adverse event summary will be clearly described with justification for exclusion. If excluded, a detailed analysis of the events reported in the ILLUMENATE FIH study will be provided with comparison to the adverse events summarized from the four other studies.

Study discontinuations due to adverse events will also be summarized as described in the ILLUMENATE Pivotal SAP.

Analysis of clinical laboratory values (serum chemistries and hematology) will not be performed for the purposes of the integrated summary report.

4.6 Other Analyses

Demographic, baseline, medical history, procedural, lesion, and other follow-up data not included in the primary and secondary endpoints may be summarized descriptively as described in the ILLUMENATE Pivotal SAP. In addition, a summary of study exits and patient accountability by visit will be provided by study and combined across studies.

4.7 Changes in Planned Analysis

Any deviations in planned analysis deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be documented with justification and rationale. Additional supportive analysis may be performed for this integrated summary report for regulatory purposes.