Data Analysis Plan

[redacted]

[redacted]

NCT 01855412

Study Title: LIBERTY 360°: Prospective, Observational, Multi-Center Clinical Study to Evaluate Acute and Long Term Clinical and Economic Outcomes of Endovascular Device Intervention in Patients with Distal Outflow Peripheral Arterial Disease (PAD)

Sponsor: Cardiovascular Systems, Inc. (CSI)

24-Mar-2018

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2 INTRODUCTION

The Data Analysis Plan (DAP) is designed to pre-define analysis and assist in the analysis of the data collected in LIBERTY study. This plan includes a description of the study objectives and endpoints listed in the LIBERTY study protocol [redacted]. This DAP should be read in conjunction with the study protocol and electronic Case Report Forms (eCRF). This version of the plan has been developed with respect to the LIBERTY 360 protocol [redacted]. Any changes to the protocol or eCRFs may necessitate updates to the DAP.

3 LIBERTY STUDY DESIGN

The LIBERTY 360° is a prospective, observational, multi-center, clinical study examining the predictors of clinical outcomes for patients undergoing endovascular treatment of lesions within or extending into the target area (10 cm above the medial epicondyle to the digital arteries). This includes disease in the distal superficial femoral artery (SFA), popliteal (POP), tibial peroneal trunk (TPT), anterior tibial (AT), posterior tibial (PT), and peroneal tibial (PR) arteries.

3.1 Study Objectives

The objectives of LIBERTY study are:

1. Evaluate procedural and long-term clinical and economic outcomes for subjects undergoing peripheral endovascular device intervention used to treat lower extremity PAD that includes a target lesion located in a native vessel located within or extending into the target area (10 cm above the medial epicondyle to the digital arteries). This includes disease in the distal SFA, POP, TPT, AT, PT, and PR arteries.

[redacted]

3.2 Patient Selection

Subjects must meet ALL of the inclusion criteria and NONE of the exclusion criteria as outlined in the LIBERTY study protocol [redacted] to be eligible to participate in this study. For a complete list of criteria refer to the study protocol.

3.3 Sample Size

Approximately 1,200 subjects will be enrolled in this study. The study cohort will be divided into three study arms according to the most severe clinical syndrome present at the time of study enrollment:

- "Claudicant" Arm (Rutherford 2-3) – 500 subjects
- "CLI Rutherford 4-5" Arm – 600 subjects
- "CLI Rutherford 6" Arm – 100 subjects

[redacted]

5 DATA ANALYSIS

The analysis of data for the LIBERTY study will be based on the objectives outlined in the [redacted] protocol. Analyses will be conducted on locked clinical study data using SAS software (SAS Institute, Inc., SAS Campus Drive, Cary, NC 27513, USA). In the event an analysis is required that is better suited for a statistical package other than SAS, this other package (e.g. R) will be used.

[redacted]

[redacted]

[redacted]

For all analyses, Rutherford category will be defined as each study arm. These will be used as the basis for comparisons of treatment and treatment location as well as clinical and economic outcomes within the study arm. The primary and secondary specific analyses for descriptive purposes and planned outcome analyses will be performed as pre-specified in this analysis plan. [redacted]

Baseline patient characteristics and risk factors will be presented by study arm. This will include frequency distributions for categorical variables and summary statistics for continuous variables as

appropriate. [redacted]

5.1 Procedure and Long-Term Clinical and Economic Outcomes (Study Objective #1)

Procedure and long-term clinical and economic outcomes include lesion success, procedural success, clinical outcomes [redacted], major adverse event rates, and economic outcomes. Treatment outcomes at a minimum will be summarized overall and by treatment group. The statistical approach to assess these outcomes is described above.

5.1.1. Endpoint 1: Procedural and Lesion Success

Procedural success is defined as a final post-procedural result of < 50% residual stenosis for all treated lesions during index procedure and without significant angiographic complications (perforation, dissection type C-F, distal embolization, acute vessel closure) as determined by the Angiographic Core Laboratory.

Lesion success is defined as a final post-procedural result of < 50% residual stenosis for a given lesion treated during index procedure and without significant angiographic complications as determined by the Angiographic Core Laboratory.

The rates of procedural success and of lesion success will be estimated in the context of a logistic regression, and will attempt to quantify the relationship between covariates or sub-group effects and success rates.

5.1.2. Endpoint 2: Rate of Major Adverse Events (MAEs)

The rate of the following MAEs as reported by the Investigators will be assessed during the subject's participation in the study:

- Death within 30 days of index procedure
- Unplanned major (above the ankle) amputation of the target limb
- Clinically-driven TLR and/or TVR of the target limb

[redacted]

The rates of the MAEs will be estimated in the context of a logistic regression, and will attempt to quantify the relationship between covariates or sub-group effects and MAE

rates. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3 Analysis Conventions

This section details the general conventions to be used for data analyses. Departures from these general conventions may be given in the specific detailed sections of this DAP. When this occurs, the rules set forth in the specific section take precedence over the general convention.

- All statistical tests and confidence intervals will use a significance level of $\alpha = 0.05$. Two-tailed tests will be performed for all analyses that use statistical testing. A p-value $\leq \alpha$ will be interpreted as evidence of statistical significance (e.g., 0.024).
- The distribution of continuous variables will be summarized using means, standard deviations (SD) or Standard Errors (SE), medians, minimums, and maximums and the number of patients with non-missing data. Ordinal variables will be summarized using categorical methods if the number of observed response categories is small (usually 4 or fewer) and with medians, minimums and maximums otherwise.
- Summary statistics for discrete variables will consist of the number and percent of responses in each category. All percentages will be rounded to one decimal place. The count and percentage of responses will be presented in the form of XX (XX.X%), where the percentage is in parentheses. If the count is "0" then the percentage may not be presented. If the percentage is "100", the decimal place may be dropped. In addition the decimal place may also be dropped due to space constraints within a table. When reporting proportions or percentages in text, provide the frequencies used to calculate the percentage. For example, "The population included 500 subjects, fifty-two percent (n = 260) of the population was male."
- Use leading zeros for decimal values less than one. For example, use "0.05" rather than ".05".
- Present findings with appropriate indicators of measurement error such as SD, SE or confidence intervals.

- Baseline is defined as the data point collected the closest, but prior to, the date and time when the first treatment of the index procedure is administered unless otherwise specified in this DAP.
- Change from baseline will be calculated by subtracting the Baseline value from the post-treatment Visit value (i.e., Change from baseline = Visit – Baseline).
- If required, for an analysis, partial dates will be completed by imputing the date using the most conservative approach for that specific date.
- All tables will have the population sample size for each treatment group in the column heading.
- All listings will be sorted for presentation in order of site number, subject number, and the date-time of the procedure or event, additional listing may be specified in the DAP or mocks – these listings will be presented per the specifications.

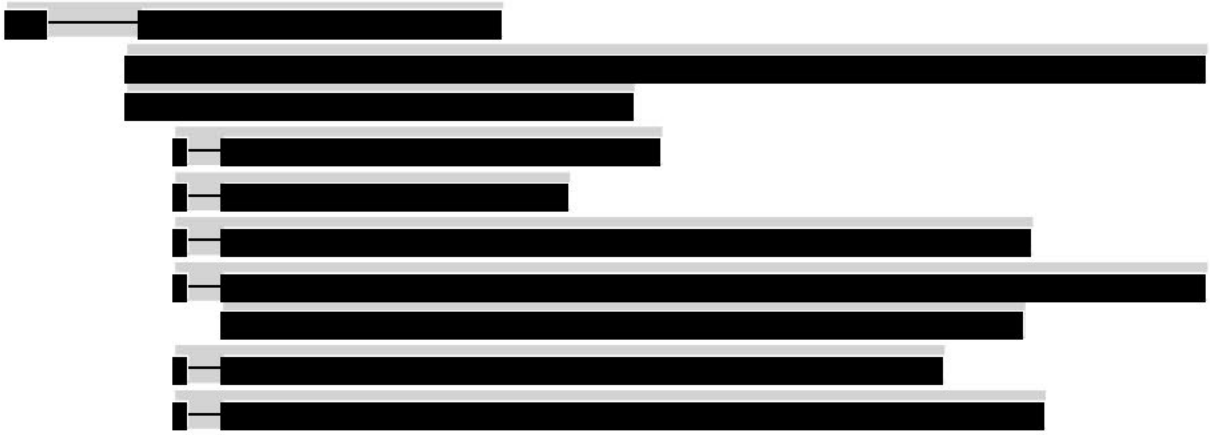
5.3.1. Definition of Baseline Value

For each patient, the last non-missing-valued observation collected prior to first application of treatment will be the baseline value for all subsequent observations. Note that the baseline value may occur on different days for different endpoints but will always fulfill the pre-treatment requirement specified above.

5.3.2. Analysis Intervals

Endpoint analysis on follow-up data may occur at each specified protocol-defined follow-up window (e.g. 30-day, 6-month, 12-month, and annually thereafter) for which it was collected.

[redacted]



5.5 Patient Demographics and Baseline Characteristics

Patient demographics and baseline lesion (s) characteristics will be summarized by study arms.