STATISTICAL ANALYSIS PLAN

Evaluation of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System to Treat Peripheral Artery Disease (FAST II Trial)

PROTOCOL NUMBER: 010-055

PROTOCOL VERSION: F

PROTOCOL DATE: February 04 , 2020

FAST II Trial

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1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analyses for the clinical investigation "*Evaluation of the Cardio Flow **F**reedomFlow™ Orbital Circumferential **A**therectomy **S**ystem to **T**reat Peripheral Artery Disease (FAST II Trial)"*

This SAP should be read in conjunction with the study protocol and case report forms (CRFs) for details of study conduct and data collection. This version of the plan is developed based upon the study protocol version F, dated February 04, 2020. If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly. Amendments to this document will be finalized prior to database lock (DBL).

2 STUDY DESIGN

The FAST II study is a prospective, multi-center, non-randomized single-arm study designed to evaluate the safety and effectiveness of the FreedomFlow™ Orbital Circumferential Atherectomy System in subjects diagnosed with peripheral arterial disease of the lower extremities.

The study may enroll up to 112 subjects and will be conducted at up to 15 investigational sites in the United States with approximately 56 patients using the Pneumatic System and approximately 56 patients using the Electric System.

Enrollment is expected to take approximately 6 months with observation periods at time of procedure, pre-discharge, 30 days, and 6 months post-procedure follow-up.

3 INTERIM ANALYSES

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

A 30-day primary endpoint report will be prepared and submitted to FDA for the 510(k) clearance. A final report will be prepared following the study completion.

4 DETERMINATION OF SAMPLE SIZE

The sample size is calculated to simultaneously power for the primary effectiveness and primary safety endpoints by comparing to the pre-specified Performance Goal (PG).

Primary Effectiveness Endpoint

Sample size estimates were calculated for the primary effectiveness outcome by comparing the technical success rate to the pre-specified performance goal of 86% (i.e., H_0: technical success rate $\leqslant$ 86% vs. Ha: technical success rate > 86%). The performance goal of 86% was derived using a random effect meta-analysis based on the technical success rates that were obtained from the results of recent atherectomy studies and the allowed 10% margin. The underlying technical

success rate was assumed 96%. Under an exact, one-sided test for a single binomial proportion, at the 0.025 significance level, a sample size of 101 mITT subjects will be required to provide 90% power to meet this technical success objective.

Primary Safety Endpoint

Literature review through a random effect meta-analysis showed a 95% freedom from MAE at 30 days. The pre-specified performance goal for the primary safety endpoint is 85% based on an allowed 10% margin. The hypotheses are H_0: Freedom from MAE at 30 days $\leqslant$ 85% vs. Ha: Freedom from MAE at 30 days > 85%. Under an exact, one-sided test for a single binomial proportion at the 0.025 significance level, a sample size of 102 mITT subjects will be required to provide at least 90% power to meet this primary safety objective.

Overall Sample Size

In order to adequately power for both primary effectiveness and primary safety hypotheses, we require a sample size of 102 mITT subjects who complete 30 days follow-up. The dropout rate of mITT subjects is assumed to be 10 %. The final sample size for the study will be 112 subjects.

5 ANALYSIS SETS

The primary analysis for effectiveness and safety will be based on a modified intent-to-treat principle. The per-protocol analysis set is designated as supportive.

Intent-to-Treat (ITT): the ITT set will be comprised of all subjects who have signed informed consent, meet all the inclusion and none of the exclusion criteria.

Modified Intent-to-Treat (mITT): the mITT set will be comprised of all ITT subjects who have the investigational device attempted.

Per-Protocol (PP): the PP set will be comprised of all subjects in the mITT set who have no major protocol deviations. All major protocol deviations will be reviewed and finalized before the data lock for final analysis.

6 STATISTICAL ANALYSES

6.1 General Statistical Considerations

6.1.1 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.

6.1.2 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.

6.1.3 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.

6.1.4 Duration Variables

Study Day 1 is the day of study device deployment (index procedure).

Study day is calculated relative to day 1 and will appear in the listings where applicable.

Study day after the index procedure will be calculated as:

Study Day = (Date of Event – Date of Study Device Deployment +1).

Study day prior to the index procedure 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+1)]

6.1.5 Kaplan-Meier Analysis

For time to event endpoints analyzed with a Kaplan-Meier method, analysis time points will be presented at 30 and 180 days. 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:

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

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

6.1.6 Missing Data

Unless otherwise specified, techniques will not be used to impute missing data. If a subject (or lesion) is missing a data point for any reason, that subject (or lesion) will not be included in that portion of the analysis. The number of data values available for each analysis will be reported so that the reader can assess the potential impact of missing data.

6.1.7 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's last contact date. In the case of adverse events and other data fields with partial start and stop dates, the imputed dates are subject to the additional condition that the start date must occur on or before the stop date.

	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.

6.1.8 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	Any follow-up CRF entered in the Discharge visit	Any follow-up CRF entered in the Discharge visit
1 Month	23-37 Days	30 Days
6 Month	166-194 Days	180 Days

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

6.1.9 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. In the cases where angiography data are available within a protocol-defined window, and duplex ultrasound assessment is not available, angiographic data will be used to determine the patency.

6.2 Primary Endpoints

The study will be considered a success if both primary effectiveness and safety objectives are met using the mITT Set at the one-sided 0.025 level of significance in the final analysis. The primary endpoint analyses will also be performed in the PP set as a supportive evidence. The primary endpoint analyses will also be performed in the mITT and PP sets by product power type (Pneumatic System and Electric System).

6.2.1 Primary Safety Endpoint

The primary safety endpoint is defined as freedom from a composite of new on-set major adverse events (MAE) at 30-day follow-up as adjudicated by an Independent Clinical Events Committee.

The components of the MAE are defined as:

- Cardiovascular related death: All cardiovascular cause mortality.
- Myocardial infarction (MI): Any newly diagnosed MI post procedure, defined as CK-MB ≥2X upper limit normal (ULN).
- Clinically driven target lesion revascularization (TLR): any repeat percutaneous or surgical intervention to treat objectively documented symptoms of recurrent ischemia attributable to the treated lesion.
- Clinically significant target vessel dissection: NHLBI grade C or greater as confirmed by angiography.
- Clinically significant target vessel perforation: NHLBI Type III as confirmed by angiography.
- Unplanned major target limb amputation: Amputation of the transmetatarsals or higher that was not previously planned as part of the overall treatment strategy.
- Clinically relevant distal embolization: Emboli requiring surgical or medical intervention and/or the presence of symptoms.
- Pseudoaneurysm: Disruption/weakening of the arterial wall at the treatment site as confirmed by angiography.

6.2.2 Analysis of Primary Safety Endpoint

The analysis of primary safety endpoint (i.e., freedom from MAE at 30 days) will be performed in the mITT analysis set. The primary safey will be assessed by calculating the proportion of subjects who have no MAE at 30 days aggregated over the mITT subjects. A 95% two-sided confidence interval will be estimated using the Clopper-Pearson interval (F-distribution method).

In this analysis, the denominator includes all subjects in the mITT set and subjects who have no events but have dropped out prematurely before 30 days will be assumed not to have experienced an event.

If the lower bound of this 95% confidence interval is greater than the performance goal 85%, we can conclude the primary safety objective is met.

Each component of the primary safety endpoint will be also analyzed in the similar fashion as the aggregated primary safety endpoint in the mITT set.

Clinically-driven TLR will be analyzed on a per-subject basis. For subjects with more than one lesions, if at least one of the lesions has a clinically-driven TLR, the subject will fail the endpoint. The date of the earliest clinically-driven TLR will be used as the basis of determining a failure for the K-M analysis.

6.2.3 Alternative Analysis of Primary Safety Endpoint

In case of missing data of concern at 30 days when the primary safety endpoint is evaluated, the probability of a subject achieving freedom from MAE at 30 days will be estimated using Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed. The Kaplan-Meier estimate and its 95% log-log confidence interval will be constructed from the day of index procedure through the 30 days follow-up. For subjects with MAE, days of follow-up will be computed as the days from the index procedure to the onset date of the first event. For subjects without MAE, days of follow-up will be computed as the days from the index procedure to the last follow-up at the time of data lock for primary analysis.

6.2.4 Sensitivity Analysis of Primary Safety Endpoint

A total of three sensitivity/robustness analyses will be conducted to investigate how missing data impacts the primary analysis results if missing data are of serious concern.

1. Complete-Case: the complete-case method uses only the subjects who have completed the 30 days follow-up or have observed the success/failure status through 30 days.
2. Worse-Case: all subjects who have dropped out prematurely will be assumed to have experienced an event.
3. A tipping-point analysis will be conducted. A tipping point is defined as the number of events in the missing cohort at which the study conclusion is changed. Let n_m be the number of missing values in the mITT cohort. Starting at 0 and ending at n_m, the event rate is changed by adding 1 event at a time. The 95% confidence interval will be calculated each time when adding 1 event.

6.2.5 Primary Effectiveness Endpoint

Primary effectiveness endpoint is technical success defined as the ability of the Cardio Flow FreedomFlow™ Orbital Circumferential Atherectomy System (Pneumatic and Electric) to achieve a residual diameter stenosis ≤50% without adjunctive therapy, as assessed by an independent Angiographic Core Laboratory.

The primary effectiveness will be assessed by calculating the proportion of subjects who have achieved technical success over the mITT subjects. A 95% two-sided confidence interval will be estimated using the Clopper-Pearson interval (F-distribution method). If the lower bound of this 95% confidence interval is greater than the performance goal 86%, we can conclude the primary effectiveness objective is met.

6.2.6 Subgroup Analysis of Primary Safety and Effectiveness Endpoints

The purpose of subgroup analyses is to demonstrate the consistency of the treatment effect among the subgroups. We will use an alpha level of 0.15 to determine if there is a potential relationship between each subgroup variable of interest and the primary endpoints based on the chi-square test or Fisher's exact test. This analysis will be conducted at the subject level on the mITT analysis set. All subgroup analyses will be deemed as exploratory and we will not state any conclusions based on the subgroup analyses results.

Subgroups of interest will include smoking status (smokers vs. non-smokers), sex (male vs. female), age (below median vs. above median), race, driveshaft tip (6 Fr vs. 5 Fr), vessel size (2-2.9 mm, 3-3.9 mm, 4-4.9 mm, 5-5.9 mm, 6-6.9 mm and 7-8 mm) and product power type (Pneumatic vs. Electric).

Within each subgroup, the analysis will include the point estimate of primary effectiveness and safety endpoints and their 95% confidence intervals. The p-value that is used to compare to the PG will not be calculated and presented.

6.2.7 Poolability of Primary Safety and Effectiveness Endpoints

A Chi-Square test or exact text will be conducted to investigate the overall homogeneity across all sites and product power type (Pneumatic vs. Electric) for the primary safety and effectiveness endpoints. The tests will be conducted at the two-sided 0.15 level of significance. If the p-value is less than 0.15 then further evaluation is warranted. In addition, a graphical display of the proportions of primary safety and effectiveness success along with 95% confidence intervals for each site will be constructed. The confidence intervals will be constructed using the Clopper-Pearson interval (F-distribution method) and be plotted relative to the performance goal.

Sites with fewer than 5 subjects will be first combined into an adjacent single super-site that shares similar site characteristics for these analyses. The site characteristics will be determined before data lock for statistical analysis. Two sets of poolability analyses will be conducted, one is to use all sites without any combination, the other is to combine low-enrolling sites into a super-site which has similar characteristics. If the sites are not poolable, we will conduct a random effect model to determine its effect on the primary endpoints.

In addition to the homogeneity test for the primary safety and effectiveness endpoints, other variables such as baseline demographics and lesion characteristics will also be compared across sites and product power type (Pneumatic vs. Electric) to assess the appropriateness of pooling data from across all sites and product power type.

6.3 Secondary Endpoints

All secondary endpoints will be analyzed descriptively without hypothesis testing for all mITT patients . All secondary endpoints will also be analyzed by product power type (Pneumatic vs. Electric).

For binary variables, counts, percentages and exact 95% confidence intervals using the Clopper-Pearson method will be calculated, unless otherwise noted. For continuous variables, means, standard deviations and 95% confidence intervals will be calculated.

6.3.1 Clinical Success

Clinical success, defined as the ability of the FreedomFlow™ Orbital Circumferential Atherectomy System to achieve a final diameter stenosis $\leq$50% immediately post treatment with or without adjunctive therapy, as assessed by an independent Angiographic Core Laboratory.

This will be reported as a binary endpoint for the mITT set, with the denominator including all subjects with evaluable angiographic data at the completion of the procedure.

6.3.2 Procedure Success

Procedure success, defined as $\leq$50% residual stenosis at target lesion with or without adjunctive therapy, no procedure-related MAE, no device malfunction causing the procedure to be aborted. In case of having more than one target lesion, all must meet the success criteria.

Major adverse events are defined as in Section **Error! Reference source not found.** in which the primary endpoint is defined 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 for the mITT set, with the denominator including all subjects with evaluable angiographic data at the completion of the procedure.

6.3.3 Change in Ankle-Brachial Index (ABI)

Change in ankle-brachial index (ABI) from pre-procedure (i.e., baseline) to 30 days and 6 months.

The endpoint will be summarized for the mITT set. 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.

6.3.4 Change in Rutherford Classification

Change in Rutherford classification from pre-procedure (i.e., baseline) to 30 days and 6 months.

The endpoint will be summarized for the mITT set. 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.

6.3.5 Change in Patient Reported Outcomes (PRO)

Change in patient reported outcomes (PRO, VascuQoL questionnaire) at 30 days and 6 months.

The total score and subdomain score will be summarized for the mITT set. Within-subject changes will be calculated as visit value minus baseline value such that a positive change reflects an improvement and a negative change signifies a deterioration. Summaries of improved/same/worsened will be provided alongside the continuous summaries.

6.3.6 Rate of Clinically-Driven Target Lesion Revascularization

Rate of clinically-driven target lesion revascularization (TLR) at 30 days and 6 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 form corresponding to the site-reported adverse event that the CEC adjudicated as a clinically-driven TLR.

Clinically-driven TLR will be analyzed on a *per-subject* basis. For subjects with more than one lesions, if at least one of the lesions has a clinically-driven TLR, the subject will fail the endpoint. The date of the earliest clinically-driven TLR will be used as the basis of determining a failure for time to event analysis in Section 6.1.5. The rates at 30 days and 6 months will be estimated for the mITT set from a Kaplan-Meier analysis.

6.3.7 Rate of Clinically-Driven Target Vessel Revascularization

Rate of clinically-driven target vessel revascularization (TVR) at 30 days and 6 months (as assessed by an independent Angiographic Core Laboratory).

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 corresponding to the CEC adjudication.

Clinically-driven TVR will be analyzed on a *per-subject* basis. The rate at 30 days and 6 months will be estimated for the mITT set from a Kaplan-Meier analysis according to Section **Error! Reference source not found.**.

6.3.8 Primary Patency, Primary Assisted Patency and Secondary Patency

Primary patency, primary assisted patency and secondary patency will be derived on a *per-lesion* level.

Primary patency is defined as the absence of target lesion restenosis evaluated by duplex ultrasound (i.e., peak systolic velocity ratio [PSVR] ≤ 2.5) and freedom from clinically-driven target lesion revascularization. The primary patency success must meet success criteria for the both components of patency. If the lesion fails either component of the patency endpoint, the lesion will be considered a failure for the efficacy endpoint.

Primary assisted patency is defined as patency of the target lesion following endovascular reintervention at the target vessel site in case of symptomatic restenosis. This is a cumulative

patency rate including patent target lesion post re-intervention for restenosis at the given follow-up timepoint.

Secondary patency reports patency of the target lesion after treatment of a (re)occlusion of the index lesion. This is a cumulative patency rate, including re-intervention (restenosis or re-occlusion) at the given follow-up timepoint.

A Kaplan-Meier (KM) survival analysis as described in Section 6.1.5 will be used to estimate the patency rates including primary, primary asissted and secondary. The patency rates will be presented as the KM estimate of freedom from loss of patency at 30 days and 180 days post-procedure. The survival curves, the KM estimate, and the 95% confidence interval will be presented. Lesions will be censored at the day of last subject follow-up for the following senarios:

- Have 6 months follow-up but no analyzable duplex ultrasound data, and no clinically-driven TLR
- Have no 6 months follow up but also have no event of interst.

6.4 Analysis of Adverse Events (AE)

The AE analyses will be presented in the ITT set. All analyses will be descriptive with no inferential statistical test.

For AE reporting, the primary analysis will be based on subject counts. A subject with more than one event will be counted only once toward the event rate based on the total number of subjects with AEs. An event count will also be presented. For example, if a subject experiences one major unplanned amputation of the treated limb and two clinically-driven TLRs within 30 days, the subject will be counted once in the rate of total subjects with a 30-day MAE; the same subject will be counted once in the individual event category of "Major Unplanned Amputation of the Treated Limb" and twice in the "Clinically-Driven TLR" category.

A by-subject listing of all AEs will be provided.

6.5 Other Analyses

6.5.1 Screening Failures

Those patients who fail screening will be tabulated with their reason(s) for screening failure.

6.5.2 Subject Disposition

Subject accountability and study discontinuation will be summarized for the 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.

6.5.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT and mITT Sets. Demographic and baseline characteristics include but not limited to age, sex, race, and ethnicity, height, weight, blood pressure, ABI, and Rutherford stage.

6.5.4 Medical History

Medical history will be summarized for the ITT Set.

6.5.5 Poolability Across Investigational Sites

This study is designed and conducted as a multicenter clinical trial. Data from all the sites will be pooled. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results.

A list of variables such as baseline demographics and lesion characteristics will be compared across sites to assess the appropriateness of pooling data from across all sites.

6.6 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 REVISION HISTORY

Version	Date	Description
A	18June2018	Initial Release
B	14Sep2018	Revision after FDA questions
C	18Feb2020	Added statistical analysis by product power type (Pneumatic System and Electric System)