Statistical Analysis Plan

Varithena versus Endothermal Ablation of the Great Saphenous Vein
VERITAS

S2473

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AT	As Treated
CRO	contract research organization
DVT	Deep Venous Thrombosis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETA	Endothermal Ablation
EVLA	Endovenous Laser Ablation
GSV	Great Saphenous Vein
I/E	Inclusion/Exclusion criteria
IQRMP	Integrated Quality Risk Management Plan
KRI	Key Risk Indicators
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
PT	Preferred Term
RFA	Radiofrequency ablation
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TLF	Tables, Listings and Figures
USPI	United States Prescribing Information

1 INTRODUCTION

The SAP is based on protocol version 1.2 dated 17Aug2023 and the electronic case report form (eCRF) version 4.0 dated 13Jul2023. On April 1st, 2024, Boston Scientific made the decision to terminate enrollment and follow-up in this study. The termination was not related to adverse event signals. Due to early termination the primary and secondary endpoints per protocol will not be performed. However, some observational tables and listings will be created for reporting requirement purposes only. This plan will therefore only include analysis to be performed for the abbreviated Clinical Study Report (CSR) and ClinicalTrials.gov.

2 PROTOCOL SUMMARY

This study was a multicenter, randomized, controlled, open-label, parallel group study.

Approximately 100 patients were planned to be randomized and treated in a 1:1 ratio between treatment groups. A total of 43 patients were randomized and 40 patients treated at the time of enrollment and study termination. At the time of study termination 21 of the 40 patients treated received Varithena treatment.

This study was performed by qualified and licensed Investigators at 9 sites located in the United States.

This study collected evidence on patient reported outcomes of Varithena compared to Endothermal Ablation (ETA) when used to treat the incompetent Great Saphenous Vein (GSV). ETA will include either Radiofrequency ablation (RFA) or Endovenous laser ablation (EVLA) according to the site's standard practice. This study planned to provide long term (1-year, 2-year, and 3-year) outcomes.

2.1 Study treatment

After consenting and meeting all inclusion criteria and none of the exclusion criteria (I/E), patients were randomized to either Varithena (test) or ETA (control). The Electronic Data Capture (EDC) system was used to assign subjects to the test or control treatment group. Commercially distributed Varithena (polidocanol injectable foam) 1% (Approved 25 Nov 2013 NDA 205098) was administered by intravenous injection using ultrasound guidance, administered via a single cannula into the lumen of the target incompetent trunk veins or by direct injection into varicosities as described in the United States Prescribing Information (USPI).

2.2 Study Population

This study was designed to collect comparative evidence on patient reported outcomes of Varithena compared to ETA when used to treat patients experiencing symptoms of superficial venous incompetence of the GSV, defined as reflux > 0.5 seconds on duplex ultrasound in a single limb. Data was collected on 43 randomized and 40 treated patients at 9 investigational sites in the United States.

2.3 Data collection schedule and assessments

SCHEDULE OF VISITS

Procedure/Assessment	Screening/ enrollment	Index procedure (Treatment)	Follow-up Visits					
			7 days post procedure (± 3 days) office visit	3 months post procedure (± 14 days) office visit	6 months post procedure (± 14 days) office visit or telephone	12 months post procedure (± 30 days) office visit	24 months post procedure (± 30 days) office visit	36 months post procedure (± 30 days) office visit
Informed consent process	X							
Demographics	X							
Medical history	X							
Physical examination	X							
Duplex ultrasound	X		X	X		X	X	X
Mapping of superficial and deep veins	X							
Randomization	X							
Varithena or ETA procedure		X						
VVSymQ	X		X	X	X	X	X	X
VEINES-QOL/sym	X		X	X	X	X	X	X
rVCSS	X		X	X	X	X	X	X
EQ-5D	X		X	X	X	X	X	X
CEAP Clinical Classification	X		X	X	X[1]	X	X	X
Adverse event assessment		X	X	X	X	X	X	X

[1]Performed only if patient returns for office visit

3 ENDPOINT ANALYSIS

Hypotheses

There was no pre-specified formal hypothesis relating to the comparison between treatment groups.

Sample Size

Approximately 100 patients were planned to be randomized and treated in a 1:1 ratio between treatment groups to allow for a minimally detectable absolute difference of 2.0 points, assuming a standard deviation of 5.0 points in both arms.

The assumption for the standard deviation was based on baseline standard deviation values observed in the Vanish 1 and Vanish 2 studies (4.96 and 4.55, respectively).

Statistical Methods

3.1 Safety Analyses

Adverse Events

Adverse Drug Reaction (ADR) / Serious Adverse Drug Reaction (SADR) related to Varithena were documented from the start of the index procedure through the latest completed visit prior to study termination, the latest subject visit being the 12-month visit at the time of termination. In addition, only SAE related to ETA or to the procedure were to be documented from the start of index procedure through the original planned 36-month follow up timeframe.

Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) the current version and will be reported by system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting the study will be the version used for coding the trial and will be specified in the clinical study report and as a footnote in the related outputs.

The Investigator or physician sub-Investigator determined the seriousness of each AE and whether it is Varithena, ETA, or procedure related.

The following summaries will be provided by treatment and total:

- Overall summary of AEs
- All AEs by primary SOC and PT
- AEs suspected to be related to procedure and/or device by primary SOC and PT
- AEs by primary SOC, PT and worst severity
- AEs leading to study discontinuation
- Most frequent AEs (≥5%) by primary SOC and PT

AEs will be summarized by presenting the number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT. A patient with multiple occurrences of an AE will be counted only once in the category.

There were no SAEs reported at the time of study termination.

Partial dates will be imputed using the rules defined in Appendix 7.1.

All AEs reported in the database will be listed with the SOC, PT, and investigator's Verbatim terms.

Deaths

There were no patient deaths reported at the time of study termination.

GENERAL STATISTICAL METHODS

The statistical analyses will be performed on the analysis datasets with appropriate software, SAS® Software version 9.4 (SAS Institute, Cary, N.C.).

Continuous data will be summarized with means, medians, standard deviations, quartiles (25^{th} and 75^{th}) minima and maxima, unless otherwise specified. Categorical data will be summarized with observed counts and percentages for each category. Unless otherwise specified, the percentage denominator will be the number of patients in the analysis population.

In case of subcategories, the relative frequencies will be calculated on the bases of the patients in the respective category; in this case a footnote will be added explaining the different denominators.

3.2 Analysis Sets

As Treated (AT)

The AT Population consists of all patients who receive treatment with either Varithena or ETA and will be analyzed according to the actual treatment they received. All tables and listings by treatment group will utilize AT Population.

3.3 Randomization Scheme

After written informed consent was obtained, patients were randomized 1:1 to either Varithena or ETA. Randomization was performed by a computer-generated block randomization scheme. The EDC system was used to randomize patients by site into the trial.

3.4 Analysis Timepoints

Point of Enrollment

Subjects were considered enrolled once the patient was determined to be eligible to participate in the study and informed consent obtained. If an I/E deviation(s) was identified at a later date (post treatment) the subject(s) will remain within the enrolled/treated cohort for analysis.

Baseline

Baseline was defined as the last non-missing assessment prior to the start of treatment.

Point of Treatment

Subjects were considered treated once randomized treatment commences. Only treated subjects were followed per study protocol safety event reporting and follow-up visit tests/assessments schedule.

Reference Day

Reference days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

- For days on or after procedure:
  - Date of Assessment - Date of Procedure + 1
- For days before randomization:
  - Date of Assessment - Date of Procedure

The Date of Procedure will then be considered relative "Day 1". The day before the Procedure will be relative "Day -1".

Time units

Unless specifically mentioned, month will be used as the time unit for analysis. A month-length is 30.4375 days (365.25/12). If duration is to be reported in months, duration in days is divided by 30.4375. If duration is to be reported in years, duration in days will be divided by 365.25.

Windows

Visits will be windowed into the following windows based on the data collection schedule in the protocol. Days will be calculated as:

Days = date of assessment – date of procedure + 1

Visit Post Procedure	Scheduled Visit Time with protocol allowed window
7 days	Day 7 ± 3 days
3 months	Day 90 ± 14 days
6 months	Day 180 ± 14 days

Visit Post Procedure	Scheduled Visit Time with protocol allowed window
12 months	Day 365 ± 30 days
24 months	Day 730 ± 30 days
36 months	Day 1095 ± 30 days

If more than one assessment occurred during the same nominal visit time window of the planned visit, select the record closest to the nominal day for that visit day/timepoint. If there were two assessments that are equidistant from the nominal planned visit day, the data of the worst assessment after the scheduled study day will be used.

Interim Analysis

No formal interim analyses were conducted.

Data Snapshot and Report Timings

A final data snapshot will be taken after all patients have exited the study. The final analysis will be performed after study closure.

3.5 Handling of Missing Data

For all analyses, unless otherwise specified, the number of subjects with valid data will be presented in the tables (for categorical data the number of subjects with missing data will be displayed), as well as the total number in the analysis set at that timepoint. The total which was used as the denominator in any percentage calculations will be identified where these numbers differ.

Missing dates imputation will follow the algorithm in Appendix 7.1.

3.6 Control of Systematic Error/Bias

Selection of subjects were made from the Investigators' general or professional referral population. All subjects meeting the inclusion/exclusion criteria and who have signed the protocol specific ICF were eligible for enrollment in the trial. Consecutively eligible subjects should have been enrolled into the trial to minimize selection bias. Study subjects were randomly assigned to a treatment group within the investigational site.

3.7 Number of Subjects per Investigative Site

The planned maximum number of randomizations per site was N=20; 20% of the total number of randomized subjects. Due to early enrollment termination, this is no longer applicable.

3.8 Changes to Planned Analyses

Any changes to the planned statistical analyses will be documented in revision to the SAP prior to performing the analyses. Changes from the planned statistical analyses after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

4 ADDITIONAL DATA ANALYSES

4.1 Subgroup Analyses

4.2 Justification of Pooling

Poolability analyses will not be conducted.

4.3 Multivariable Analyses

Multivariable analyses will not be conducted.

4.4 Other Analyses

Other analyses will be summarized including but not limited to the following:

Patient Disposition

Patient disposition will be summarized for all patients for all available data collected through study termination. The following categories will be summarized:

- Number of patients screened, enrolled, randomized, and treated
- Number and percentage of patients in the AT population. The percentage is based on number of patients screened.
- Number and percentage of patients who discontinued. The percentage is based on number of patients in the AT population. Possible reasons for discontinuation:
  - Subject completed study
  - Investigator withdrawal
  - Subject withdrawal
  - Lost to follow up
  - Subject died
  - Other
- Duration on study (months)
  - Duration (months) = (earlier date of study exit/death – date of first treatment + 1)/30.4375

Additionally, listings of inclusion/exclusion criteria, disposition, reason for discontinuation and completion will be provided.

Baseline Characteristics

Demographic and baseline characteristics are collected at screening. Descriptive summaries and/or listings will be provided for the AT population for the synoptic CSR.. The number and percentages (categorical variables) and descriptive statistics (continuous variables) will be summarized including but not limited to the following.

4.4.1.1 Demographics

- Age at time of consent (years), age group (≥ 18 to < 65 years, ≥ 65 to < 75 years, ≥75 years)
- Gender (Male, Female, Other)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown, Other, Not reported)
- Ethnicity (Hispanic, Latinx, or of Spanish origin, Not Hispanic, Latinx, or of Spanish origin)
- Weight (kg)
- Height (cm)
- BMI (kg/m2), which is calculated as 703 × weight (lbs) / [height (in)]^2

4.4.1.2 Medical History

- DVT (Yes, No, Unknown)
- Congestive Heart Failure (Yes, No, Unknown)
- Clotting Abnormality (Yes, No, Unknown)

Protocol Deviations

All protocol deviations will be listed as finalized after the database lock and prior to listing generation.

Criteria for protocol deviations will be defined and reviewed prior to database lock and major protocol deviations are defined within the Key Risk Indicators (KRI) in the Integrated Quality Risk Management Plan (IQRMP). This analysis will be performed for the final data snapshot at the final analysis.

The following protocol deviations will be considered:

- Violation of inclusion or exclusion criteria that could potentially directly impact analyses of interest
- Non-compliance to treatment (major deviations from the planned schedule of administration)
- Continuously missed evaluations of efficacy variables or major deviations in the timing of efficacy related assessments

Any protocol deviations that were classified will be summarized by the number and percentage by category and classification (major, minor) in the AT population. Classification will be confirmed by the medical director or designee and communicated to the statistical programming team for analyses. Additionally, a listing of protocol deviations with verbatim description and outcome will also be presented.

Study Treatment

4.4.1.3 Varithena Arm

The following will be summarized in the AT population for the test arm at index procedure and additional procedure:

- Manometer tubing utilized (Yes, No)

4.4.1.4 ETA Arm

No analyses will be performed on the ETA arm.

5 VALIDATION

Statistical analyses and validation will be done by the independent contract research organization (CRO). All clinical data reports generated per this plan will be validated through the internal validation process used by the CRO. BSC-00444 "Quality Control Specification and Validation of Statistical and Reporting Programs" may be used as a guidance.

6 PROGRAMMING CONSIDERATIONS

SAS code and other programming considerations will be provided in the mock-up TLF document with the relevant analysis as needed.

7 APPENDIX

7.1 AE date imputation

The following algorithm should be used to impute AE start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first treatment, then the day and month of the start date of treatment will be assigned to the missing fields
  - If the year is prior to the year of first treatment, then December 31 will be assigned to missing fields
  - If the year is after the year of first treatment, then January 1 will be assigned to the missing fields
- Missing month only
  - Treat day as missing and replace both month and day accordingly to the procedure above
- Missing day only
  - If the month and year are the same as the month and year of first treatment, then the start date of treatment will be assigned to the missing day
  - If the month and year are before the month and year of first treatment, then the last day of the month will be assigned to the missing day
  - If the month and year are after the month and year of the first treatment, then the first day of the month will be assigned to the missing day

If the imputed AE start date is after the AE stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate AE stop dates for which only partial information is known:

- Missing year
  - Date left missing
- Missing month
  - Impute “December”
- Missing day
  - Impute last day of that month

8 REFERENCES

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

2. Bland et al. BMC Cardiovascular Disorders (2015) 15:85 DOI 10.1186/s12872-015-0080-7