SUPPLEMENTARY APPENDICES

TABLE OF CONTENTS

Appendix 3

STATISTICAL ANALYSIS PLAN

A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support

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Table of Contents

REVISION HISTORY

Revision	Description	Date

ABBREVIATIONS AND DEFINITIONS

BMI	Body Mass Index
CABG	Coronary artery bypass grafting
CCSC	Canadian Cardiovascular Society Classification
CI	Confidence Interval
CV	Coefficient of Variance
EAC	Event Adjudication Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IFU	Instructions For Use
IMA	Internal Mammary Artery
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Coronary Artery
LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MI	Myocardial Infarction
PMA	Premarket Approval Application
NYHA	New York Heart Association
QCA	Quantitative Coronary Angiography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SVG	Saphenous Vein Grafts
TTFM	Transit Time Flow Measurement
VEST	Venous External Support

PURPOSE OF STATISTICAL ANALYSIS PLAN (SAP)

The purpose of this SAP is to outline the planned analyses to be completed for the VEST trial. The planned analyses identified in this SAP will be included in abstracts and manuscripts reporting the results of the trial. Exploratory analyses not necessarily identified in this SAP may also be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published papers from this study. This SAP may be modified as result of changes in the protocol or in the adjudication of the events. All revisions will be made prior to the data lock and the primary analysis.

1. STUDY OBJECTIVES AND METHODS

Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease (1). Despite the proposed benefits of multiple arterial grafts (2), autologous saphenous vein grafts (SVGs) are still, numerically, the most frequently used bypass conduits in CABG. However, progressive SVG failure after CABG remains a key limitation to the long-term success of surgery (3,4). As many as 25% of SVGs occlude within 1 year of CABG; an additional 1-2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which are disease free (5). Intimal hyperplasia and subsequent SVG failure have significant effects on clinical outcomes such as onset of angina, need for revascularization intervention (surgical or percutaneous), myocardial infarction (MI), and death. Over the longer term, proliferation of intimal hyperplasia renders the vein graft lumen vulnerable to atherosclerosis leading to SVG stenosis and occlusion (6,7,8,9,10).

The VEST (Venous External Support) manufactured by Vascular Graft Solutions Ltd, is an external mechanical support for autologous saphenous vein grafts that are created during CABG. The VEST is designed to target the underlying factors leading to SVG disease progression and, in particular, proliferation of intimal hyperplasia.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of this study is to demonstrate the safety and effectiveness of the VEST for its intended use: Limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease.

1.1.2 Secondary Objectives

Secondary objectives of this study are to demonstrate the effectiveness of the VEST in achieving lumen diameter uniformity and reducing graft failure rate.

1.2 Study Methods

1.2.1 Study Design

This study is a prospective, multi-center, randomized, within-subject-controlled, trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison between two sets of SVGs: A VEST supported set; and an unsupported set.

1.2.2 Study duration and time points

Primary and secondary endpoints will be ascertained at 12 months to support a Premarket Approval Application (PMA) application. Long term data, up to 5 years follow-up, will be monitored in the post-approval period.

1.2.3 Randomization and masking

For every patient, a pair of grafts will be designated for participation in the trial; one to be supported with the VEST device and the other to serve as a control. Grafts to the LAD do not participate in the randomization.

Patients will be block randomized by territory and/or by SVG length.

If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will assign the treatment and control vessels by their lengths.

Only grafts originating proximally from the aorta will be considered for randomization. Sequential grafts will not be included in the study. Where more than one graft may be performed per territory, the vein grafts will be uniquely distinguished by their pre-measured length as "Longest" and "Shortest". This design will allow for within-subject comparisons, which is expected to increase power relative to a between-subject design.

To prevent any bias as well as exclude any ineligible patients, randomization will be performed only after the procedure has reached the stage where all venous bypass distal anastomoses have been constructed.

The nature of the study precludes masking surgeons from treatment assignment. In order to prevent selection bias, randomization into treatment assignment is performed intraoperatively only after all distal anastomoses have been completed. Investigators will also be blinded to all data from other clinical sites, as well as the primary outcomes data and aggregate data regarding clinical outcome. Serious unexpected AEs will be reported to Institutional Review Board (IRB) as usual. Clinical events including serious and protocol- defined adverse events will be reviewed by an Event Adjudication Committee. All angiograms and intimal hyperplasia scoring will be analyzed, according to predefined analysis protocols, by independent core laboratory personnel who will be blinded to clinical outcomes.

2. EFFICACY ENDPOINTS

2.1 Primary Endpoint

The primary endpoint is defined as intimal hyperplasia (plaque+media) area [mm^2] as assessed by intravascular ultrasound (IVUS) at 12 months. This endpoint is measured for each study graft (VEST supported and unsupported) and is measured as a continuous variable.

2.2 Second Confirmatory Endpoints

Second confirmatory endpoints are measured at 12 months post randomization. The following second confirmatory endpoints will be analyzed.

2.2.1 Lumen Diameter Uniformity (Fitzgibbon)

Lumen diameter uniformity will be assessed by angiography for each study graft separately and expressed by the Fitzgibbon classification (11), on a 3-point ordinal scale:

- I – No intimal irregularity
- II – Irregularity of <50% of estimated intimal surface
- III – Irregularity of >50% of estimated intimal surface

2.2.2 Graft Failure

Graft failure will be assessed by quantitative coronary angiography (QCA) for each study graft and defined as:

- Failure: ≥50% stenosis
- Success: Otherwise

2.3 Additional Secondary Endpoints

Additional secondary endpoints are measured at 12 months post randomization. The following additional secondary endpoints will be analyzed.

2.3.1 Intimal Hyperplasia Thickness

Intimal hyperplasia (plaque + media) thickness [mm] will be assessed by IVUS. This endpoint is measured for each study graft and is measured as a continuous variable.

2.3.2 TIMI Flow Grade

TIMI flow grade will be assessed by angiography on the following 4-point ordinal scale for each study graft:

- Grade 0: No perfusion
- Grade 1: Penetration without perfusion
- Grade 2: Partial perfusion
- Grade 3: Complete perfusion

2.3.3 Graft Failure

Graft failure, as defined above, will be analyzed separately for right and left territories.

2.3.4 Repeat Revascularization

Repeat ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be reported over the 5 years of observation.

2.3.5 Lumen Diameter Uniformity (CV)

Lumen diameter uniformity will be expressed by the coefficient of variation (CV) by QCA, computed for each graft separately, and scored continuously as follows:

$$CV_{Uniformity} = SD_{Diameter} / Mean_{Diameter}$$

2.3.6 Ratio of Vein Graft Lumen Diameter to Target Artery Lumen Diameter

The ratio of each study vein graft mean lumen diameter to its target artery mean lumen diameter will be assessed by QCA.

2.3.7 Additional Lumen Measurements and Flow Parameters

Ectasia, blood flow, and blood velocity for each study vein graft will be measured.

Ectasia will be defined as a segmental dilation more than 50% compared to the normal adjacent segments assessed by QCA.

Blood velocity (cm/s) will be calculated using frame count approach with the following formula: [Velocity=Length/[end frame-start frame]/(frames per second)/10], where start frame is defined as the frame where "dye first fully enters injected artery: dye must extend across nearly entire width of artery or vein (at least 70%) and there must be antegrade motion to dye" and the end frame is the frame where "dye first enters distal landmark branch; complete opacification of the target artery is nor required".

Blood flow (mL/s) is calculated as velocity multiplied by cross sectional area.

3. CLINICAL ENDPOINTS

The following clinical endpoints will be analyzed:

3.1 Mortality

All-cause mortality will be assessed annually over the 5 years of observation.

3.2 Hospitalizations

3.2.1 Length of Index Hospitalization

Overall post-operative length of stay for the index hospitalization will be measured and broken down by days spent in the ICU versus days spent on telemetry and regular floors. Discharge disposition will also be captured. Days in ICU, telemetry, and regular floor will be reported for US and Canadian sites separately. Length of stay will be reported separately for US and Canadian centers.

3.2.2 Readmissions

All inpatient hospitalizations lasting ≥24 hours will be considered. Readmission rates will be calculated for the first 30 days following intervention and annually over the 5 years of follow-up. Hospitalizations will be classified for all causes including for cardiovascular reasons.

3.3 Safety

Serious adverse events (SAEs) occurring post randomization and up to 12 months after the CABG procedure.

3.4 MACCE

Major adverse cardiac and cerebrovascular events (MACCE) occurring within 12 months and annually up to 60 months after the index CABG procedure. MACCE components include:

- All-cause **mortality**

- **Stroke**: Defined as any new, rapidly developing focal neurological deficit, lasting longer than 24 hours, ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests, imaging and neurology consultation note). The Modified Rankin Scale and the NIH Stroke Scale must be administered within 24 hours following the event to document the presence and severity of neurological deficits.
  Each neurological event must be subcategorized as:
  - Hemorrhagic stroke
  - Ischemic stroke
  - Other
- **Myocardial infarction (MI)**: Any one of the following criteria meets the diagnosis of MI
  - Acute MI - Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the Upper Reference Limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumably new significant ST-T changes or new LBBB;
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy
  - CABG related MI - defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either
  - New pathological Q waves or new LBBB, or
  - Angiographic documented new graft or new native coronary artery occlusion, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Prior MI – Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence on non-ischemic cause.
  - Pathological finding of prior MI

- **Ischemic Driven Target Vessel Revascularization**: (CABG or PCI) of **VEST supported** vein graft or associated target coronary artery.
  Revascularization is considered ischemic driven if the subject has clinical or functional ischemia manifesting in any of the following:
  - A history of angina pectoris presumably related to the target vessel
  - Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel

- Abnormal results of any invasive functional diagnostic test [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

The angiography and IVUS procedure performed at 12 months to assess the graft integrity by the study plan will not be counted as MACCE. Clinical evaluation for the 12 months visit will be completed and MACCE will be recorded prior to performance of the planned interventional procedure. If revascularization of the VEST supported graft or associated bypassed coronary artery is performed as a result of the angiography, it will be reported and adjudicated according to the definition given above for ischemic driven target vessel revascularization, for assessment of MACCE at time points >12 months.

All adverse events (including MACCE) and causes of mortality will be adjudicated by an independent event adjudication committee (EAC).

4. FIVE-YEAR FOLLOW-UP ENDPOINTS

Patients participating in the trial will be followed for an additional 4 years after completing the 12-month pivotal trial to assess the endpoints below. COVID-19 related AEs will also be recorded.

4.1 Time to Revascularization

Time to ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

4.2 Revascularization Rate

Ischemic driven target vessel revascularization rate for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

4.3 Time to MI

Time to MI in culprit vessels (when available) for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

4.4 Rate of MI

Rate of MI in culprit vessels (when available) for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

5. SAMPLE SIZE ESTIMATION

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing CABG. The primary endpoint of the study will be the intimal hyperplasia (plaque + media) area [mm^2] as assessed by IVUS at 12 months post randomization. Sample size is based on the assumption that IH will be normally distributed with standard deviation of 1.7 mm^2 in both the VEST supported and the unsupported vessels. We also assume that the mean IH in the unsupported vessel is 5.1 mm^2 and that the correlation between IH measured on grafts within the same patient is equal to 0.5. In addition, we anticipate

that approximately 13% of patients will have the supported and/or unsupported grafts occluded or severely stenosed and so unable to have IH measured through IVUS; in approximately 50% of these patients IH will not be obtained in either graft while in the rest, the occlusion will only affect one of the two graft, in 25% the VEST graft will be occluded and in 25% the control graft will be occluded. Although it is unclear to what extent occlusion is related to IH one year post CABG, we will treat missing values of IH resulting from occluded vessels as non-ignorable missing using an imputation model that will penalize these vessels and reduce the effect size. Therefore, we assume a conservative effect size of 0.4 mm^2, or a reduction of IH in the VEST vessels compared to the control vessel of about 8%. Under these assumptions, fixing the power at 90% we need to enroll 190 patients, before adjustment for loss to follow-up.

5.1 Lost to follow-up considerations

Lost to follow-up and refusals: The term "lost to follow-up" is used to describe an individual who has withdrawn consent to be in the study or who can no longer be located or assessed. Such individuals represent those for whom primary outcome assessment is no longer possible. We anticipate that the loss to follow-up rate or refusal to perform an IVUS in this study will be around 15%. To account for this loss to follow-up or refusal rate, a total of 224 eligible participants will be enrolled in the study.

6. ANALYSIS POPULATIONS

6.1 Full Analysis Set

The full analysis set (FAS) will, consistent with ICH Guideline E9 (12), include all randomized vessels for which the study procedure was initiated in either arm according to the intention-to-treat (ITT) principle. If the Month 12 angiogram was not done, a vessel can still be included in the FAS if information is available on randomized vessels from angiograms prior to the Month 12 visit. Vessels of patients who do not undergo angiography at Month 12 due to contraindications will be included as well. All other vessels of patients without the Month 12 visit will be excluded.

6.2 Safety Analysis Set

The safety analysis set will consist of all patients who are considered enrolled in the study, once they are randomized and an identification code is generated.

6.3 Per Protocol Analysis Set

The per protocol analysis set will consist of all patients in the full analysis set who do not have deviations on VEST implantation and any protocol violation/deviation likely to affect the primary endpoint.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Principles

Variables will be presented using descriptive statistical methods. Depending on the purpose of the analysis, the presentation can be for all randomized patients or stratified by randomization group (VEST supported vs. control vein graft).

Continuous and ordinal variables will be summarized using number of non-missing values, means, standard deviations, medians, interquartile range, maximum, and minimum.

Categorical variables will be summarized using number of non-missing values, counts and percentages.

Count variables will be summarized using rates. Rates of events will be calculated as the ratio of the total number of events recorded over a period of time over the total patient-time.

Time-to-event variables will be presented with Kaplan-Meier estimates or cumulative incidences in the presence of competing risks.

Numerical results from statistical models will be presented with confidence intervals.

Should any of the statistical methods proposed prove unsuitable during data analysis, more appropriate methods will be used. These include data transformation (e.g., logarithmic scale) or a different choice of model for the same type of outcomes (e.g., Poisson to negative binomial; proportional odds model to partial proportional odds model) to better satisfy model assumptions and obtain a better model fit.

Statistical analysis will be performed using SAS V9.4 or higher and R V3.6.1 or higher.

7.2 Handling of Missing Data

7.2.1 Missing baseline data

Missing baseline values that are needed to compute absolute, relative, or percent change from baseline will be imputed using mean imputation (13). The missing values of a variable will be replaced with the observed sample mean of that variable. Mean imputation is appropriate because baseline variables are independent of randomization assignment.

7.2.2 Missing primary outcome data due to vessel occlusion

It is anticipated that roughly 13% of vessels will be obstructed and unsuitable for IVUS, and thus intimal hyperplasia will be measured only on non-obstructed vessels. Although the degree of intimal hyperplasia may be independent of the mechanism of obstruction, we will consider an obstructed vessel as a failed vessel in the analysis. Specifically, we will assume a non-ignorable mechanism (not missing at random or NMAR) for the data missing due to obstructed vessels.

The problem of missing IVUS data due to occluded vessels at 12 months will be addressed by multiple imputation — i.e., creating several potential imputed observations for each missing data using a predictive modeling (14). The underlying model will use the pattern-mixture approach, which posits a separate distribution of the true IVUS measurement for missing and non-missing observations. The model will include but not limited to the following subject specific covariates: hypertension, diabetes, hyperlipidemia, and smoking status; and the following vessel specific covariates: treatment assignment, coronary territory, vein graft length, vein harvest, preservation techniques, Transit Time Flow Measurement (TTFM) values, and target vessel baseline stenosis.

Let *Y* represent the continuous outcome variable (i.e. intimal hyperplasia) and let *R* be an indicator variable that assumes different values according to whether *Y* is observed or missing. Under a pattern-mixture model, the joint distribution of the outcome *Y* and the missing indicator variable *R, f(Y,R),* is factorized into the density of the outcome, conditional on the pattern of missingness of *Y, f(Y|R),* and the marginal distribution of the missing indicator variable, *P(R).*

$f(Y,R)=f(Y|R)P(R)$

In longitudinal studies, the probability distribution *P(R)* refers to the probabilities of the different possible patterns of missingness. In this situation we distinguish only two patterns of missing data: we define a case to be complete *(R=1)* if a vessel is able to be evaluated at follow-up, and to be incomplete *(R=0)* if the follow-up measurement is missing due to occlusion.

Under the NMAR framework, the density *f (Y|R)* is specified differently depending on whether *R=0* (*Y* is missing) or *R=1* (*Y* is observed), reflecting the fact that the missing values may come from a different distribution than the observed ones. In this study, we will assume that the distribution function of intimal hyperplasia is normal, with $f(Y|R=1)\sim N(\mu, \sigma^2)$ for the observed data and $f(Y|R=0)\sim N(\mu+\delta, \gamma\sigma^2)$ for the missing data. The parameters δ and γ are sensitivity parameters. In order to "penalize" the obstructed vessels we will assume that δ is positive to reflect, on average, larger values of intimal hyperplasia. Specifically, we will assume that the non-observed values come from a normal distribution with mean equal to the 90th percentile of the distribution of intimal hyperplasia in the VEST I trial, which was equal to 6.84 mm^2.

The procedure will be implemented in two stages: First a set of imputations for intimal hyperplasia will be created for each vessel with missing data. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. Characteristics of the vessels, like laterality, length, vein harvest, preservation techniques, TTFM values, and baseline stenosis, as well as patients' characteristics will be used to inform the predictive models. This corresponds to the usual imputation under a missing at random (MAR) mechanism. In the second stage, values will be generated from a prior distribution $N(\delta, \sigma_\delta^2)$, where δ is such that $\delta+\mu$ is equal to the 6.84 mm^2, and added to the imputed response from the first stage for the occluded vessels.

The imputation process will be repeated 30 times to achieve maximal stability of the procedure.

7.2.3 Missing primary outcome data due to reasons other than vessel occlusion

Missing values on the primary outcome may be due to reasons other than occluded vessels. They are listed in Table 1 and the rules for handling the missing data are provided.

Table 1: Rules for handling missing IVUS other than vessel occlusion

Situation	Solution
Patient is lost to follow-up or refused to undergo IVUS at 12 months and do not have a previous angiogram	They will be excluded from the FAS.
Death prior to the 12-month visit and do not have a previous angiogram or an autopsy that determines the culprit vessel	They will be excluded from the FAS.
Study grafts that are patent, are not completely occluded, but have some degree of stenosis in which cannulation for IVUS is unsafe and therefore, patient cannot undergo IVUS imaging	They will be treated like occluded vessels and considered NMAR.
Missing intimal hyperplasia because of: Poor image quality//technical difficulties with imaging//missing or unreadable images due to deviations from acquisition protocol// missing or incomplete images due to contraindications//other reasons unrelated to stenosis or occlusion	They will be considered MAR and imputed values from the first stage of the multiple imputation procedure will be used as described in Section 7.2.2.
Patient had an angiogram prior to the 12- month visit and does not return for the study angiogram and IVUS at 1 year	Several scenarios to consider: o If the previous angiogram(s) indicated vessel stenosis of ≥ 50% on the VEST supported and/or unsupported vein grafts, they will be considered NMAR at 12 months. o If the previous angiogram(s) indicated vessel stenosis of < 50% on the VEST supported and/or unsupported vein grafts, they will be considered MAR at 12 months. Note: If the previous angiogram(s) indicated some degree of stenosis on one study vein graft and did not provide information on the other randomized vein graft, the latter will be considered MAR at 12 months. o If the previous angiogram(s) did not provide any information on any of the study vein grafts, the vessels of patient will be excluded from the FAS.

7.2.4 Missing secondary outcomes data

Table 2 presents the rule for handling missing data on the secondary confirmatory endpoint of graft failure and any secondary endpoints related to graft failure.

Table 2: Rules for handling missing graft patency measurement at 12 months

Situation	Solution
Patient had an angiogram prior to the 12- month visit and does not have a study angiogram at 1 year	Apply worst observation carried forward method. That is, use the most severe % stenosis based on previous angiograms, if available. If the previous angiogram showed some degree of stenosis or total occlusion in only one of the study grafts and no information is available for the other study graft, the latter will be considered a non-graft failure at 12 months.
Graft patency cannot be determined at 12 months	Use information from previous angiograms, if available. Apply worst observation carried forward method as described above

Only observed values will be used to analyze safety data; i.e. missing safety data will not be imputed.

7.3 Handling of Crossovers

Vessels randomized to VEST but not supported will be considered crossovers. Similarly, vessels randomized as control but VEST supported will be considered crossovers. We anticipate very few crossovers in this trial. As the primary analysis is by intention-to-treat with respect to randomization assignment, crossovers will be analyzed as belonging to the group to which they were randomized. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect on trial outcomes.

7.4 Multiple Testing

Hypothesis testing will be conducted at a two-sided significance level of 0.05 for the primary endpoint and the two secondary confirmatory endpoints using a hierarchical testing procedure (see Section 10). Hypothesis testing for other secondary endpoints and long term outcomes will be carried out at the 0.05 significance level as well. However, there will be no formal correction of the type I error rate for multiple testing of statistical hypotheses related to these endpoints.

7.5 Data Rules

Some differences may occur between the vessels in the randomization electronic case report form (eCRF) and those recorded on the index surgical procedure eCRF. In some

cases, the SVG would be placed into the closest distal target that is bypassable and not placed in the same vessel as the qualifying lesion. In a few instances, the vessels in the randomization eCRF were the arteries with the qualifying lesion and do not reflect the target coronary artery. The names of the randomized vessels should be the target coronary arteries that bypass the qualifying lesions. The vessels that undergo IVUS imaging are those identified in the index surgical procedure form as the target arteries. All analyses will be based on the vessel information collected on the index surgical procedure form which notes the target vessels.

7.6 Data Lock

The dataset for the primary outcome analysis will be locked when all data through the last one year follow-up have been entered and all queries have been resolved and data management processes have been completed. The entire database will be locked when all data for the 5-year observation period have been entered and all queries have been addressed.

7.7 Blinded Review

Angiograms and revascularizations prior to the 12-month assessment may be informative for missing primary and secondary endpoints at 1 year. While several rules have been developed for handling missing outcome data in Sections 7.2.3 and 7.2.4, the list is not exhaustive. A blinded review of data entered in the EDC for event-driven angiograms and revascularizations may be conducted prior to data set lock to ensure that all scenarios have been accounted for and designation of NMAR/MAR (for primary endpoint) and graft failure (yes/no) is correct. This is important for patients who do not return for their 12-month visit but underwent prior revascularization which may contribute information to the primary and secondary endpoints.

8. STUDY SUBJECTS

8.1 Subject Disposition

Subject disposition will summarize patients' status at different stages of the study. This includes:

- The number (%) of patients assessed for eligibility
- The number (%) of patients eligible and ineligible for the study and reasons for non-eligibility
- The number (%) of patients who signed informed consent
- The number (%) of patients randomized
- The number (%) of patients for whom the VEST was deployed
- The number (%) of patients who completed each annual follow up visit
- The number (%) of patients lost to follow-up (including withdrawals) by 12 months and annually thereafter and reasons for study dropout
- The number (%) of patients who died by 12 months and annually thereafter.
- The number (%) of patients who underwent coronary angiography at 12 months
    - The number (%) of patients who did not undergo coronary angiography and reasons for procedure not completed
    - The number (%) of patients for whom QCA is available
- The number (%) of patients who underwent IVUS at 12 months

    - The number (%) of patients who did not undergo IVUS and reasons for procedure not completed
- The number (%) of patients in the Full Analysis Set and reasons for exclusions
- The number (%) of patients in the Safety Analysis Set
- The number (%) of patients in the Per Protocol Analysis Set and reasons for exclusions

8.2 Protocol Violations

The number (%) of each type of protocol violations and deviations will be tabulated.

9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

9.1 Subject Demographics and Baseline Factors

The following patient baseline data will be summarized:

- Age (years)
- Gender (female/male)
- Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other; More than One Race; Unknown or Not Reported)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Unknown or Not Reported)
- Body Mass Index (BMI) (kg/cm^2)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Smoking status (current, former, never)
- Pack Year History where applicable
- Dialysis (yes/no) and dialysis type if yes (hemodialysis; peritoneal dialysis; CVVH; CVVHD)
- Diabetes (No history; Type 1; Type 2; Other) and whether treated
- Hypertension (yes/no)
- Hyperlipidemia (yes/no)
- Prior stroke in the past year (yes/no)
- Prior MI (yes/no)
- Atrial Fibrillation (yes/no)
- Peripheral Arterial Disease (yes/no) and treatment status if yes
- Carotid Artery Disease (yes/no) and treatment status if yes
- Prior PCI (yes/no)
- Prior cardiac surgery (yes/no)
- Chronic Pulmonary Disease (yes/no)
- New York Heart Association class (NYHA) (No heart failure, Class I; Class II; Class III; Class IV)
- Canadian Cardiovascular Society Classification (CCSC) (No angina; Grade I; Grade II; Grade III; Grade IV)
- Pre-operative Logistical EuroScore
- Left ventricular ejection fraction (LVEF) (%)
- Creatinine (mg/dL)
- SYNTAX score at baseline

9.2 Characteristics of Saphenous Vein Grafts

Baseline characteristics of SVGS SVGs will be presented by randomization assignment (VEST supported vs. unsupported) and will include the following variables:

- Native coronary artery stenosis (%)
- Target coronary artery diameter (mm)
- Graft length (cm)
- Systolic pressure at TTFM flow (ml/min)
- Final TTFM flow (ml/min)
- Final TTFM pulsatility index
- The number (%) of Right Short, Right Long, Right single, Left Short, Left Long, Left single vein grafts
- Distribution of vein graft randomized to VEST and Control

10. EFFICACY ANALYSES

10.1 Analysis of Primary Endpoint

10.1.1 Analysis of Primary Endpoint

The primary outcome is the degree of intimal hyperplasia (plaque+media) area [mm^2] at 12 months post-surgical intervention, assessed by IVUS. The null hypothesis is that there is no difference in the 12-month intimal hyperplasia area between vessels randomized to the VEST compared to control vessels. The primary null hypothesis will be tested in the full analysis set with vessels analyzed according to their randomization group using a two-tailed 0.05 alpha level. The analysis will be conducted using a Wilcoxon signed-rank test.

We will account for the occluded vessels in the computation of the Wilcoxon sign-rank test as follows. If two vessels in the same individual are both occluded, we will assign an absolute value of zero for the difference between the two scores irrespective of the imputed values. Pairs with a value of zero will be excluded from the computation of the test statistic as usual for the Wilcoxon rank-sign test. If only one of the two vessels is occluded in the same individual, then we will assign an absolute value equal to the difference between the observed and the imputed score. The sign associated with the rank for this difference, however, will be in favor of the non-occluded vessel. If both vessels are not occluded they will be treated as usual in the computation of the Wilcoxon sign-rank test.

A multiple imputation approach will be used to impute the intimal hyperplasia values of the occluded vessels as outlined in Section 7.2.2. The imputation process will be repeated 30 times to achieve maximal stability of the procedure. A separate analysis will be conducted for each completed-and-imputed dataset. Rubin's rule (14) will be used to combine the 30 analyses and test the difference between intimal hyperplasia area of the treated and control vessels.

The primary analysis will not be stratified by clinical center although the randomization will stratify by clinical center. This should result in only a small loss of efficiency.

This is a multicenter trial with the clinical protocol and IVUS acquisition protocol rigorously standardized across all sites and thus, a large cluster effect is not expected.

10.1.2 Sensitivity Analysis for Primary Endpoint

We will conduct a series of sensitivity analyses to determine the stability of the estimate of the treatment effect obtained with the multiple imputation pattern-mixture approach outlined in Section 7.2.2. Specifically, we will work with different values of the sensitivity parameters δ and γ to determine how our assumptions about the distribution of the missing data influence the results. For example, assuming $\delta = 0$ corresponds to a missing-at-random (MAR) assumption, which posits that there is no information in the fact that a vessel is occluded and therefore cannot be measured. These analyses will allow us to determine how large δ has to be to change the outcome of the final analysis with respect to statistical significance of the treatment effect.

10.1.3 Per Protocol Analysis of Primary Endpoint

A per protocol analysis will be performed on the primary endpoint and will include patients with no deviations on VEST implantation and no protocol violations/deviations that could affect the primary outcome.

10.2 Analysis of Secondary Confirmatory Endpoints

Following are the study's two secondary confirmatory hypotheses that will be tested in the full analysis set in the order presented using a sequential strategy:

10.2.1 Secondary Confirmatory I

H_0: (Lumen Diameter Uniformity)$_{VEST}$ = (Lumen Diameter Uniformity)$_{CONTROL}$
H_1: (Lumen Diameter Uniformity)$_{VEST} \neq$ (Lumen Diameter Uniformity)$_{CONTROL}$

where lumen diameter uniformity is measured using Fitzgibbon classification as described in Section 2.2.1. The proportional odds model for clustered data will be used to test the null hypothesis that the odds ratio (VEST vs. control) for getting lower Fitzgibbon classification is equal to 1 at a two-sided alpha = 0.05. If the proportional odds assumption is not satisfied, a partial proportional odds model may be considered. We will declare success on this endpoint if we will have succeeded on the primary efficacy endpoint and rejected the null hypothesis in this section.

10.2.2 Secondary Confirmatory II

H_0: (Graft Failure)$_{VEST}$ = (Graft Failure)$_{CONTROL}$
H_1: (Graft Failure)$_{VEST} \neq$ (Graft Failure)$_{CONTROL}$

where graft failure is defined as $\geq$ 50% stenosis is as described in Section 2.2.2.
Hypotheses will be tested using McNemar's test for paired binary observations with two-sided alpha = 0.05. We will declare success on this endpoint if we will have succeeded on both confirmatory endpoints.

10.2.2.1 Sensitivity Analysis for Secondary Confirmatory II

Different sensitivity analyses can be conducted to evaluate the robustness of imputing missing graft patency measurements using information from previous angiograms.

For instance, assumptions that the graft patency is the same, better, and worse for the imputed VEST supported graft compared to the control can be performed.

10.3 Analysis of Additional Secondary Endpoints

The following additional secondary endpoints will be analyzed:

10.3.1 Intimal Hyperplasia (plaque + media) thickness [mm]

Intimal hyperplasia thickness as assessed by IVUS at 12 months for each study graft (supported and unsupported) is a continuous variable and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed.

10.3.2 TIMI Flow Grade

TIMI flow grade as assessed by angiography at 12 months is measured on a 4-point ordinal scale as described in Section 2.3.2 and will be analyzed using Wilcoxon signed-rank test. Occluded vessels will be assigned a TIMI grade of 0 (no perfusion).

10.3.3 Graft Failure

Graft failure, defined as ≥ 50% stenosis at 12 months, will be analyzed separately for right and left territories depending on where the VEST device was implanted. This endpoint will be analyzed using McNemar's test for binary observations.

10.3.4 Repeat Revascularization

See analysis for 5-year endpoint.

10.3.5 Lumen Diameter Uniformity

Lumen diameter uniformity as expressed by the CV by QCA at 12 months is a continuous variable as described in Section 2.3.5 and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed.

10.3.6 Ratio of Vein Graft Lumen Diameter to Target Artery Lumen Diameter

This endpoint as assessed by QCA at 12 months is a continuous variable and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed.

10.3.7 Additional Lumen Measurements and Flow Parameters

Ectasia (yes/no) will be compared between VEST supported and unsupported vein grafts using McNemar's test. Blood flow and blood velocity are continuous variables and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed.

10.3.8 TTFM results

Correlation analysis for clustered data will be used to summarize relationships between intimal hyperplasia area and TTFM results; Fitzgibbon classification and TTFM results; and graft failure and TTFM results.

10.3.9 Non-study vessels and grafts

The proportion of patent non-study target vessels and grafts (arterial grafts and other SVGs) will be reported.

11. CLINICAL EVENT ANALYSES

11.1 Mortality

The proportion of deaths recorded annually over 5 years will be computed along with 95% confidence interval (CI). Time to death will be described using Kaplan-Meier curves. Patients who withdraw consent will be censored at the date of withdrawal. Patients who are lost to follow-up will be censored at the date of last known proof of life. Patients who are alive at and have not exited the study early for any reason will be censored at the time the study window closes.

11.2 Hospitalization

11.2.1 Index Hospitalization

The median post-operative length of index hospitalization stay will be presented with the interquartile range for US and Canadian sites separately.

11.2.2 Readmissions

The rate of readmissions will be considered for the first 30 days following intervention and annually over 5 years. Readmission rates will be calculated as the ratio of number of readmissions during the specified period of time (e.g., 30 days) over the number of days alive out of hospital. The total number of days alive and out of hospital will be calculated as the total number of days, from the day of randomization to the specified time point (e.g., 30 days), during which the patient is not in the hospital. For patients who die or are lost to follow-up (including withdrawals) before the specified time point, the total number of days alive out of the hospital will be calculated as the total number of days, from the day of randomization to death or study discontinuation during which the patient is not in the hospital. A 95% CI will be constructed around the rate estimates. A robust estimate of the variance will be used in the computation of the confidence intervals.

11.3 Safety

All safety analyses will be based on the safety analysis set. The rate of serious adverse events over 6 weeks and 12-months post-randomization will be presented. Serious adverse events rates will be calculated as the total number of events recorded during the specified time period over the total patient-time. Total patient-time will be calculated by summing the time (e.g., months) that patients were at risk for a specific event from the time they were randomized in the study. For patients who die or are lost to follow-up (including withdrawals), their patient-time will be calculated as the time from randomization to death or study discontinuation. A 95% CI will be constructed around the rate estimates. A robust estimate of the variance will be used in the computation of the confidence intervals.

11.4 MACCE

MACCE consists of all-cause mortality, stroke, MI, and ischemic driven target vessel revascularization of VEST supported vein graft or associated target coronary artery. The rate and 95% CI for MACCE and individual components of MACCE will be calculated similarly as the analysis of SAEs over 6 weeks and 12-months post-randomization and annually up to 60 months. Time to first MACCE will be summarized using Kaplan-Meier analysis.

12. FIVE-YEAR FOLLOW-UP ANALYSES

12.1 Time to Revascularization

The time to first ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 1, 3, and 5 years will be described using Kaplan-Meier curves and analyzed using Cox proportional hazards model with robust standard errors. Additional covariates will be added as needed.

12.2 Revascularization Rate

Differences in the rate of ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be assessed using Poisson regression with robust variance estimation at 1, 3 and 5 years (or McNemar's test if there are no recurrent events).

12.3 Time to MI

Similar to time to revascularization, time to MI in culprit vessels for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 1, 3, and 5 years will be analyzed using Cox proportional hazards model with robust standard errors.

12.4 Rate of MI

Similar to revascularization rate, rate of MI in culprit vessels for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be assessed using Poisson regression with robust variance estimation at 1, 3 and 5 years (or McNemar's test if there are no recurrent events).

13. SUBGROUP AND EXPLORATORY ANALYSES FOR PRIMARY ENDPOINT

13.1 Subgroup Analyses

Subgroup analyses will be considered exploratory and hypothesis-generating only. Specific subgroup analyses will be performed on the primary outcome (intimal hyperplasia area) and secondary confirmatory endpoints (lumen diameter uniformity and graft failure) in the FAS.

Subgroups of interest include:

- Territory of graft (right vs. left)
- TTFM results (including flow velocity (<20 vs. ≥20) and pulsatility index (≤5 vs. >5))

- SVG harvesting technique
- Target location
- Total number of grafts (arterial + venous)
- Diabetes status

Subgroup analyses will be conducted using models for clustered data (e.g., linear mixed model for continuous data, generalized linear mixed model or generalized estimating equation for binary and count data) with an interaction term between presence of VEST and subgroup specification. A test of the interaction term will indicate whether the treatment effect is differential across different subgroups and will be performed at the 5% level of significance. The endpoints will be examined descriptively if the number of vessels within the relevant subgroups is not sufficiently large.

13.2 Exploratory Analysis

A learning curve analysis will be conducted to explore the effect of surgeon experience using the VEST device on degree of intimal hyperplasia area.

14. INTERIM ANALYSIS

There is no planned interim analysis for this study.

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STATISTICAL ANALYSIS PLAN

A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support

Sponsored By Vascular Graft Solutions Inc.

Data Coordinating Center
InCHOIR
Icahn School of Medicine at Mount Sinai
New York

August 13, 2020

CONFIDENTIAL

Version 2.0

Table of Contents

REVISION HISTORY

Revision	Section	Description
1.0	N/A	Not applicable – first version
2.0	6	Added the following Analysis Populations: Completer Analysis Set; All Available Data Analysis Set; Intent-to-Treat Analysis Set
2.0	7	Pre-specified values for the following imputation parameters: δ; γ; and σ_δ^2 for the primary analysis
2.0	10	Included the alternative hypothesis for the primary endpoint and the mathematical formula for both the null and alternative hypotheses
2.0	10	Added analysis section for Completer Analysis Set; Intent-to-Treat Analysis Set; and Poolability Analysis on the primary endpoint. Included a statement on reporting the summary statistic of the treatment effect between the two study arms in terms of averaged within-patient difference of the 12-month intimal hyperplasia area as assessed by IVUS overall and by site.
2.0	10	Clarified the null and alternative hypotheses for Secondary Confirmatory Endpoint I; included details on the proportional and non-proportional odds model; and method for assessing proportional odds assumption. Changed partial proportional odds model to non-proportional odds model. The partial proportional odds model reduces to the non-proportional odds model when there is only 1 covariate (i.e., VEST device) in the model. Clarified the Analysis Population that will be used.
2.0	10	Clarified the null and alternative hypotheses for Secondary Confirmatory Endpoint II and the Analysis Population that will be used
2.0	10	Clarified the Analysis Population for all additional secondary endpoints
2.0	11	Added a sensitivity analysis that excludes MACCE occurring in patients after they contract COVID-19
2.0	12	Clarified the Analysis Population for all 5-year follow-up endpoints

ABBREVIATIONS AND DEFINITIONS

BMI	Body Mass Index
CABG	Coronary artery bypass grafting
CCSC	Canadian Cardiovascular Society Classification
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CV	Coefficient of Variance
EAC	Event Adjudication Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IFU	Instructions For Use
IMA	Internal Mammary Artery
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Coronary Artery
LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MI	Myocardial Infarction
PMA	Premarket Approval Application
NYHA	New York Heart Association
QCA	Quantitative Coronary Angiography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SVG	Saphenous Vein Grafts
TTFM	Transit Time Flow Measurement
VEST	Venous External Support

PURPOSE OF STATISTICAL ANALYSIS PLAN (SAP)

The purpose of this SAP is to outline the planned analyses to be completed for the VEST trial. The planned analyses identified in this SAP will be included in abstracts and manuscripts reporting the results of the trial. Exploratory analyses not necessarily identified in this SAP may also be performed. Any post hoc, or unplanned, analyses not explicitly identified in this SAP will be clearly identified as such in any published papers from this study. This SAP may be modified as result of changes in the protocol or in the adjudication of the events. All revisions will be made prior to the data lock and the primary analysis.

1. STUDY OBJECTIVES AND METHODS

Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease (1). Despite the proposed benefits of multiple arterial grafts (2), autologous saphenous vein grafts (SVGs) are still, numerically, the most frequently used bypass conduits in CABG. However, progressive SVG failure after CABG remains a key limitation to the long-term success of surgery (3,4). As many as 25% of SVGs occlude within 1 year of CABG; an additional 1-2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which are disease free (5). Intimal hyperplasia and subsequent SVG failure have significant effects on clinical outcomes such as onset of angina, need for revascularization intervention (surgical or percutaneous), myocardial infarction (MI), and death. Over the longer term, proliferation of intimal hyperplasia renders the vein graft lumen vulnerable to atherosclerosis leading to SVG stenosis and occlusion (6,7,8,9,10).

The VEST (Venous External Support) manufactured by Vascular Graft Solutions Ltd, is an external mechanical support for autologous saphenous vein grafts that are created during CABG. The VEST is designed to target the underlying factors leading to SVG disease progression and, in particular, proliferation of intimal hyperplasia.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of this study is to demonstrate the safety and effectiveness of the VEST for its intended use: Limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease.

1.1.2 Secondary Objectives

Secondary objectives of this study are to demonstrate the effectiveness of the VEST in achieving lumen diameter uniformity and reducing graft failure rate.

1.2 Study Methods

1.2.1 Study Design

This study is a prospective, multi-center, randomized, within-subject-controlled, trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison between two sets of SVGs: A VEST supported set; and an unsupported set.

1.2.2 Study duration and time points

Primary and secondary endpoints will be ascertained at 12 months to support a Premarket Approval Application (PMA) application. Long term data, up to 5 years follow-up, will be monitored in the post-approval period.

1.2.3 Randomization and masking

For every patient, a pair of grafts will be designated for participation in the trial; one to be supported with the VEST device and the other to serve as a control. Grafts to the LAD do not participate in the randomization.

Patients will be block randomized by territory and/or by SVG length.

If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will assign the treatment and control vessels by their lengths.

Only grafts originating proximally from the aorta will be considered for randomization. Sequential grafts will not be included in the study. Where more than one graft may be performed per territory, the vein grafts will be uniquely distinguished by their pre-measured length as "Longest" and "Shortest". This design will allow for within-subject comparisons, which is expected to increase power relative to a between-subject design.

To prevent any bias as well as exclude any ineligible patients, randomization will be performed only after the procedure has reached the stage where all venous bypass distal anastomoses have been constructed.

The nature of the study precludes masking surgeons from treatment assignment. In order to prevent selection bias, randomization into treatment assignment is performed intraoperatively only after all distal anastomoses have been completed. Investigators will also be blinded to all data from other clinical sites, as well as the primary outcomes data and aggregate data regarding clinical outcome. Serious unexpected AEs will be reported to Institutional Review Board (IRB) as usual. Clinical events including serious and protocol- defined adverse events will be reviewed by an Event Adjudication Committee. All angiograms and intimal hyperplasia scoring will be analyzed, according to predefined analysis protocols, by independent core laboratory personnel who will be blinded to clinical outcomes.

2. EFFICACY ENDPOINTS

2.1 Primary Endpoint

The primary endpoint is defined as intimal hyperplasia (plaque+media) area [mm^2] as assessed by intravascular ultrasound (IVUS) at 12 months. This endpoint is measured for each study graft (VEST supported and unsupported) and is measured as a continuous variable.

2.2 Second Confirmatory Endpoints

Second confirmatory endpoints are measured at 12 months post randomization. The following second confirmatory endpoints will be analyzed.

2.2.1 Lumen Diameter Uniformity (Fitzgibbon)

Lumen diameter uniformity will be assessed by angiography for each study graft separately and expressed by the Fitzgibbon classification (11), on a 3-point ordinal scale:

- I – No intimal irregularity
- II – Irregularity of <50% of estimated intimal surface
- III – Irregularity of >50% of estimated intimal surface

2.2.2 Graft Failure

Graft failure will be assessed by quantitative coronary angiography (QCA) for each study graft and defined as:

- Failure: ≥50% stenosis
- Success: Otherwise

2.3 Additional Secondary Endpoints

Additional secondary endpoints are measured at 12 months post randomization. The following additional secondary endpoints will be analyzed.

2.3.1 Intimal Hyperplasia Thickness

Intimal hyperplasia (plaque + media) thickness [mm] will be assessed by IVUS. This endpoint is measured for each study graft and is measured as a continuous variable.

2.3.2 TIMI Flow Grade

TIMI flow grade will be assessed by angiography on the following 4-point ordinal scale for each study graft:

- Grade 0: No perfusion
- Grade 1: Penetration without perfusion
- Grade 2: Partial perfusion
- Grade 3: Complete perfusion

2.3.3 Graft Failure

Graft failure, as defined above, will be analyzed separately for right and left territories.

2.3.4 Repeat Revascularization

Repeat ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be reported over the 5 years of observation.

2.3.5 Lumen Diameter Uniformity (CV)

Lumen diameter uniformity will be expressed by the coefficient of variation (CV) by QCA, computed for each graft separately, and scored continuously as follows:

$$CV_{Uniformity} = SD_{Diameter} / Mean_{Diameter}$$

2.3.6 Ratio of Vein Graft Lumen Diameter to Target Artery Lumen Diameter

The ratio of each study vein graft mean lumen diameter to its target artery mean lumen diameter will be assessed by QCA.

2.3.7 Additional Lumen Measurements and Flow Parameters

Ectasia, blood flow, and blood velocity for each study vein graft will be measured.

Ectasia will be defined as a segmental dilation more than 50% compared to the normal adjacent segments assessed by QCA.

Blood velocity (cm/s) will be calculated using frame count approach with the following formula: [Velocity=Length/[end frame-start frame]/(frames per second)/10], where start frame is defined as the frame where "dye first fully enters injected artery: dye must extend across nearly entire width of artery or vein (at least 70%) and there must be antegrade motion to dye" and the end frame is the frame where "dye first enters distal landmark branch; complete opacification of the target artery is nor required".

Blood flow (mL/s) is calculated as velocity multiplied by cross sectional area.

3. CLINICAL ENDPOINTS

The following clinical endpoints will be analyzed:

3.1 Mortality

All-cause mortality will be assessed annually over the 5 years of observation.

3.2 Hospitalizations

3.2.1 Length of Index Hospitalization

Overall post-operative length of stay for the index hospitalization will be measured and broken down by days spent in the ICU versus days spent on telemetry and regular floors. Discharge disposition will also be captured. Days in ICU, telemetry, and regular floor will be reported for US and Canadian sites separately. Length of stay will be reported separately for US and Canadian centers.

3.2.2 Readmissions

All inpatient hospitalizations lasting ≥24 hours will be considered. Readmission rates will be calculated for the first 30 days following intervention and annually over the 5 years of follow-up. Hospitalizations will be classified for all causes including for cardiovascular reasons.

3.3 Safety

Serious adverse events (SAEs) occurring post randomization and up to 12 months after the CABG procedure.

3.4 MACCE

Major adverse cardiac and cerebrovascular events (MACCE) occurring within 12 months and annually up to 60 months after the index CABG procedure. MACCE components include:

- All-cause **mortality**

- **Stroke**: Defined as any new, rapidly developing focal neurological deficit, lasting longer than 24 hours, ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests, imaging and neurology consultation note). The Modified Rankin Scale and the NIH Stroke Scale must be administered within 24 hours following the event to document the presence and severity of neurological deficits.
  Each neurological event must be subcategorized as:
  - Hemorrhagic stroke
  - Ischemic stroke
  - Other
- **Myocardial infarction (MI)**: Any one of the following criteria meets the diagnosis of MI
  - Acute MI - Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the Upper Reference Limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumably new significant ST-T changes or new LBBB;
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy
  - CABG related MI - defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either
  - New pathological Q waves or new LBBB, or
  - Angiographic documented new graft or new native coronary artery occlusion, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Prior MI – Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence on non-ischemic cause.
  - Pathological finding of prior MI

- **Ischemic Driven Target Vessel Revascularization**: (CABG or PCI) of **VEST supported** vein graft or associated target coronary artery.
  Revascularization is considered ischemic driven if the subject has clinical or functional ischemia manifesting in any of the following:
  - A history of angina pectoris presumably related to the target vessel
  - Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel

- Abnormal results of any invasive functional diagnostic test [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

The angiography and IVUS procedure performed at 12 months to assess the graft integrity by the study plan will not be counted as MACCE. Clinical evaluation for the 12 months visit will be completed and MACCE will be recorded prior to performance of the planned interventional procedure. If revascularization of the VEST supported graft or associated bypassed coronary artery is performed as a result of the angiography, it will be reported and adjudicated according to the definition given above for ischemic driven target vessel revascularization, for assessment of MACCE at time points >12 months.

All adverse events (including MACCE) and causes of mortality will be adjudicated by an independent event adjudication committee (EAC).

4. FIVE-YEAR FOLLOW-UP ENDPOINTS

Patients participating in the trial will be followed for an additional 4 years after completing the 12-month pivotal trial to assess the endpoints below. Diagnosis of COVID-19 will also be recorded.

4.1 Time to Revascularization

Time to ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

4.2 Revascularization Rate

Ischemic driven target vessel revascularization rate for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

4.3 Time to MI

Time to MI in culprit vessels (when available) for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

4.4 Rate of MI

Rate of MI in culprit vessels (when available) for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be calculated at 1, 3, and 5 years.

5. SAMPLE SIZE ESTIMATION

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing CABG. The primary endpoint of the study will be the intimal hyperplasia (plaque + media) area [mm^2] as assessed by IVUS at 12 months post randomization. Sample size is based on the assumption that IH will be normally distributed with standard deviation of 1.7 mm^2 in both the VEST supported and the unsupported vessels. We also assume that the mean IH in the unsupported vessel is 5.1 mm^2 and that the correlation between IH measured on grafts within the same patient is equal to 0.5. In addition, we anticipate

that approximately 13% of patients will have the supported and/or unsupported grafts occluded or severely stenosed and so unable to have IH measured through IVUS; in approximately 50% of these patients IH will not be obtained in either graft while in the rest, the occlusion will only affect one of the two graft, in 25% the VEST graft will be occluded and in 25% the control graft will be occluded. Although it is unclear to what extent occlusion is related to IH one year post CABG, we will treat missing values of IH resulting from occluded vessels as non-ignorable missing using an imputation model that will penalize these vessels and reduce the effect size. Therefore, we assume a conservative effect size of 0.4 mm^2, or a reduction of IH in the VEST vessels compared to the control vessel of about 8%. Under these assumptions, fixing the power at 90% we need to enroll 190 patients, before adjustment for loss to follow-up.

5.1 Lost to follow-up considerations

Lost to follow-up and refusals: The term "lost to follow-up" is used to describe an individual who has withdrawn consent to be in the study or who can no longer be located or assessed. Such individuals represent those for whom primary outcome assessment is no longer possible. We anticipate that the loss to follow-up rate or refusal to perform an IVUS in this study will be around 15%. To account for this loss to follow-up or refusal rate, a total of 224 eligible participants will be enrolled in the study.

6. ANALYSIS POPULATIONS

6.1 Full Analysis Set

The full analysis set (FAS) will, consistent with ICH Guideline E9 (12), include all randomized vessels for which the study procedure was initiated in either arm according to the intention-to-treat (ITT) principle. If the Month 12 angiogram was not done, a vessel can still be included in the FAS if information is available on randomized vessels from angiograms prior to the Month 12 visit. Vessels of patients who do not undergo angiography at Month 12 due to contraindications will be included as well. All other vessels of patients without the Month 12 visit will be excluded.

6.2 Completer Analysis Set

The Completer Analysis Set will consist of randomized vessels of patients for which imaging outcomes can be ascertained in both the VEST and control grafts at Month 12. The imaging outcome may be angiography- or IVUS-related, depending on the endpoint of interest.

6.3 All Available Data Analysis Set

The All Available Data Analysis Set will consist of randomized vessels for which imaging outcomes can be ascertained in either the VEST and/or control grafts at Month 12. A patient can contribute 0, 1, or 2 vessels for analysis. The imaging outcome may be angiography- or IVUS-related, depending on the endpoint of interest.

6.4 Intent-to-Treat Analysis Set

The Intent-to-Treat Analysis Set will consist of all randomized vessels and includes the FAS and vessels of patients excluded from the FAS.

6.5 Per Protocol Analysis Set

The per protocol analysis set will consist of all patients in the FAS who do not have deviations on VEST implantation and any protocol violation/deviation likely to affect the primary endpoint.

6.6 Safety Analysis Set

The safety analysis set will consist of all patients who are considered enrolled in the study, once they are randomized and an identification code is generated.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Principles

Variables will be presented using descriptive statistical methods. Depending on the purpose of the analysis, the presentation can be for all randomized patients or stratified by randomization group (VEST supported vs. control vein graft).

Continuous and ordinal variables will be summarized using number of non-missing values, means, standard deviations, medians, interquartile range, maximum, and minimum.

Categorical variables will be summarized using number of non-missing values, counts and percentages.

Count variables will be summarized using rates. Rates of events will be calculated as the ratio of the total number of events recorded over a period of time over the total patient-time.

Time-to-event variables will be presented with Kaplan-Meier estimates or cumulative incidences in the presence of competing risks.

Numerical results from statistical models will be presented with confidence intervals.

Should any of the statistical methods proposed prove unsuitable during data analysis, more appropriate methods will be used. These include data transformation (e.g., logarithmic scale) or a different choice of model for the same type of outcomes (e.g., Poisson to negative binomial; proportional odds model to non-proportional odds model) to better satisfy model assumptions and obtain a better model fit.

Statistical analysis will be performed using SAS V9.4 or higher and R V3.6.1 or higher.

7.2 Handling of Missing Data

7.2.1 Missing baseline data

Missing baseline values that are needed to compute absolute, relative, or percent change from baseline will be imputed using mean imputation (13). The missing values of a variable will be replaced with the observed sample mean of that variable. Mean imputation is appropriate because baseline variables are independent of randomization assignment.

7.2.2 Missing primary outcome data due to vessel occlusion

It is anticipated that roughly 13% of vessels will be obstructed and unsuitable for IVUS, and thus intimal hyperplasia will be measured only on non-obstructed vessels. Although the degree of intimal hyperplasia may be independent of the mechanism of obstruction, we will consider an obstructed vessel as a failed vessel in the analysis. Specifically, we will assume a non-ignorable mechanism (not missing at random or NMAR) for the data missing due to obstructed vessels.

The problem of missing IVUS data due to occluded vessels at 12 months will be addressed by multiple imputation — i.e., creating several potential imputed observations for each missing data using a predictive modeling (14). The underlying model will use the pattern-mixture approach, which posits a separate distribution of the true IVUS measurement for missing and non-missing observations. The model will include but not limited to the following subject specific covariates: hypertension, diabetes, hyperlipidemia, and smoking status; and the following vessel specific covariates: treatment assignment, coronary territory, vein graft length, vein harvest, preservation techniques, Transit Time Flow Measurement (TTFM) values, and target vessel baseline stenosis.

Let *Y* represent the continuous outcome variable (i.e. intimal hyperplasia) and let *R* be an indicator variable that assumes different values according to whether *Y* is observed or missing. Under a pattern-mixture model, the joint distribution of the outcome *Y* and the missing indicator variable *R, f(Y,R),* is factorized into the density of the outcome, conditional on the pattern of missingness of *Y, f(Y|R),* and the marginal distribution of the missing indicator variable, *P(R).*

$f(Y,R)=f(Y|R)P(R)$

In longitudinal studies, the probability distribution *P(R)* refers to the probabilities of the different possible patterns of missingness. In this situation we distinguish only two patterns of missing data: we define a case to be complete *(R=1)* if a vessel is able to be evaluated at follow-up, and to be incomplete *(R=0)* if the follow-up measurement is missing due to occlusion.

Under the NMAR framework, the density *f (Y|R)* is specified differently depending on whether *R=0* (*Y* is missing) or *R=1* (*Y* is observed), reflecting the fact that the missing values may come from a different distribution than the observed ones. In this study, we will assume that the distribution function of intimal hyperplasia is normal, with $f(Y|R=1)\sim N(\mu,\sigma^2)$ for the observed data and $f(Y|R=0)\sim N(\mu+\delta,\gamma\sigma^2)$ for the missing data. The parameters δ and γ are sensitivity parameters. In order to "penalize" the obstructed vessels we will assume that δ is positive to reflect, on average, larger values of intimal hyperplasia. For the primary analysis, we will assume that the standard deviations of intimal hyperplasia for observed and missing data are the same (γ=1). In addition, we will assume that the non-observed values come from a normal distribution with mean $(\mu+\delta)$ equal to the 90th percentile of the distribution of intimal hyperplasia.

The parameter δ will be specified using data from the VEST I and the VEST III studies and determined as follows:

- In the VEST I trial the 90th percentile of the distribution of IH was 6.84 mm^2 and the aggregate mean was 4.77 mm^2, resulting in δ = 2.07 (6.84 - 4.77; n=43).

- In the VEST III trial the 90th percentile for the IH distribution was 4.99 mm^2 and the aggregate mean was 3.48 mm^2, resulting in δ = 1.51 (4.99 - 3.48; n=93).

The parameter δ is determined as the weighted average (based on number of vessels) of the δ from the two VEST studies, which is 1.70 mm^2. A simple simulation of 100000 random draws from a normal distribution with mean=1.70 and standard deviation=0.25 showed a minimum value of 0.60 and maximum value of 2.69. These values provide a reasonable range for which intimal hyperplasia can be shifted to higher values for missing data due to occlusion.

The procedure will be implemented in two stages: First a set of imputations for intimal hyperplasia will be created for each vessel with missing data. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. Characteristics of the vessels, like laterality, length, vein harvest, preservation techniques, TTFM values, and baseline stenosis, as well as patients' characteristics will be used to inform the predictive models. This corresponds to the usual imputation under a missing at random (MAR) mechanism. In the second stage, values will be generated from a prior distribution $N(\delta, \sigma_\delta^2)$, where δ = 1.70 mm^2 and $\sigma_\delta^2 = 0.25^2$ and added to the imputed response from the first stage for the occluded vessels.

The imputation process will be repeated 30 times to achieve maximal stability of the procedure.

7.2.3 Missing primary outcome data due to reasons other than vessel occlusion

Missing values on the primary outcome may be due to reasons other than occluded vessels. They are listed in Table 1 and the rules for handling the missing data are provided.

Table 1: Rules for handling missing IVUS other than vessel occlusion

Situation	Solution
Patient is lost to follow-up or refused to undergo IVUS at 12 months and do not have a previous angiogram	They will be excluded from the FAS.
Death prior to the 12-month visit and do not have a previous angiogram or an autopsy that determines the culprit vessel	They will be excluded from the FAS.
Study grafts that are patent, are not completely occluded, but have some degree of stenosis in which cannulation for IVUS is unsafe and therefore, patient cannot undergo IVUS imaging	They will be treated like occluded vessels and considered NMAR.

Missing intimal hyperplasia because of: Poor image quality//technical difficulties with imaging//missing or unreadable images due to deviations from acquisition protocol// missing or incomplete images due to contraindications//other reasons unrelated to stenosis or occlusion	They will be considered MAR and imputed values from the first stage of the multiple imputation procedure will be used as described in Section 7.2.2.
Patient had an angiogram prior to the 12- month visit and does not return for the study angiogram and IVUS at 1 year	Several scenarios to consider: o If the previous angiogram(s) indicated vessel stenosis of ≥ 50% on the VEST supported and/or unsupported vein grafts, they will be considered NMAR at 12 months. o If the previous angiogram(s) indicated vessel stenosis of < 50% on the VEST supported and/or unsupported vein grafts, they will be considered MAR at 12 months. Note: If the previous angiogram(s) indicated some degree of stenosis on one study vein graft and did not provide information on the other randomized vein graft, the latter will be considered MAR at 12 months. o If the previous angiogram(s) did not provide any information on any of the study vein grafts, the vessels of patient will be excluded from the FAS.

7.2.4 Missing secondary outcomes data

Table 2 presents the rule for handling missing data on the secondary confirmatory endpoint of graft failure and any secondary endpoints related to graft failure.

Table 2: Rules for handling missing graft patency measurement at 12 months

Situation	Solution
Patient had an angiogram prior to the 12- month visit and does not have a study angiogram at 1 year	Apply worst observation carried forward method. That is, use the most severe % stenosis based on previous angiograms, if available. If the previous angiogram showed some degree of stenosis or total occlusion in only one of the study grafts and no information is available for the other study graft, the latter will be

	considered a non-graft failure at 12 months.
Graft patency cannot be determined at 12 months	Use information from previous angiograms, if available. Apply worst observation carried forward method as described above

Only observed values will be used to analyze safety data; i.e. missing safety data will not be imputed.

7.3 Handling of Crossovers

Vessels randomized to VEST but not supported will be considered crossovers. Similarly, vessels randomized as control but VEST supported will be considered crossovers. We anticipate very few crossovers in this trial. As the primary analysis is by intention-to-treat with respect to randomization assignment, crossovers will be analyzed as belonging to the group to which they were randomized. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect on trial outcomes.

7.4 Multiple Testing

Hypothesis testing will be conducted at a two-sided significance level of 0.05 for the primary endpoint and the two secondary confirmatory endpoints using a hierarchical testing procedure (see Section 10). Hypothesis testing for other secondary endpoints and long term outcomes will be carried out at the 0.05 significance level as well. However, there will be no formal correction of the type I error rate for multiple testing of statistical hypotheses related to these endpoints.

7.5 Data Rules

Some differences may occur between the vessels in the randomization electronic case report form (eCRF) and those recorded on the index surgical procedure eCRF. In some cases, the SVG would be placed into the closest distal target that is bypassable and not placed in the same vessel as the qualifying lesion. In a few instances, the vessels in the randomization eCRF were the arteries with the qualifying lesion and do not reflect the target coronary artery. The names of the randomized vessels should be the target coronary arteries that bypass the qualifying lesions. The vessels that undergo IVUS imaging are those identified in the index surgical procedure form as the target arteries. All analyses will be based on the vessel information collected on the index surgical procedure form which notes the target vessels.

7.6 Data Lock

The dataset for the primary outcome analysis will be locked when all data through the last one year follow-up have been entered and all queries have been resolved and data management processes have been completed. The entire database will be locked when all data for the 5-year observation period have been entered and all queries have been addressed.

7.7 Blinded Review

Angiograms and revascularizations prior to the 12-month assessment may be informative for missing primary and secondary endpoints at 1 year. While several rules have been developed for handling missing outcome data in Sections 7.2.3 and 7.2.4, the list is not exhaustive. A blinded review of data entered in the EDC for event-driven angiograms and revascularizations may be conducted prior to data set lock to ensure that all scenarios have been accounted for and designation of NMAR/MAR (for primary endpoint) and graft failure (yes/no) is correct. This is important for patients who do not return for their 12-month visit but underwent prior revascularization which may contribute information to the primary and secondary endpoints.

8. STUDY SUBJECTS

8.1 Subject Disposition

Subject disposition will summarize patients' status at different stages of the study. This includes:

- The number (%) of patients assessed for eligibility
- The number (%) of patients eligible and ineligible for the study and reasons for non-eligibility
- The number (%) of patients who signed informed consent
- The number (%) of patients randomized
- The number (%) of patients for whom the VEST was deployed
- The number (%) of patients who completed each annual follow up visit
- The number (%) of patients lost to follow-up (including withdrawals) by 12 months and annually thereafter and reasons for study dropout
- The number (%) of patients who died by 12 months and annually thereafter.
- The number (%) of patients who underwent coronary angiography at 12 months
    - The number (%) of patients who did not undergo coronary angiography and reasons for procedure not completed
    - The number (%) of patients for whom QCA is available
- The number (%) of patients who underwent IVUS at 12 months
    - The number (%) of patients who did not undergo IVUS and reasons for procedure not completed
- The number (%) of patients in the Full Analysis Set and reasons for exclusions
- The number (%) of patients in the Per Protocol Analysis Set and reasons for exclusions
- The number (%) of patients in the Safety Analysis Set

8.2 Protocol Violations

The number (%) of each type of protocol violations and deviations will be tabulated.

9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

9.1 Subject Demographics and Baseline Factors

The following patient baseline data will be summarized:

- Age (years)
- Gender (female/male)

- Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other; More than One Race; Unknown or Not Reported)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Unknown or Not Reported)
- Body Mass Index (BMI) (kg/cm^2)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Smoking status (current, former, never)
- Pack Year History where applicable
- Dialysis (yes/no) and dialysis type if yes (hemodialysis; peritoneal dialysis; CVVH; CVVHD)
- Diabetes (No history; Type 1; Type 2; Other) and whether treated
- Hypertension (yes/no)
- Hyperlipidemia (yes/no)
- Prior stroke in the past year (yes/no)
- Prior MI (yes/no)
- Atrial Fibrillation (yes/no)
- Peripheral Arterial Disease (yes/no) and treatment status if yes
- Carotid Artery Disease (yes/no) and treatment status if yes
- Prior PCI (yes/no)
- Prior cardiac surgery (yes/no)
- Chronic Pulmonary Disease (yes/no)
- New York Heart Association class (NYHA) (No heart failure, Class I; Class II; Class III; Class IV)
- Canadian Cardiovascular Society Classification (CCSC) (No angina; Grade I; Grade II; Grade III; Grade IV)
- Pre-operative Logistical EuroScore
- Left ventricular ejection fraction (LVEF) (%)
- Creatinine (mg/dL)
- SYNTAX score at baseline

9.2 Characteristics of Saphenous Vein Grafts

Baseline characteristics of SVGS SVGs will be presented by randomization assignment (VEST supported vs. unsupported) and will include the following variables:

- Native coronary artery stenosis (%)
- Target coronary artery diameter (mm)
- Graft length (cm)
- Systolic pressure at TTFM flow (ml/min)
- Final TTFM flow (ml/min)
- Final TTFM pulsatility index
- The number (%) of Right Short, Right Long, Right single, Left Short, Left Long, Left single vein grafts
- Distribution of vein graft randomized to VEST and Control

10. EFFICACY ANALYSES

10.1 Analysis of Primary Endpoint

10.1.1 Analysis of Primary Endpoint

The primary outcome is the degree of intimal hyperplasia (plaque+media) area [mm^2] at 12 months post-surgical intervention, assessed by IVUS. The null hypothesis is that there is no difference in the distribution of the 12-month intimal hyperplasia area between vessels randomized to the VEST compared to control vessels. The alternative hypothesis is that there is a difference in the distribution of the 12-month intimal hyperplasia area between vessels randomized to the VEST compared to the control. That is,

H_0: $FVEST = FCONTROL$

H_1: $FVEST \neq FCONTROL$

where *FVEST* and *FCONTROL* represent the distribution of the 12-month intimal hyperplasia area for the VEST and control group, respectively.

The primary null hypothesis will be tested in the full analysis set with vessels analyzed according to their randomization group using a two-tailed 0.05 alpha level. The analysis will be conducted using a Wilcoxon signed-rank test.

We will account for the occluded vessels in the computation of the Wilcoxon signed-rank test as follows. If two vessels in the same individual are both occluded, we will assign an absolute value of zero for the difference between the two scores irrespective of the imputed values. Pairs with a value of zero will be excluded from the computation of the test statistic as usual for the Wilcoxon signed-rank test. If only one of the two vessels is occluded in the same individual, then we will assign an absolute value equal to the difference between the observed and the imputed score. The sign associated with the rank for this difference, however, will be in favor of the non-occluded vessel. If both vessels are not occluded they will be treated as usual in the computation of the Wilcoxon signed-rank test.

A multiple imputation approach will be used to impute the intimal hyperplasia values of the occluded vessels as outlined in Section 7.2.2. The imputation process will be repeated 30 times to achieve maximal stability of the procedure. A separate analysis will be conducted for each completed-and-imputed dataset. Rubin's rule (14) will be used to combine the 30 analyses and test the difference between intimal hyperplasia area of the treated and control vessels.

10.1.2 Sensitivity Analysis for Primary Endpoint

We will conduct a series of sensitivity analyses to determine the stability of the estimate of the treatment effect obtained with the multiple imputation pattern-mixture approach outlined in Section 7.2.2. Specifically, we will work with different values of the sensitivity parameters δ and γ to determine how our assumptions about the distribution of the missing data influence the results. For example, assuming $\delta = 0$ corresponds to a missing-at-random (MAR) assumption, which posits that there is no information in the fact that a vessel is occluded and therefore cannot be measured. These analyses will

allow us to determine how large δ has to be to change the outcome of the final analysis with respect to statistical significance of the treatment effect.

10.1.3 Completer Analysis of Primary Endpoint

A complete case analysis will be performed on the primary endpoint and will include all vessels of patients with non-missing 12-month intimal hyperplasia area for both the VEST and control grafts.

10.1.4 Intent-to-Treat Analysis of Primary Endpoint

An intent-to-treat analysis will be performed on the primary endpoint and will include all randomized vessels. Missing values of vessels for patients who refused the 12-month visit or who are lost to follow-up (including withdrawals) prior to the 12-month assessment and without previous informative angiograms will be considered MAR. Missing values of vessels for patients who died prior to the 12-month assessment without previous informative angiograms will be considered as equivalent for the VEST and control vessel and receive a 0 in the computation of the test statistic for the Wilcoxon signed-rank test.

10.1.5 Per Protocol Analysis of Primary Endpoint

A per protocol analysis will be performed on the primary endpoint and will include patients with no deviations on VEST implantation and no protocol violations/deviations that could affect the primary outcome.

10.1.6 Poolability Analysis of Primary Endpoint

The primary analysis will not be stratified by clinical center although the randomization will stratify by clinical center. This should result in only a small loss of efficiency. This is a multicenter trial with the clinical protocol and IVUS acquisition protocol rigorously standardized across all sites and thus, a large cluster effect is not expected. As a sensitivity analysis, the clustered Wilcoxon signed-rank test (15) will be performed on the primary endpoint to account for the effect of site. In addition, treatment effect between the VEST and control arms will be summarized in terms of averaged within-patient differences of the 12-month intimal hyperplasia area overall and by site.

10.2 Analysis of Secondary Confirmatory Endpoints

Following are the study's two secondary confirmatory hypotheses that will be tested in the order presented using a sequential strategy:

10.2.1 Secondary Confirmatory I

H_0: $OR(\text{Fitzgibbon classification})_{\text{VEST vs. Control}} = 1$
H_1: $OR(\text{Fitzgibbon classification})_{\text{VEST vs. Control}} \neq 1$

where lumen diameter uniformity is measured using Fitzgibbon classification (scale of 1 to 3) . The proportional odds model for clustered data will be used to test the null hypothesis that the odds ratio (OR; VEST vs. control) for getting lower Fitzgibbon classification (i.e., more favorable response) is equal to 1 at a two-sided alpha = 0.05. The null hypothesis will be tested in the All Available Data Analysis Set since the Fitzgibbon classification measures lumen diameter uniformity in non-occluded vessels only.

The proportional odds model will be fitted using generalized estimating equations with an exchangeable correlation structure and is expressed as follow:

$\text{logit}[\Pr(Y \leq j)] = \alpha_j + \beta * x$, for j=1,2

The Fitzgibbon classification (Y) consists of j=3 ordered categories. The set of models consists of 2 intercepts and 1 common parameter β that describes the effect of the VEST device (x) on the log odds of response in category j or below. The model assumes that the effect of the VEST device is the same for all cumulative logits. This assumption, known as the proportional odds assumption, will be assessed by the Rotnitzky and Jewell Generalized Score test provided in the SAS macro *GEEORD* (16). If the p-value is not statistically significant ($p > 0.05$), we will not reject the null hypothesis of proportionality and will proceed with the proportional odds model for analysis. However, if the proportional odds assumption is not satisfied, a non-proportional odds model will be used. Relaxing the proportionality assumption will allow for different β coefficients between cumulative logit models. We will declare success on this endpoint if we will have succeeded on the primary efficacy endpoint and rejected the null hypothesis in this section.

10.2.2 Secondary Confirmatory II

H_0: $P(\text{Graft Failure})_{VEST} = P(\text{Graft Failure})_{CONTROL}$
H_1: $P(\text{Graft Failure})_{VEST} \neq P(\text{Graft Failure})_{CONTROL}$

where $P(\text{Graft Failure})_{VEST}$ and $P(\text{Graft Failure})_{CONTROL}$ represent the proportion of graft failure (defined as ≥ 50% stenosis) in the VEST and control arms, respectively. The null hypothesis will be tested in the Completer Analysis Set (including patients without the 12-month visit but with a previous angiogram informative of study vessels, Table 2) using McNemar's test for paired binary observations with two-sided alpha = 0.05. We will declare success on this endpoint if we will have succeeded on both confirmatory endpoints.

10.2.2.1 Sensitivity Analysis for Secondary Confirmatory II

Different sensitivity analyses can be conducted to evaluate the robustness of using information from previous angiograms for missing graft patency measurements at Month 12. For instance, assumptions that the graft patency is the same, better, and worse for the missing VEST supported graft compared to the control can be performed.

10.3 Analysis of Additional Secondary Endpoints

The following additional secondary endpoints will be analyzed:

10.3.1 Intimal Hyperplasia (plaque + media) thickness [mm]

Intimal hyperplasia thickness as assessed by IVUS at 12 months for each study graft (supported and unsupported) is a continuous variable and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed. The All Available Data Analysis Set will be used for this analysis.

10.3.2 TIMI Flow Grade

TIMI flow grade as assessed by angiography at 12 months is measured on a 4-point ordinal scale as described in Section 2.3.2 and will be analyzed using Wilcoxon signed-rank test. Occluded vessels will be assigned a TIMI grade of 0 (no perfusion). The Completer Analysis Set will be used for this analysis.

10.3.3 Graft Failure

Graft failure, defined as ≥ 50% stenosis at 12 months, will be analyzed separately for right and left territories depending on where the VEST device was implanted. This endpoint will be analyzed using McNemar's test for binary observations. The Completer Analysis Set will be used for this analysis.

10.3.4 Repeat Revascularization

See analysis for 5-year endpoint.

10.3.5 Lumen Diameter Uniformity

Lumen diameter uniformity as expressed by the CV by QCA at 12 months is a continuous variable as described in Section 2.3.5 and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed. The All Available Data Analysis Set will be used for this analysis.

10.3.6 Ratio of Vein Graft Lumen Diameter to Target Artery Lumen Diameter

This endpoint as assessed by QCA at 12 months is a continuous variable and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed. The All Available Data Analysis Set will be used for this analysis.

10.3.7 Additional Lumen Measurements and Flow Parameters

Ectasia (yes/no) will be compared between VEST supported and unsupported vein grafts using McNemar's test. Blood flow and blood velocity are continuous variables and will be analyzed using linear mixed effects model with a random subject effect and presence of VEST as a fixed effect. Additional covariates will be added as needed. The All Available Data Analysis Set will be used for this analysis.

10.3.8 TTFM results

Correlation analysis for clustered data will be used to summarize relationships between intimal hyperplasia area and TTFM results; Fitzgibbon classification and TTFM results; and graft failure and TTFM results.

10.3.9 Non-study vessels and grafts

The proportion of patent non-study target vessels and grafts (arterial grafts and other SVGs) will be reported.

11. CLINICAL EVENT ANALYSES

11.1 Mortality

The proportion of deaths recorded annually over 5 years will be computed along with 95% confidence interval (CI). Time to death will be described using Kaplan-Meier curves. Patients who withdraw consent will be censored at the date of withdrawal. Patients who are lost to follow-up will be censored at the date of last known proof of life. Patients who are alive at and have not exited the study early for any reason will be censored at the time the study window closes.

11.2 Hospitalization

11.2.1 Index Hospitalization

The median post-operative length of index hospitalization stay will be presented with the interquartile range for US and Canadian sites separately.

11.2.2 Readmissions

The rate of readmissions will be considered for the first 30 days following intervention and annually over 5 years. Readmission rates will be calculated as the ratio of number of readmissions during the specified period of time (e.g., 30 days) over the number of days alive out of hospital. The total number of days alive and out of hospital will be calculated as the total number of days, from the day of randomization to the specified time point (e.g., 30 days), during which the patient is not in the hospital. For patients who die or are lost to follow-up (including withdrawals) before the specified time point, the total number of days alive out of the hospital will be calculated as the total number of days, from the day of randomization to death or study discontinuation during which the patient is not in the hospital. A 95% CI will be constructed around the rate estimates. A robust estimate of the variance will be used in the computation of the confidence intervals.

11.3 Safety

All safety analyses will be based on the safety analysis set. The rate of serious adverse events over 6 weeks and 12-months post-randomization will be presented. Serious adverse events rates will be calculated as the total number of events recorded during the specified time period over the total patient-time. Total patient-time will be calculated by summing the time (e.g., months) that patients were at risk for a specific event from the time they were randomized in the study. For patients who die or are lost to follow-up (including withdrawals), their patient-time will be calculated as the time from randomization to death or study discontinuation. A 95% CI will be constructed around the rate estimates. A robust estimate of the variance will be used in the computation of the confidence intervals.

11.4 MACCE

MACCE consists of all-cause mortality, stroke, MI, and ischemic driven target vessel revascularization of VEST supported vein graft or associated target coronary artery. The rate and 95% CI for MACCE and individual components of MACCE will be calculated similarly as the analysis of SAEs over 6 weeks and 12-months post-randomization and annually up to 60 months. Time to first MACCE will be summarized using Kaplan-Meier analysis.

The impact of the COVID-19 pandemic on MACCE rates is unknown. Therefore, a sensitivity analysis that excludes MACCE occurring in patients after they contract COVID-19 will be performed.

12. FIVE-YEAR FOLLOW-UP ANALYSES

12.1 Time to Revascularization

The time to first ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 1, 3, and 5 years will be described using Kaplan-Meier curves and analyzed using Cox proportional hazards model with robust standard errors. Additional covariates will be added as needed. The Intent-to-Treat Analysis Set will be used for this analysis.

12.2 Revascularization Rate

Differences in the rate of ischemic driven target vessel revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be assessed using Poisson regression with robust variance estimation at 1, 3 and 5 years (or McNemar's test if there are no recurrent events). The Intent-to-Treat Analysis Set will be used for this analysis.

12.3 Time to MI

Similar to time to revascularization, time to MI in culprit vessels for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 1, 3, and 5 years will be analyzed using Cox proportional hazards model with robust standard errors. The Intent-to-Treat Analysis Set will be used for this analysis.

12.4 Rate of MI

Similar to revascularization rate, rate of MI in culprit vessels for supported and unsupported vein grafts (or respective bypassed target coronary artery) will be assessed using Poisson regression with robust variance estimation at 1, 3 and 5 years (or McNemar's test if there are no recurrent events). The Intent-to-Treat Analysis Set will be used for this analysis.

13. SUBGROUP AND EXPLORATORY ANALYSES FOR PRIMARY ENDPOINT

13.1 Subgroup Analyses

Subgroup analyses will be considered exploratory and hypothesis-generating only. Specific subgroup analyses will be performed on the primary outcome (intimal hyperplasia area) and secondary confirmatory endpoints (lumen diameter uniformity and graft failure) in the FAS.

Subgroups of interest include:

- Territory of graft (right vs. left)
- TTFM results (including flow velocity (<20 vs. ≥20) and pulsatility index (≤5 vs. >5))
- SVG harvesting technique
- Target location
- Total number of grafts (arterial + venous)

- Diabetes status

Subgroup analyses will be conducted using models for clustered data (e.g., linear mixed model for continuous data, generalized linear mixed model or generalized estimating equation for binary and count data) with an interaction term between presence of VEST and subgroup specification. A test of the interaction term will indicate whether the treatment effect is differential across different subgroups and will be performed at the 5% level of significance. The endpoints will be examined descriptively if the number of vessels within the relevant subgroups is not sufficiently large.

13.2 Exploratory Analysis

A learning curve analysis will be conducted to explore the effect of surgeon experience using the VEST device on degree of intimal hyperplasia area.

14. INTERIM ANALYSIS

There is no planned interim analysis for this study.

15. REFERENCES

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