A Prospective Safety and Effectiveness Study: VenaCure Endovenous Laser Treatment (EVLT) 400 µm Fiber Procedure Kit for Treatment of Incompetent Perforator Veins

(SECURE STUDY)

STATISTICAL ANALYSIS PLAN

Study Code: PV-VC300, Version 1.3

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1 Purpose

The purpose of this Statistical Analysis Plan (SAP) is to document the data analyses that are planned for the Prospective Safety and Effectiveness Study: VenaCure Endovenous Laser Treatment (EVLT) 400µm Fiber Procedure Kit for Treatment of Incompetent Perforator Veins (SeCure Study). The results of the analyses documented here are to be presented in the clinical study final report. Additional analyses of the study data beyond the analyses pre-specified in this plan are a possibility, therefore the SAP does not preclude ad hoc analyses that may provide additional useful description of the performance of the device system.

2 Scope

This SAP should be read in conjunction with the Clinical Study Protocol (PV-VC300) and Case Report Forms (CRF).

3 Applicable Documents

Document Number	Document Title
CIP Number: PV-VC300	Prospective Safety and Effectiveness Study: VenaCure Endovenous Laser Treatment (EVLT) 400µm Fiber Procedure Kit for Treatment of Incompetent Perforator Veins, Version 1.3, 11Jan2017
eCRF	AngioDynamics, Inc. Electronic Case Report Forms
NAMSA STATSOP-002	Statistics Standard Operating Procedure – Statistical Analysis Plan

4 Software

Statistical analyses will be conducted in SAS version 9.4 (SAS Institute, Cary, N.C.), R version 3.2 or above (R Core Team, http://www.R-project.org) or another validated statistical software package.

5 Abbreviations

The following list provides acronyms used in this document and their meaning:

Table 1. List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ADE	Adverse device event
CEAP	Clinical, Etiologic, Anatomic, and Pathophysiologic
CRF	Case report form
DUS	Duplex ultrasound
EC	Ethics committee
EVLT	Endovenous Laser Treatment
FDA	Food and Drug Administration

IC	Informed consent
ICF	Informed consent form
IPV	Incompetent Perforator Veins
MedDRA	Medical Dictionary for Regulatory Activities
PG	Performance goal
rVCSS	Revised Venous Clinical Severity Score
SAE	Serious adverse event
SADE	Serious adverse device event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
SUADE	Serious unanticipated adverse device event
TS	Technical success
UADE	Unanticipated adverse device event
VAS	Visual Analog Scale
VEINES-QOL/SYM	Venous Insufficiency Epidemiological and Economic Study Questionnaire – Quality of Life/Symptoms

6 Design and Objectives

The SeCure Study is a single-arm, prospective, multi-center, non-blinded clinical trial to characterize the safety and effectiveness of the VenaCure EVLT 400µm Fiber Procedure Kit for the treatment of subjects with IPVs. The study data will be summarized and submitted to the FDA in a premarket notification once all treated subjects have complete their 3 month follow-up visit. Longer-term follow-up (i.e. 6 month, 9 month, and 12 month data) will be performed for publication purposes.

7 Study Variables

7.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is "Acute Primary Ablation Success" defined as complete (100%) lack of flow or IPV disappearance in the entire treated segment. Success will be measured via DUS imaging performed 10 days (± 3 days) post procedure.

7.2 Additional Treatment Outcomes

Additional treatment variables collected and reported are listed below.

- Primary ablation rate
- Primary assisted ablation rate
- Secondary (retreatment) ablation rate
- Change from baseline in rVCSS
- Change from baseline in CEAP
- Change from baseline in VEINES-QOL/SYM score
- Ulcer healing
- Post-procedure pain assessment

7.3 Safety Outcomes

Safety outcomes that will be collected and reported during the treatment period, 10 day, 1 month and 3 month follow-up visits are the occurrence and frequency of:

- Adverse events (AEs),
- Adverse device events (ADEs),
- Serious adverse events (SAEs),
- Serious adverse device events (SADEs),
- Unanticipated adverse device events (UADE),
- Serious unanticipated adverse device events (SUADE)

Note that AEs will continue to be reported until the 12 month follow-up visit and will be reported in a subsequent publication.

Additional safety outcomes to be collected include vital signs and device malfunctions.

8 Data Collection

Table 2 outlines the study visits, at each evaluation time point from baseline through the 12 month follow-up visit.

Table 2. Schedule of assessments

	Screening	Baseline	Pre-Procedure	Intra-Procedure	Post-Procedure	10 Day Follow-up	1, 3, 6, 9 Month Follow-up	12 Month Follow-up	Unscheduled
Informed Consent	×								
Inclusion/Exclusion	×								
Medical/Surgical History	×								
Medication History	×								
DUS	×					×	×	×	
Venous Mapping	×								
Limb Girth Measurements	×					×	×	×	
CEAP	×					×	×	×	
rVCSS	×					×	×	×	
Pregnancy Test			×						
Demographics		×							
Vital Signs		×	×		×	×	×	×	×
VAS		×				×	×	×	
Physical Examination (Full)		×							
VEINES-QOL/SYM		×					×	×	
Ulcer Measurement		×					×	×	
Physical Examination (Abbreviated)			×			×	×	×	×
Procedure Details				×					
Concomitant Medications			×	×	×	×	×	×	×
Concomitant Procedures				×	×	×	×	×	×
Adverse Event(s) Assessment				×	×	×	×	×	×
Study Exit								×	

9 Sample Size

For this study, a PG of 70% was used for hypothesis testing, whereby the sample size was based on the assumption that the EVLT primary ablation success rate is 80%. Using a binomial exact test for a single proportion, assuming a one-sided test with $\alpha = 0.05$ and a power of 80%, as minimum of 119 IPVs must be treated. For safety, within a sample size of 75 patients, it was determined that there is greater than an 80% chance to detect at least one medically significant AE if the true event rate in this population is at least 2.2%. As such, assuming a 15% attrition rate, a minimum of 86 patients need to be included to meet the minimum number of patients needed to detect at least one medically significant adverse event.

In addition, each investigator will be allowed to treat up to three patients as lead-in cases. With an expected 15% attrition rate and assuming two investigators across seven sites performing three lead-in cases, the maximum number of veins that may be treated in this study is 182.

10 Analysis Populations

The following analysis populations are defined:

- **Enrolled Population:** All enrolled subjects that met all eligibility criteria, regardless if vein access was attempted with the VenaCure EVLT 400µm Fiber Procedure Kit. Lead-in patients are included in the Enrolled population.

- **Intention to Treat (ITT)/Procedure Attempt Population**: All enrolled subjects where vein access was attempted and energy was delivered with the VenaCure EVLT 400µm Fiber Procedure Kit. Lead-in patients are not included in the ITT population.

- **Per-Clinical Investigation Plan (PCIP)/Per-Protocol Population**: All subjects in the ITT population that have had a technically successful procedure and completed the study without any major CIP deviation (see below). Lead-in patients are not included in the PCIP population.

- **Safety Population**: All subjects enrolled in the study where vein access was attempted with the VenaCure EVLT 400µm Fiber Procedure Kit. Lead-in patients are included in the Safety Population.

- **Lead-in Population:** All subjects enrolled in the study that were considered lead-ins, which comprises no more than three subjects per investigator.

Conclusions about device performance will be evaluated with the ITT population. The ITT population will be used for the primary analysis for the effectiveness endpoints, secondary technical success endpoint and other clinical outcome variables. The PCIP population will be used as the secondary or supportive analysis for the effectiveness endpoints and other clinical outcome data to provide insight into the potential impact of protocol deviations on the analysis results.

Subjects with CIP deviations that seriously affect the integrity of the data will be excluded from the PCIP population. The following will be considered major CIP deviations that will result in subject data being excluded from the PCIP population:

- Major inclusion/exclusion criterion deviation
- Major procedural deviation
- Missing primary endpoint data (no DUS performed)
- Significant CIP non-compliance that may confound the incidence of AEs

Protocol deviations may be reviewed prior to performing analysis of study outcomes, in addition to those identified above that may result in excluding a subject from the PCIP population. Reviewing protocol deviations prior to analysis of outcomes is intended to prevent bias in the analysis results while still allowing for identification of significant protocol deviations that could impact outcomes but that were not anticipated at the time that the SAP was written.

The reasons that ITT subjects are excluded from the PCIP will be tabulated and described.

11 Statistical Analyses

11.1 Primary Effectiveness Endpoint Analysis

The primary endpoint effectiveness analysis will be based on the primary ablation success measured at the 10 day follow-up visit (± 3 days). The analysis will be performed on both the ITT and PCIP populations with the ITT population being of primary interest. Primary ablation success will be compared to an objective PG of 70%, with the study hypothesis test presented as follows:

$$H_0 = P_{VenaCureEVLT} < 0.70$$
$$H_A = P_{VenaCureEVLT} \geq 0.70$$

Where $P_{VenaCureEVLT}$ is the proportion of treated IPVs demonstrating acute primary ablation success.

The proportion of treated IPVs being classified as "Acute Primary Ablation Successes" will be compared to the PG of 70% using a GEE model to account for within subject correlated data, with a significance level of 0.05, and one-sided p-value computed. In conjunction with the proportion test, the 95% one-sided lower confidence bound for the treatment success rate will be provided.

11.2 Secondary Technical Success Analysis

In the event that the primary endpoint has been met, the secondary analysis for labeling will be evaluated. The secondary endpoint technical success (TS) analysis will be based on procedural technical success defined as successful access and entry into the IPV to be ablated and the ability to deliver the intended laser energy. The analysis will be performed on both the ITT and PCIP populations. Similar to the primary effectiveness endpoint analysis, the hypothesis test for the secondary TS analysis is as follows:

$$H_0 = TS_{VenaCureEVLT} < 0.75$$
$$H_A = TS_{VenaCureEVLT} \geq 0.75$$

Where $TS_{VenaCureEVLT}$ is the proportion of treated IPVs demonstrating technical success.

The proportion of IPVs being classified as "Technical Successes" will be compared to the PG of 75% using a GEE model to account for within subject correlated data, with a significance level of 0.05, and a one-

sided p-value computed. In conjunction with the proportion test, the 95% one-sided lower confidence bound for the TS rate will be provided.

11.3 Additional Treatment Outcomes

11.3.1 Primary Ablation, Primary Assisted Ablation, & Secondary (Retreatment) Ablation

For all three ablation treatment outcomes, treated IPVs will be summarized by proportion for each time-point (up to the 3 month follow-up visit), where both counts and percentages will be provided. Note that all three ablation treatment outcomes are at the IPV level, thus the denominator will be number of IPVs.

11.3.2 Change from Baseline in rVCSS

The Total rVCSS will be assessed at baseline ($rVCSS_{BL}$) and each scheduled follow-up visit ($rVCSS_t$) (up to 3 months) and descriptively summarized (on the patient level). In addition, the per-subject paired change from baseline will be calculated and descriptive statistics reported for each scheduled follow-up visit.

The rVCSS comprises 10 clinical parameters scored on level of severity (None:0, Mild:1, Moderate:2, and Severe:3), where the overall Total rVCSS is the summation of all 10 clinical parameter values. These analyses may be repeated for each of the 10 clinical parameters if appropriate. Specifically, the 10 clinical parameters include the following:

- Pain
- Varicose veins
- Venous edema
- Skin pigmentation
- Inflammation
- Induration
- Number of active ulcers
- Active ulcer site
- Active ulcer duration
- Compression therapy

The distribution of the data will be examined, whereby if the data are distributed normally then a paired t-test will be conducted to determine if there is a significant change between $rVCSS_{BL}$ and each time-point ($rVCSS_t$). In the event that the data are not normally distributed, then a Wilcoxon Signed-Rank Test will be used instead.

Longitudinal analysis of the rVSCC scores may be performed using a Linear Mixed Effects/GEE repeated measures model to estimate the mean (with 95% confidence intervals) of the rVSCC over time while accounting for within subject correlation. Baseline score ($rVCSS_{BL}$) and visit (categorical) will be included as covariates in the model. The estimate of the rVCSS during the 3 month follow-up is of primary interest.

11.3.3 Change from Baseline in CEAP

The CEAP score will be assessed at baseline ($CEAP_{BL}$) and each scheduled follow-up visit ($CEAP_t$) (up to 3 months) and descriptively summarized (on the patient level). In addition, the per-subject paired change from baseline will be calculated and descriptive statistics reported for each scheduled follow-up visit.

The CEAP is comprised of four distinct classifications, including the following:

- Clinical Classification (including Symptomology)
- Etiologic Classification (no change)
- Anatomic Classification (no change)
- Pathophysiologic Classification

The distribution of the data will be examined, whereby if the data are distributed normally then a paired t-test will be conducted to determine if there is a significant change between $CEAP_{BL}$ and each time-point ($CEAP_t$). In the event that the data are not normally distributed, then a Wilcoxon Signed-Rank Test will be used instead.

Longitudinal analysis of the CEAP scores may be performed using a Linear Mixed Effects/GEE repeated measures model to estimate the mean (with 95% confidence intervals) of the CEAP score over time while accounting for within subject correlation. Baseline score ($CEAP_{BL}$) and visit (categorical) will be included as covariates in the model. The estimate of the CEAP during the 3 month follow-up is of primary interest.

11.3.4 Quality of Life Assessments

The VEINES-QOL/SYM scores will be assessed at baseline (VEINES-QOL_{BL} and VEINES-SYM_{BL}) and each scheduled follow-up visit (VEINES-QOL_t and VEINES-SYM_t) (up to 3 months) and descriptively summarized (on the patient level). In addition, the per-subject paired change from baseline will be calculated and descriptive statistics reported for each scheduled follow-up visit.

The VEINES-QOL/SYM questionnaire comprises 26 items (among eight global questions), where these analyses may be repeated for each of the five sub-domains if appropriate. Specifically, the five sub-domains include the following:

- Symptoms (10 items)
- Limitations in daily activities (9 items)
- Time of day of greatest intensity (1 item)
- Change over the past year (1 item)
- Psychological impact (5 items)

Of the 26 items in the questionnaire, 25 items are summed to create a summary score (VEINES-QOL). One item, which asks about “the time of day the leg problem is most intense” provides only descriptive information and is not scored. A subset of 10 of these items is summed to create a symptom score (VEINES-SYM). For both the VEINES-QOL and VEINES-SYM scores, high values indicate better outcomes.

The VEINES-QOL summary score (25 items) provides an estimate of the respondent's overall QOL, including the impact of CVDL on quality of life, symptoms and the amount of change in the respondent's leg problem over a one year period. The VEINES-SYM score (10 items) includes questions on the frequency of 9 CVDL symptoms--heavy legs, aching legs, swelling, night cramps, heat or burning sensation, restless legs, throbbing, itching, and tingling sensation, as well as the intensity of leg pain.

Item Reversals and Recoding

Three items (Q14, Q17 and Q18) are reverse scored so that high scores indicate better outcomes. These items were recoded as follows: Q3 (1=5, 2=4, 3=3, 4=2, 5=1, 6=missing); Q6 (1=5, 2=4, 3=3, 4=2, 5=1); Q7 (1=6, 2=5, 3=4, 4=3, 5=2, 6=1). For Q4a, responses of 0 ("I do not work") were recoded to missing.

Imputing Missing Data

Missing data are imputed according to the same algorithm recommended for scoring the SF-36. A person-specific estimate is imputed for any missing item in cases where the respondent answered at least 50 percent of the items in the scale.

Scoring

The VEINS QOL/SYM Questionnaire scoring program has been validated by the questionnaire developers and is provided without copyright or licensing fee[1]. The file ''VQOL SPSS scoring pgm REVISED Nov 07.SPS'' is an SPSS (statistical software) file and should not be opened in any other program than SPSS. The software and program will be used to score the questionnaire.[1]

The distribution of the data will be examined, whereby if the data are distributed normally then a paired t-test will be conducted to determine if there is a significant change between VEINES-QOL_{BL} and VEINES-SYM_{BL} and each time-point (VEINES-QOL_t and VEINES-SYM_t). In the event that the data are not normally distributed, then a Wilcoxon Signed-Rank Test will be used instead.

Longitudinal analysis of the VEINES-QOL/SYM scores may be performed using a Linear Mixed Effects/GEE repeated measures model to estimate the mean (with 95% confidence intervals) of the VEINES-QOL/SYM scores over time while accounting for within subject correlation. Baseline scores (VEINES-QOL_{BL} and

[1] Abenhaim L, Kurz X. The VEINES study (VEnous INsufficiency Epidemiologic and Economic Study) (an international cohort study on chronic venous disorders of the leg). Angiology. 1997;48:59–66

Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluating outcomes in chronic venous disorders of the leg (development of a scientifically rigorous, patient-reported measure of symptoms and quality of life). J Vasc Surg.2003;37:410–419

Kahn SR, Lamping DL, Ducruet T, Arsenault L, Miron MJ, Roussin A, et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. J Clin Epidemiol. 2006; 59(10): 1049-56.

VEINES-SYM$_{BL}$) and visit (categorical) will be included as covariates in the model. The estimate of the VEINES-QOL/SYM scores during the 3 month follow-up is of primary interest.

11.3.5 Ulcer Healing

Ulcer healing will be evaluated by the total wound surface, wound depth, and whether or not a patient had an ulcer. Ulcer healing will be descriptively summarized at baseline and at the 1 month and 3 month follow-up visits.

11.3.6 Pain Assessment

The pain assessment, measured on a VAS, will be assessed at baseline (VAS$_{BL}$) and each scheduled follow-up visit (VAS$_t$) (up to 3 months) and descriptively summarized (on the patient level). In addition, the per-subject paired change from baseline will be calculated and descriptive statistics reported for each scheduled follow-up visit.

11.4 Safety Endpoint Analysis

11.4.1 Adverse Events

For AEs, both event counts and counts of subjects experiencing those events will be reported in tabular summaries. Rates will be reported based on the number of subjects experiencing one or more events as a proportion of all subjects in the Safety Population and these subject rates will serve as the primary analysis.

The timing of AEs relative to the initial use of the VenaCure EVLT 400µm Fiber Procedure Kit will be tabulated by reporting the event counts, subject counts, and subject rates of events that occur within the following phases:

- **Intra-Procedure:** From the beginning of the procedure with the VenaCure EVLT 400µm Fiber Procedure Kit until end of the procedure
- **Post-Procedure:** During the post-operative period after the procedure with the VenaCure EVLT 400µm Fiber Procedure Kit was completed.
- **10 Day Follow-up Visit:** From discharge until the 10 day follow-up visit post-procedure assessment.
- **1 Month Follow-up Visit:** From the 10 day follow-up visit until the 1 month follow-up visit.
- **3 Month Follow-up Visit:** From the 1 month follow-up visit until the 3 month follow-up visit.

Based on MedDRA, the tabulation of event type and cross-tabulation of event type by seriousness and relationship to device will be repeated, for the following sets of events:

- All Adverse Events (AEs)
- Serious Adverse Events (SAEs)
- Adverse Device Events (ADEs)
- Serious Adverse Device Events (SADEs)
- Unanticipated Adverse Device Events (UADEs)

- Unanticipated Serious Adverse Device Events (USADEs)

Additionally, the following tables of each type of AE based on MedDRA will be provided:

- AE rates by {body system X preferred term} overall
- AE rates by {body system X preferred term X strongest relationship to therapy} overall
- AE rates by {body system X preferred term X maximum severity} overall

AEs leading to death or to discontinuation from the study, serious AEs (SAEs, SADEs, and USADEs), and unexpected AEs (UADEs and USADEs) will be listed separately.

11.4.2 Evaluation of Vital Signs

Vital signs will be descriptively summarized for each time-point (up to the 3 month follow-up visit), as well as the change from baseline to each time-point. Vitals signs include:

- Blood pressure
- Heart rate
- Respiratory rate
- Temperature
- Weight
- Height
- BMI

A paired t-test will be used to determine if there is a significant change between baseline and each time-point.

11.4.3 Evaluation of Device Malfunctions

Device malfunctions will be tabulated and listed similar to the AE analysis. Device malfunctions will not be coded but will be categorized into like events. Any device malfunction leading to an AE or to study termination will be listed separately.

12 General Statistical Considerations

12.1 Descriptive Statistics

Standard summary statistics will be calculated for all study variables to be reported. For continuous variables, statistics will include means, standard deviations, medians, 25% and 75% percentiles, and ranges. Binary and categorical variables will be summarized by counts and frequency distributions.

Confidence intervals may be reported, as appropriate, using the methods listed below, unless otherwise specified:

- A 95% confidence interval for the mean may be reported using the t-distribution method.
- A 95% confidence interval for the proportion may be reported using the Clopper-Pearson exact method.

12.2 Disposition of Subjects

All subjects that sign the informed consent form (ICF) will be accounted for by reporting the following, with a separate delineation on the lead-in patients:

- Number of subjects that sign the ICF and enroll
- Number of subjects that enroll and meet all eligibility criteria
- Number of subjects that are eligible for treatment
- Number of subjects that exit the study prior to undergoing the procedure with the use of the VenaCure EVLT 400µm Fiber Procedure Kit
- Number of subjects that undergo the procedure with use of the VenaCure EVLT 400µm Fiber Procedure Kit
- Number of subjects that complete the 10 day, 1 month, and 3 month follow-up visits, respectively.

Additional descriptive summary tables across all visits when collected will be provided for both the ITT and PCIP populations:

- Demographics
- Inclusion/Exclusion criteria
- Medical history
- Surgical history
- Medication history
- Doppler ultrasound
- Procedure details
- IPV treatment
- Physical exam (both full/abbreviated)
- Concomitant medications
- Concomitant procedures
- Post-procedure details

12.3 Protocol Deviations

The number of protocol deviations, number of subjects in which the deviations occur, and proportion of subjects with at least one deviation will be reported for all deviations and by sub-categories of deviations (e.g. informed consent (IC), visit compliance, etc.).

12.4 P-values

P-values will be used to report comparisons with PGs and changes between baseline and each time-point (up to the 3 month follow-up visit). P-values will be reported to a maximum of three decimal places with values < 0.001 being denoted as "<0.001". For p-values greater or equal to 0.1, two decimal places will generally be reported. One-sided p-values < 0.05 (for both the primary effectiveness endpoint and the secondary technical success endpoint), and two-sided p-values < 0.05 (for all other additional outcomes and safety outcomes) will be considered statistically significant.

13 Subgroup Analyses

No subgroup analyses are planned for this study.

14 Data Handling

14.1 Partial Dates

In the case that only partial dates are available for AEs, the dates will be imputed. If only the month and year are known, any duration calculated with the partially known date will assume that the date is the first day of the known month. If only the year is known, any duration calculated with the partially known date will assume that the date is July 1 of the known year. In the event that the imputed date is before the procedure date, the imputed date will be equal to the procedure date. If the imputed date is after the last follow-up date or event resolution date, the imputed date will be the latest possible date.

14.2 Visit Windows

All data attributed to a time-point per the CRF will be included in the analysis at that time point, regardless of whether the actual visit date was out of window.

14.3 CEC Adjudication

There is no planned CEC adjudication of events.

15 Interim Analyses

No formal interim analyses are defined for purposes of early study termination.

16 Missing Data Analyses

Every effort will be made to reduce the incidence of missing data. The study will be conducted with proper screening of study subjects, complete training of participating investigators, study coordinators and monitors. All subject data that are available on subjects who drop out during the study will be included.

The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. Furthermore, missing observations will be described in detail and evaluated for assessment of possible bias. To examine the assumption that data are missing at random, an analysis will be performed to compare baseline characteristics and symptomatic status (at earlier time points). Sensitivity analyses, such as multiple imputation or worst case imputation, may be performed to assess the robustness of study conclusions to the potential impact of missing data, provided statistical assumptions of these methods are satisfied.

In worst case imputation, for binary endpoints the worse of the two possible outcomes will be imputed (i.e. “Missing-Equals-Failures”). The timing of the imputed event will be the last known event-free date for subjects that exit the study prematurely. For continuous endpoints assessed, “Last Observation

Carried Forward" (LOCF) will be used. For rates corresponding to a specific follow-up time interval, any partial observed data for a subject will be used.

17 Sensitivity Analyses

A sensitivity analyses may be performed to describe the potential impact of various factors on the observed study results. With respect to the primary effectiveness endpoint, a "tipping point" analysis may be performed to assess sensitivity without need for postulating any missing data technique.

18 Poolability of Data

This study is designed and conducted as a multicenter clinical trial. All participating sites will be selected using the same criteria and trained prior to enrolling subjects. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results. Poolability of the data across centers in a multicenter study is assumed without burden of proof.

Nevertheless, poolability of data across sites will be examined for apparent violation of the poolability assumption. The results of a poolability analysis will be used to assess the robustness of the study results, but not to change the study conclusion. Additionally, a chi-square statistic will be used to describe the degree of variation in these proportions across sites.

Sites with fewer than five subjects will be combined into a "small numbers" site for these analyses since the smaller the number of enrollments at a site, the less likely it is that the observed results reflect the expected results if the site had a greater number of enrollments. Results may also be presented separately for each site to describe the study variables across sites.

19 Deviations from the Statistical Analysis Plan

Any deviation from these planned statistical methods will be documented and discussed in the clinical study report along with statistical rationale for deviation.