Statistical Analysis Plan, Vasculera® in patients with Lipedema: an exploratory controlled case study

NCT05616962

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Statistical Analysis Plan (SAP)

Protocol Title:	Vasculera® in patients with Lipedema: an exploratory controlled case study
Protocol Number:	PLP-01
SAP Date:	05-Sep-2019
Version:	1.1
Study Design:	Open-label, double-blind, case study
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SIGNATURES

I have read and approved of this statistical analysis plan for use in the study.

STATISTICIAN:

Meredith L. Wilcox, MPH	Oct 24, 2019
Statistician	Date

STUDY DIRECTOR

:

Robert M. Levy, M.D.	Sept 5, 2019
Robert M. Levy, MD	Date
Director of Clinical Development	
Primus Pharmaceuticals, Inc.	

1 STUDY SYNOPSIS

1.1 Overview

The objective of this study is to gain preliminary information regarding the clinical effects of Vascular and the possible role of the glycocalyx as a physiological target for Vasculera activity. It is anticipated that the results of the results of this study will inform the development of a randomized, double-bline, place controlled trial.

Study design: This is an open-label case study. This study will consist of a single 3-month treatment period.

In order to evaluate the efficacy, exploratory, and safety endpoints, study assessments will be conducted at screening/baseline (visit 1), visit 2 (month 1), visit 3 (month 2) and end-of-study (visit 4, month 3).

Study population: The planned sample size for this study is 30 subjects with lipedema present for at least 1 year who have not taken any diosmin containing medications within the 1 year prior to screening and meet all other inclusion and exclusion criteria.

Investigational Products: The investigational product is Vasculera® 1260 mg/day (one 630 mg tablet administered twice a day).

Efficacy Outcomes: The efficacy outcomes are the changes in the following clinical assessments from baseline to month 3:

- Weight
- Leg circumference 2 and 12 inches above lateral malleoli of both legs
- Body mass index (BMI)
- Short Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score
- Subject assessments, on a 0-10 scale (10=worst), for:
  - Leg discomfort
  - Feeling of leg swelling/tightness
  - Leg tenderness
  - Leg bruising
  - Leg skin redness
  - Fatigue
  - Ability to perform activities of daily living (ADL)
  - Overall sense of well-being
- Investigator assessment of response to therapy by Likert scale (0-5)

Sample Size: The planned sample size for this study is 30 subjects. Because this is an exploratory study, no formal sample size calculations were completed.

1.2 Efficacy Outcomes

Efficacy outcomes include the following clinical assessments:

- Change in weight from basline to month 3;
- Change in leg circumference, measured 2 and 12 inches above lateral malleoli of both legs, from baseline to month 3;
- Change in body mass index (BMI) from baseline to month 3;
- Change in the short WOMAC total score from baseline to month 3;
- Changes in the following subject assessments from baseline to month 3:
  - Leg discomfort
  - Feeling of leg swelling/tightness
  - Leg tenderness
  - Leg bruising
  - Leg skin redness
  - Fatigue
  - Ability to perform activities of daily living (ADL)
  - Overall sense of well-being;
- Investigator assessment of response to therapy at month 3.

1.3 Exploratory Outcomes

Exploratory outcomes include changes in plasma glycocalyx markers from baseline to month 3.

1.4 Safety Outcomes

Safety outcomes will include adverse events (AEs) reported at month 1, month 2, and month 3.

2 Statistical Analysis

2.1 Hypothesis Tests

All efficacy, secondary, and safety outcomes will be tested using a two-sided alpha of 0.05 with recognition of the increased risk of making a type I error due to testing of multiple outcomes.

Statistical analyses will be conducted using IBM SPSS Statistics for Windows, version 24 or higher (IBM Corp., Armonk, N.Y., USA).

2.2 Analytical Populations

The populations for analysis will include the following:

The **Safety Population** will consist of all subjects who received any amount of study product, and on whom any post-enrollment safety information is available.

The modified **Intent-to-Treat (ITT) Population** consists of subjects in the safety population who provided any post-enrollment information on the efficacy outcomes.

The **Per Protocol (PP) Population** consists of all subjects who consumed 80% to 120% (inclusive) of study product doses, do not have any major protocol violations and complete all study visits and procedures connected with measurement of the efficacy outcomes.

All outcomes will be analyzed for the ITT and PP populations. The safety endpoints will be analyzed for the Safety population.

2.3 Demographic and Screening/Baseline Characteristics

Demographic and screening/baseline characteristics of the enrolled subjects will be presented (e.g., age, gender, race/ethnicity). Descriptive statistics [number of subjects, mean, standard error of the mean (SEM), median, minimum, maximum, and interquartile range] will be reported for continuous variables. Frequency and percent of total will be reported for categorical variables.

2.4 Continuous Outcomes

Descriptive statistics [number of subjects, mean, standard error of the mean (SEM), median, minimum, maximum, and interquartile range] will be presented for the following outcomes at screening/baseline, month 1, month 2, and month 3: weight, leg circumference, short WOMAC individual item scores, short WOMAC total score, leg discomfort, leg swelling/ tightness, leg tenderness, leg bruising, leg skin redness, fatigue, ability to perform ADL, and overall sense of well-being. Descriptive statistics for BMI and plasma glycocalyx markers will be presented at screening/baseline and month 3. Descriptive statistics for the change from baseline to each corresponding post-enrollment time point will also be presented for the above outcomes. Descriptive statistics will be presented for response to treatment at month 3.

The short WOMAC score will be calculated by summing the individual item scores (formula provided below). Each item will be scored as follows: None=0, Mild=1, Moderate=2, Severe=3, Extreme=4.

$$\boldsymbol{Short\ WOMAC\ score} = \sum_{\boldsymbol{i=1}}^{\boldsymbol{8}} (\boldsymbol{Score\ for\ item_i})$$

Leg discomfort, leg swelling/tightness, leg tenderness, leg bruising, and leg skin redness will be reported as a number ranging from 0 to 10 where 0= “none” and 10= “worst you have ever seen or felt”. These outcomes will be treated as scale variables.

Fatigue, ability to engage in ADL, and overall sense of well-being will be reported as a number ranging from 0 to 10 where 0= “none” and 10= “worst you have ever felt”. These outcomes will be treated as scale variables.

Response to treatment will be assessed using a Likert scale (0-5). Response to treatment will be treated as a scale variable.

Change from baseline will be calculated as:

$$\boldsymbol{Change\ from\ Baseline\ to\ Visit_i} = (\boldsymbol{Value\ at\ Visit_i}) - (\boldsymbol{Value\ at\ baseline})$$

2.5 Analysis of Continuous Outcomes

For weight, leg circumference, short WOMAC total score, leg discomfort, leg swelling/tightness, leg tenderness, leg bruising, leg skin redness, fatigue, ability to perform ADL, and overall sense of well-being, change from baseline to each post-enrollment time point will be assessed using a repeated measures ANCOVA model with baseline value included as a covariate. Least square means (LSMs) will be calculated for the change from baseline to each time point. In the case of nonnormality, a rank transformation will be applied and medians and interquartile limits will be reported. The change from baseline to each post-enrollment time point will be tested independently, however the primary time point for effacicy analysis will be change from baseline to month 3.

For BMI and plasma glycocalyx markers, change from baseline to month 3 will be assessed using a paired t-test or the Wilcoxon signed rank test, depending on the distribution of the data.

2.6 Safety Analysis

Adverse events reported at month 1, month 2, and month 3 will be presented with counts and percentages of the following:

Subjects with any AEs by body system (also by maximum severity)
Subjects with any serious AEs by body system
Subjects with any AEs related to investigational product by body system
Subjects with any AEs related to discontinuation by body system

Listings of SAEs and AEs leading to discontinuation will be provided including date started and stopped, duration, severity, relationship to investigational product, action taken with investigational product, and outcome.

3 Statistical Methods

3.1 Assessment of Model Fit

Assumptions of normality of residuals will be investigated for each continuous outcome. Normality will be assessed by examining blox plots, Q-Q plots, measures of skewness and kurtosis, and the results of Shapiro-Wilk tests. In the case of nonnormality, a rank transformation will be applied and medians and interquartile limits will be reported.

3.2 Missing Data

Missing outcome data will estimated using multiple imputation.

3.3 Outliers

Every outlier will be checked at data validation. Continuous variables will be checked by visual inspection using histograms, box-plots or scatter plots, and verified by referral back to source documents. If the values are not erroneous, they will be included in the analysis.

3.4 Subgroup Analyses

Exploratory subgroup analyses based on baseline characteristics or compliance values may be performed using the same methodology as described in Section 2.4.