Protocol CP13-001
The WEB® Intrasaccular Therapy Study (WEB-IT)

Study Sponsor

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1 Statistical Analysis

Statistical analysis is described generally here. A separate Statistical Analysis Plan will describe all analyses to be performed.

1.1 General Approach

The study will use a standard, frequentist approach to statistical analysis. Descriptive statistics (mean, standard deviation, frequency charts, etc.) for baseline participant characteristics, patient disposition and other relevant study parameters will be reported.

1.2 Analysis Populations

The subject populations represented in the final analyses will be determined after CEA adjudication of all AEs and Protocol Deviations. The analysis populations include:

- The intent to treat (ITT) population includes every study subject in whom there is an attempt to place the WEB device. The primary safety and effectiveness analyses will be performed on this population.
- The completed cases (CC) population includes the group of subjects who complete the 12 month visit. Supportive analyses of the primary safety and effectiveness endpoints will be completed with this population.
- The per-protocol (PP) population includes all CC cases who additionally meet all study eligibility criteria, have available study data for the study endpoint and do not have a major protocol violation that affects primary safety or effectiveness. Selected sensitivity analyses will be done with the PP population.

1.3 Data Pooling

The issue of poolability of the data entails two features: the combining of data across study sites and the method of computation of an overall estimate for study endpoints. The justification for combining of data across sites is based on the clinical assessment provided by Meinert (1986): the clinical study will be conducted under a common protocol for each investigational site, the study sites will be monitored for protocol compliance, the same data gathering instrument and method will be used in every site, all clinical events will be adjudicated by a common Clinical Events Adjudicator, and a Core Lab will provide the effectiveness analysis.

A test of homogeneity within US or OUS sites will be done to determine if the study sites within a location have reasonably homogeneous responses. If the responses are not homogeneous, a logistic regression analysis will be done to determine if the lack of homogeneity is due to the site or a possible imbalance in baseline characteristics of the subjects or aneurysms within a study site. If the site effect is no longer significant at $P<0.10$ after adding the potentially unbalanced baseline covariates then it will not be considered a source of lack of homogeneity.

If the above analysis indicates that study site responses are homogeneous, an analysis of the homogeneity across US or OUS sites in aggregate will be done. A logistic regression analysis of the primary effectiveness endpoint be done and will include a covariate for US or OUS sites. This will determine if the OUS sites have a performance difference after adjustment for rupture status or other baseline subject or rupture characteristics that differ in by location in the

comparability analyses described below. If the P-value of location (US or OUS) has a P-value <0.10 after adjustment, it will be deemed to have a difference in response by location and the analysis will be done by stratifying the study sites by location and performing an analysis adjusting for the location.

In study sites with small numbers of subjects, it will be difficult to evaluate a site by treatment interaction. For this reason, study sites with fewer than 6 subjects will be combined into pseudosites. Pseudosites will be used for all multivariate analyses including the analysis to determine a site by treatment interaction for pooling.

Since the study has only one group, it is not possible to do a treatment comparison by logistic regression to account for any study site effects or location difference. Instead, the sites or locations (whichever retains non-homogeneity) will be grouped into subgroups with similar responses these will be combined to get an overall treatment effect by the method of Fleiss. This will result is a z-statistic test provided in the analysis section below.

1.4 Multiplicity

Since there is only one hypothesis tested for effectiveness, there is no inflation to alpha and no multiplicity adjustment is needed.

1.5 Missing Data

Subjects whose data are not missing at random, such as those who exit the study due to a device-related primary safety event will be imputed as a safety and effectiveness failure. These subjects are not missing at random. Subjects who are absent at twelve months and missing at random will have their success or failure imputed for the primary effectiveness endpoint by multiple imputations with random selection from subjects with outcomes with similar aneurysm locations, rupture status and if indicated, aneurysm size or geographic location, followed by sensitivity analyses.

1.6 Primary Endpoint Analyses

Effectiveness

The null and alternative hypotheses for this endpoint are presented below.

H_0: $P_{WEB} \leq 0.203$ versus H_a: $P_{WEB} > .0.203$

where P_{WEB} is the success rate at 12 months in the treated population.

Safety

The null and alternative hypotheses for this endpoint are presented below.

H_0: $P_{WEB} \geq 0.28$ versus H_a: $P_{WEB} < 0.28$

where P_{WEB} is the rate of primary safety events at 12 months as defined above in the treated population.

1.7 Study Success

The study will be considered a success if both the primary effectiveness endpoint and the primary safety endpoint are met.

1.8 Justification for Effectiveness Threshold

The WEB device was designed for the treatment of WNBAs. No prospective clinical trial has focused specifically on the rate of complete IA occlusion in WNBAs. Therefore, the observed success rate in this study will be compared to a performance goal (Objective Performance Characteristic (OPC)) of
0.203. This OPC was derived from the data of a matched subset of patients with WNBAs from a recent randomized trial, adjusted for a different anticipated mix of aneurysm locations (anterior or posterior) and rupture status, and includes a margin of noninferiority. The WEB-IT effectiveness outcome will be considered a success if the success rate observed in this study is statistically significantly greater than 20.3%.

1.9 Justification for Safety Threshold

The WEB device was designed for the treatment of WNBAs. No prospective clinical trial has focused specifically on the rates of major stroke or death in patients with WNBAs. Therefore, the observed safety failure rate in this study will be compared with a performance goal (Objective Performance Characteristic (OPC)) of 0.28. This performance goal was derived from the rates of primary safety events reported in the clinical literature for other endovascular or neurosurgical methods of treatment of bifurcation and wide neck IAs which was 0.1993. The OPC represents the upper two-sided confidence limit on this rate. The WEB-IT safety outcome will be considered a success if the safety failure rate observed in this study is statistically significantly less than 28%.

1.10 Sample Size Calculations

The sample size for the primary effectiveness endpoint for this single arm study is computed using Pass 2008 software for a single binomial proportion. If the effectiveness rate in the WEB group is expected to be 0.323 with core laboratory adjudication, then 80% power is achieved with a one-sided alpha of
0.05 with 84 evaluable subjects. This sample size has been adjusted upward to 95 based on statistical simulations in which all five seeds had to have power of at least 80%. Assuming a loss to follow-up of about 15% in this critically ill population, the recruited sample size will be 95/0.85 = 111.8 or 112 subjects. The planned analysis is anticipated to take place when the requisite number of evaluable subjects has completed the 12 month follow-up visit.

Pass 2008 was also used to estimate the sample size for the primary safety endpoint. To have 80% power to detect a difference between an expected observed primary safety event rate (as defined for this population above) of 0.147 and the OPC = 0.28, the sample size is 62 subjects. The sample size for effectiveness is larger and thus 112 will be the sample size for the study.

1.11 Secondary Effectiveness Analysis

The proportion of subjects with angiographic aneurysmal recurrence at 1 year will be presented descriptively with the rate and its exact 95% confidence interval.

1.12 Additional Safety Analyses

In addition to the primary safety endpoint, additional safety analyses focus on the proportion of subjects in the safety cohort who experienced any of the events listed in Table 12. Additional safety events to be reported. Analyses will focus on rates of events as well as event severity and relatedness.

Table 12. Additional safety events to be reported.

- Serious adverse events
- Device and procedure-related adverse events
- Device-related neurological complications occurring during the WEB procedure
- Device- and procedure-related stroke within 30 days of the WEB placement procedure
- Device- and procedure-related death within 30 days of the WEB placement procedure
- Nonserious adverse events
- Rebleed rates (for ruptured aneurysms)
- New bleed rates (for unruptured aneurysms)
- Clinical assessment by mRS (all Subjects, Subjects with ruptured IAs and Subjects with unruptured IAs)
- Change in mRS from baseline (for Subjects with unruptured IAs only)
- Adverse events vs. operator experience
- Total procedure and WEB fluoroscopy time and total dose
- Statistical summary of procedure and fluoroscopy time
- Mortality at 30 days, 6 months, and 1 year
- Proportion of subjects with a change of 2 more points in mRS at follow-up compared to baseline
- Change in NIHSS among subjects with stroke
- Quality of Life at 6 months by EQ-5D

The following safety analyses will be conducted using Kaplan-Meier methodology:

- Overall survival
- Survival free from an AE rated as probably or definitely related to WEB
- Survival free from rebleeding from the index IA in subjects with ruptured IA at baseline
- Survival free from new bleeding from the index IA in subjects with unruptured IA at baseline
- Survival free from any intracranial bleeding due to IA rupture
- Survival free from any intracranial bleeding
- Survival free from stroke of any severity
- Survival free from major stroke
- Survival free from retreatment of the index IA

1.13 Subgroup Analysis

Subgroup analyses for all safety and effectiveness endpoints described above will be reported for the

following subgroups:

- Ruptured vs. unruptured index IA at baseline
- Aneurysm size (3-7 mm vs. 8-11 mm)
- Aneurysm location (basilar tip vs. MCA vs. ACoA)
- Patients with non-index procedures
- Primary outcome vs. operator experience
- Complete occlusion + neck remnant vs. operator experience
- Gender

1.14 Statistical Software

These analyses will be completed using SAS version 9.2 or later and StaXact Version 8 or later.