COMPLEWARE®

Statistical Analysis Plan

Date of Plan:	**2020-Sep-18**
Title:	**Comparison of the Viveve Treatment and Cryogen-Only Treatment Versus Sham Treatment for Stress Urinary Incontinence**
Protocol Number:	**VI-19-01 Amendment 2**
Version	**1.0**
Product:	**Viveve System**
Phase:	**N/A**
Sponsor:	**Viveve, Inc.** **345 Inverness Drive South** **Building B, Suite 250** **Englewood, CO 80112** **Phone: 720.696.8100** **Fax: 720.696.8199**
Prepared by CRO:	**CompleWare Corporation** **PO Box 3090** **Iowa City, IA 52244** **Phone: 319.626.8888** **Fax: 319.626.8750**

Statistical Analysis Plan Approval:

This version of the Statistical Analysis Plan has been read and approved by:

Douglas M. Massey — 19 September 2020

Douglas M. Massey, Ph.D.
Acting Vice President, Clinical & Medical Affairs
Viveve, Inc.

Date

Theresa Stern — 19Sep20

Theresa Stern, PhD
Biostatistician
Advisor to Viveve, Inc.

Date

Sara Lynn Beaty Nichols — 2020Sep21

Sara Nichols, PhD
Biostatistician
CompleWare Corporation

Date

Revision History:

Revision	Date	Description of Changes	Requested by
0.1	2020-Aug-05	Initial Document (Not signed)	Sara Nichols
1.0	2020-Sep-18	First Signed Version	Sara Nichols

Table of Contents

1. TABLE OF ABBREVIATIONS

AE	Adverse Event
AMC	Adjusted Mean Change
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFB	Change from Baseline
CI	Confidence Interval
CRO	Contract Research Organization
FAS	Full Analysis Set (also referred to as Intent-to-Treat)
I-QOL	Incontinence Quality of Life
MedDRA	Medical Dictionary for Regulatory Activities
n	Number
PPP	Per Protocol Population
PT	MedDRA Preferred Term
RF	Radiofrequency
SE	Standard Error
SOC	MedDRA System Organ Class
SP	Safety Population
SUI	Stress Urinary Incontinence
TEAE	Treatment-Emergent Adverse Event
WHO-DDE	WHO-Drug Dictionary Enhanced

2. INTRODUCTION

Stress urinary incontinence (SUI) is a major challenge for many women particularly those who have experienced child birth or are menopausal. Upwards of 55% of women with a previous vaginal delivery may exhibit signs and symptoms of SUI (Tahtinen 2016). The overarching effects of SUI impact a women's health and quality of life and have been shown to result in depression, social stigma and lack of self-confidence. The need to use an external pad to absorb urine leakage from even normal daily activities such as laughing, or coughing is unsatisfactory and can be extremely inconvenient, and often embarrassing for women.

Currently available treatment options for women are limited. Pelvic floor exercises (such as Kegels) offer some benefit to a percentage of women but compliance and sustained benefit can be issues. More aggressive approaches to manage SUI include pelvic surgery, slings and mesh. These invasive options involve more risk and recovery time and are a last resort for many patients.

The gap between conservative and invasive treatment options for SUI represents an opportunity to address an enormous unmet healthcare need for women. Minimally invasive treatments for SUI would be a highly appealing solution provided they offered a safe, consistent improvement in symptoms without significant time commitment or recovery. Any effective treatment would represent a major advance in women's health.

The Viveve Procedure, SUI protocol, offers a non-surgical alternative to traditional surgery using non-ablative, monopolar radiofrequency (RF) energy to improve SUI. It induces a mild, controlled reaction in the submucosal tissues that stimulates the body to restore collagen, thereby remodeling the tissue without causing scarring.

This Statistical Analysis Plan describes the analyses planned for protocol VI-19-01 Amendment 2 version dated 15April2020, to demonstrate that the active treatment (i.e., Viveve Treatment, SUI protocol) is superior to the sham treatment.

3. OBJECTIVES

3.1. Primary Objective

The primary objective of this single-blind study is to compare the effect of both the Viveve Treatment (RF plus cryogen) and cryogen alone treatment versus sham treatment, using the SUI treatment protocol (220 pulses), in improving mild to moderate SUI, assessed using the 1-hour pad weight test at 5 months post-treatment.

3.2. Secondary Objectives

The secondary objectives of this single-blind study are:

- Efficacy in decreasing the number of incontinence episodes using the 3 day voiding diary from Baseline to 5 months post-treatment.
- Efficacy in decreasing the number of pads utilized using the 3 day voiding diary from Baseline to 5 months post-treatment.
- Efficacy in decreasing the 24-hour pad weight from Baseline to 5 months post-treatment.
- Quality of Life benefits as measured by changes from Baseline to 5 months post-treatment in the Incontinence Quality of Life (I-QOL).
- Safety through 5 months post-treatment

4. VARIABLES

4.1. Response Variables

4.1.1. Primary Endpoints

The primary efficacy endpoint for this trial is:

- Change from baseline (CFB) to 5 months post-treatment in the 1-hr pad weight.

4.1.2. Secondary Endpoints

- CFB to 5 months post-treatment in incontinence episodes as measured with the 3-day bladder voiding diary.
- CFB to 5 months post-treatment in pads utilized as measured with the 3-day bladder voiding diary.
- CFB to 5 months post-treatment in 24-hr pad weight.
- CFB to 5 months post-treatment in I-QOL.

4.1.3. Safety Endpoints

Safety endpoints for this trial include:

- Safety as assessed by adverse event (AE) reporting from the initiation of treatment to study completion for each subject.

5. STATISTICAL ANALYSIS ISSUES

5.1. Populations to be Analyzed

Subjects in the following population could be enrolled in this study: pre-menopausal (≥18 age) female subjects with a normal, or abnormal but not clinically significant, physical, pelvic and neurologic exam; 1-hr pad weight at Baseline ranging from ≥5 to ≤50 g as the net increase from the pre-test pad weight; and at least one incontinence episode per day as determined in the 3-day voiding diary.

5.1.1. Analysis Populations

The analysis populations will consist of subjects categorized into the 3 populations described below.

5.1.1.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects who have 1-hour pad weight data at both Baseline and 5 months post-treatment. The FAS will be used for all of the efficacy analyses.

5.1.1.2 Per Protocol Population

The Per Protocol Population (PPP) is defined as all randomized subjects, who receive a complete treatment, and who complete the 5 month study without major protocol deviations. The PPP will be used for confirmatory analysis of the primary efficacy endpoint.

5.1.1.3 Safety Population

The Safety Population (SP) includes all randomized subjects in whom the treatment procedure is started, regardless of if the procedure is completed. The SP will be used for all of the safety summaries.

5.2. Statistical Analysis of Primary Measures

The primary efficacy endpoint for this study is CFB to 5 months post-treatment in 1-hour pad weight test. Analysis of covariance (ANCOVA) will be used, with treatment group and study site as independent variables and Baseline 1-hour pad weight as the covariate. Baseline 1-hour pad weight is defined as the 1-hour pad weight from the Baseline visit (Visit 2). The FAS will be used. Only observed case data will be used; that is, no imputation for missing data will be performed. The adjusted mean change (AMC) and standard error (SE) will be provided for each treatment group, along with the sham-AMC, 95% confidence interval (CI) and p-value for the Viveve Treatment group and for the cryogen alone treatment group. If the data is determined to be non-normally distributed, then a ranked ANCOVA will be used for the analysis.

A confirmatory analysis of the primary efficacy endpoint will be performed using the PPP.

5.3. Secondary Efficacy Analyses

The secondary efficacy endpoints include the CFB to 5 months post-treatment in total number of incontinence episodes as measured by the 3-day voiding diary, CFB to 5 months post-treatment in total number of pads utilized as measured with the 3-day

voiding diary, CFB to 5 months post-treatment in 24-hour pad weight, and CFB to 5 months post-treatment in
I-QOL. The same ANCOVA that was used for the primary efficacy endpoint will be used for each of the secondary endpoints, with the relevant Baseline as the covariate. Baseline for each endpoint is the analogous measurement from the Baseline visit (Visit 2). The FAS will be used, with observed case data only. For each endpoint, the AMC and SE will be provided for all 3 treatment groups, along with the sham-adjusted mean change, 95% CI and p-value for the Viveve Treatment group and the cryogen alone treatment group. If, for any of the endpoints, the data is determined for be non-normally distributed, then a ranked ANCOVA will be used for the analysis.

For all of the secondary efficacy endpoints, a confirmatory analysis will be performed using the PPP.

The analyses described above for the primary and secondary efficacy endpoints will be carried out using SAS (Version 9.4 or above) Proc Mixed.

5.4. Statistical Analyses of Safety Measures

No statistical analyses will be performed on any of the safety data in this study. The SP will be used for all safety summarizations, with subjects included in the treatment group they actually received regardless of their randomized treatment group. AEs will be coded using definitions in the most recent version of Medical Dictionary for Regulatory Activities (MedDRA; Version 23.0). Each AE will be coded with its appropriate Preferred Term (PT), and linked with its associated System Organ Class (SOC). Based Section 3.3.2 of the Study Protocol (Section 4.1.3 of this document) all AEs are by definition treatment emergent (TEAE) so the term AE is equivalent TEAE. AEs will be summarized by SOC, severity, and relationship to study treatment for each treatment group.

No descriptive statistics are planned for vital signs or safety laboratory measurements, but data will be available in a listing. Screening data for the physical/pelvic/neurological examination will also not be summarized but will be provided in a listing.

5.5. Sample Size Justification

The primary efficacy endpoint for this study is the CFB to 5 months post-treatment in 1-hour pad weight. The study will compare both the Viveve Treatment (RF plus cryogen) and cryogen alone treatment versus sham treatment. The sample size for this study will be approximately 36 randomized subjects, in a 1:1:1 ratio. The sample size is expected to provide approximately 70% power to detect an effect size (difference in group means / standard deviation) of 1.06, and approximately 80% power to detect an effect size of 1.19, for the CFB to 5 months post-treatment in 1-hour pad weight between the Viveve Treatment and sham, and between the cryogen alone treatment versus sham. Assuming a common standard deviation of 15, an effect size of 1.06 relates to a difference in means = 15.9, while an effect size of 1.19 relates to a difference in means = 17.9.

5.6. Experiment Design and Randomization

5.6.1. Experimental Design

This is a randomized, single-blind, sham controlled multicenter clinical trial. This study is designed to evaluate the Viveve Treatment (RF plus cryogen, SUI protocol) and

Cryogen only treatment versus sham treatment for the primary efficacy endpoint, 1-hr pad weight test. Approximately 36 subjects (12 per treatment arm) who meet the entry criteria will be randomized on Day 1 in a 1:1:1 ratio to one of the treatment groups. The Viveve Treatment group will receive a therapeutic dose of 90 J/cm2 of RF energy plus cryogen colling, the Cryogen only treatment group will receive a sub-treatment dose of ≤ 1 J/cm2 of RF energy plus cryogen cooling, and the sham group will be treated with an unpowered tip (i.e. treatment will be given without turning on the machine).

Subjects will be followed up with at 10 days and 5 months post-treatment. At the Baseline Visit and Month 5 Visit, subjects will be asked to provide a completed 3-Day Bladder Voiding Diary, complete a 24 hour pad-weight test, complete a 1-hour Pad Weight Test and I-QOL questionnaire. The subjects will be assessed for AEs at all study contacts and visits from the time the patient begins the treatment at the randomization visit.

5.6.2. Randomization

Subjects will be randomized in a 1:1:1 ratio. Randomization will be stratified by study site, with a maximum of 20 subjects randomized at an individual site. Randomization codes will be generated over the entire study population. A randomization scheme will be employed with randomly permuted blocks. Randomization assignments will be generated by statistical software. The randomization number for each subject who is randomized will be assigned after confirmation of trial eligibility.

5.7. Handling of Dropouts and Missing Data

Subjects who discontinue the study prior to completion will not be replaced. Missing data will be considered left as missing.

5.8. Multiple Comparisons/Multiplicity

In this study, the Type 1 error is controlled at 0.05 two-sided for the primary efficacy endpoint.

The secondary efficacy endpoints will be compared to a significance level of 0.05 two-sided. No adjustment will be made for multiplicity for these endpoints. Given the number of comparisons, all p-values for secondary efficacy endpoints will be considered descriptive.

5.9. Checks of Validity and Robustness

Confirmatory analyses for the primary and secondary endpoints are detailed in Section 5.2 and Section 5.3.

5.10. Subject Characteristics and Disposition

The following subject demographic characteristics will be summarized by treatment group for the FAS:

- Age
- Height, weight, body mass index (BMI)
- Race

- Ethnic origin
- Baseline 1-hr pad weight
- Baseline 24-hr pad weight
- Baseline 3-day voiding diary pads used and incontinence episodes
- Baseline I-QOL scores

Descriptive statistics for age, height, weight, BMI, 1-hr pad weight, 24-hr pad weight, 3-day voiding diary data, and I-QOL scores will include N, mean, standard deviation, minimum value, median, 25th and 75th percentiles (not for age and BMI), and maximum value.

Descriptive statistics for race and ethnic origin will be number (n) and percent (%).

A separate summary of Age, Race, and Ethnic origin will be provided for subjects who were classified as screen failures.

A summary of medical, sexual and gynecological history by treatment group, using the FAS, will also be provided.

Subject disposition will be summarized by treatment group, for all screened subjects. This summary table will include the total number of subjects screened, the reason for screen failure (n and % of subjects for each reason); the n and % of subjects randomized, and the n and % of subjects included in the FAS, PPP and SP; the n and % of subjects completing the study and withdrawing from the study, and the reason for early withdrawal. The determination of the placement of each subject into the different populations, such as those who complete the study, those who withdraw from the study, the FAS, the SP, etc will be done prior to treatment unblinding at the end of the study. A separate listing will include the reason for screen failure for subjects who were classified as screen failures.

Investigational product administration will be summarized in the SP by treatment group using summary statistics. The number of treatment pulses used, as well as the reasons for deviation from the treatment schedule will be listed.

5.11. Identification of Subgroup and Session Factors

Study site will be used a factor in all ANCOVA analyses as previously discussed in Sections 5.2 and 5.3. Data Tables and Listings

5.11.1. Templates of Tables

Table templates and listing templates are found in the separate Table Shells Plan.

5.12. Derived Variables and Derived Files

5.12.1. Questionnaire Scoring

The scoring of the I-QOL questionnaire is addressed in a separate questionnaire scoring document. This is the document developed for the initial SUI protocol, VI-17-01.

5.12.2. Coding

Medical history and AEs will be coded using MedDRA version 23.0. Concomitant medications will be coded using WHO-Drug Dictionary Enhanced (WHO-DDE) format B3 from the March 2020 release.

6. REFERENCES

Clinical Study Protocol: Evaluation of the Safety and Efficacy of the Viveve Treatment for Stress Urinary Incontinence. 23Oct2018.

Krhut J, Zachoval R, Smith PP, Rosier PF, Valansky L, Martan A, Zvara P, Pad weight testing in the evaluation of urinary incontinence. Neurourol Urodynam, 2014. 33:507-10.

O´Sullivan R, Karantanis E, Stevermuer TL, Allen W, Moore KH, Definition of mild, moderate and severe incontinence on the 24-hour pad test. BJOG, 2004. 111: 859-862.

SAS SUPPORT/SAMPLES & SAS NOTES, Usage Note 30715, *http://support.sas.com/kb/30/715.html*

Tahtinen RM, Cartwright R, Tsui JF, Aaltonen RL, Aoki Y, Cardenas JL, El Dib R, Joronen KM, Al Juaid S, Kalantan S, Kochana M, Kopec M, Lopes LC, Mirza E, Oksjoki SM, Pesonen JS, Valpas A, Wang L, Zhang Y, Heels-Ansdell D, Guyatt GH, Tikkinen KAO, Long-term Impact of Mode of Delivery on Stress Urinary Incontinence and Urgency Urinary Incontinence: A Systematic Review and Meta-analysis. Eur Urol, 2016. 70(1): 148-158.