LIBERATE International
VI-17-01
Evaluation of the Safety and Efficacy of the Viveve Treatment for Stress Urinary Incontinence

CLINICAL PROTOCOL

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Confidentiality Statement

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Protocol Synopsis

Sponsor/Company: Viveve, Inc.

Investigational Product: Viveve System

Title of Study: VIVEVE #: Evaluation of the Safety and Efficacy of the Viveve Treatment for Stress Urinary Incontinence (VI-17-01)

Number of Study Center(s): Up to 15 centers will participate in this study

Country: Canada

Total Number of Randomized Subjects: ~99 randomized subjects

Treatment Groups:

	# of Subjects	Treatment
Group A (Active Tx)	~66	Active
Group B (Sham Tx)	~33	Sham

Duration: Follow-up to 6 months post-treatment

Study Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of the Viveve treatment, SUI protocol, in improving stress urinary incontinence (SUI), assessed using the change from Baseline (CFB) to 6 months post-treatment in 1-hr pad weight.

Secondary Objective

The secondary objective of this study includes the determination of:

- Safety through 6 months post-treatment.

Exploratory Objectives

The exploratory objectives include the determination of:

- Efficacy in decreasing the 1-hr pad weight from Baseline to 3 months post-treatment.
- Efficacy in decreasing the 24 hr pad weight from Baseline to 6 months post-treatment.
- Efficacy in reducing the number of incontinence episodes in the 3-day bladder voiding diary at 3 and 6 months post-treatment.
- Quality of Life benefits as measured by changes from Baseline to 3 and 6 months post-treatment in the Urogenital Distress Inventory (UDI-6), International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF) and Incontinence Quality of Life (I-QOL).
- Efficacy to improve Female Sexual Function Index (FSFI) total scores from Baseline to 3 and 6 months post-treatment, in subjects who had FSFI total score ≤26.5 at Baseline.

Intended Use: The Viveve Treatment, SUI protocol, is being evaluated for the improvement of stress urinary incontinence (SUI).

Overview of Study Design

This is a prospective, randomized, double-blind, sham-controlled clinical study. The study is designed to demonstrate that active is superior to sham for the efficacy endpoints and is deemed to have appropriate safety as compared to sham.

Approximately ninety-nine (99) subjects meeting the inclusion/exclusion criteria will be randomized in a 2:1 ratio to either the active or sham group. Randomization will be stratified by study site, with a maximum of 30 subjects randomized in an individual site. The active treatment group will receive a treatment dose of 90 J/cm^2 and the sham group will receive a sub-therapeutic dose of ≤1 J/cm^2.

Subjects will be followed up with at 10 days and at 3 and 6 months post-treatment. Subjects will be assessed for adverse events at all study contacts and visits from the time the informed consent is signed.

Inclusion Criteria

A subject must meet the following criteria to participate in this study:

I.1 Able to understand and has voluntarily signed and dated the informed consent form (ICF) prior to initiation of any screening or study-specificprocedures.

I.2 Willing to comply with study requirements and instructions.

I.3 Documented diagnosis of stress urinary incontinence with urethral hypermobility as determined by

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Q-tip test. If there are mixed symptoms there must be a predominant stress component as determined by investigator or designee. I.4 Pre-menopausal females, ≥ 18 years of age. Premenopausal is defined as a woman who has had menstrual cycles over the previous 12 months. If menstrual cycles cannot be established, premenopausal can be defined as FSH levels <30.0 mIU/mL. I.5 Subjects with a BMI of ≤ 35 kg/m². I.6 Normal, or abnormal but not clinically significant (as determined by the investigator), physical, pelvic and neurologic exam at the Screening visit. I.7 Negative pregnancy test at Screening and Randomization visit. I.8 Subject uses an acceptable form of birth control started ≥3 months prior to screening. Acceptable forms of birth control include: abstinence from heterosexual vaginal intercourse, hysterectomy, double tubal ligation, vasectomy, double barrier contraception, intrauterine device or hormonal contraceptive. Rhythm and withdrawal are not considered acceptable forms of contraception. I.9 Patient-reported or documented diagnosis of SUI symptoms for > 6 months. I.10 Positive Bladder Stress Test at Screening. I.11 1-hr pad weight at Baseline with a 5 to 50 g net increase from the pre-test pad weight. I.12 Subjects must complete 3 days in the 3-day voiding diary during the 3 consecutive days prior to the Screening Visit, AND subjects must report a minimum of 1 incontinence episode per day as determined in the 3-day voiding diary.
Exclusion Criteria
A subject will be excluded from participating in the study for any of the following reasons: E.1 Subjects who are currently breastfeeding or have discontinued breastfeeding fewer than 6 months prior to screening. E.2 Subjects who are pregnant or plan to become pregnant during the course of the study. E.3 Subjects who have undergone other stress urinary incontinence treatments, excluding behavioral modifications (e.g., Kegel exercises). E.4 Urinary Tract Infection (UTI) at the Screening or Randomization Visit based on the results of a urine dipstick. If the subject has a UTI at the Screening or Randomization Visit they may be treated with antibiotics, at the Investigator's discretion, and return within 7 days after UTI treatment completion. Subjects may return once, within 7 days after completion of UTI treatment. E.5 Abnormal, clinically significant laboratory results at the Screening Visit (as determined by the Investigator). E.6 History of any condition, illness, or surgery that might confound the results of urinary incontinence assessment, including, but not limited to: a. Prominent (i.e. greater than Stage II as defined by the International Continence Society) pelvic organ prolapse (e.g., cystocele, rectocele) as determined by investigator. b. Neurological disorders (e.g., multiple sclerosis, Parkinson's disease) c. History of recurrent Urinary Tract Infections (UTI) d. Vesicoureteral reflux e. Bladder stones at time of enrollment or history of recurrent bladder stones f. History of or current diagnosis of bladder tumors g. Interstitial cystitis E.7 Has any implantable electrical device [e.g., implantable pacemaker, automatic implantable cardioverter-defibrillator (AICD)]. E.8 Subjects with conditions that may pose unreasonable risks, including but not limited to: a. Concurrent infection (e.g., active UTI, cystitis, urethritis) b. Coagulation abnormalities c. Abnormal kidney function d. Uncontrolled diabetes E.9 Medical or immunological condition, including, but not limited to: a. Uncontrolled cardiovascular, respiratory, neoplastic, infectious, and/or endocrinological

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condition that could impact the subject's ability to complete the trial.

b. Untreated chronic abdominal/pelvic pain disorder [including, but not limited to, dyspareunia, vaginismus, endometriosis, vulvovaginal atrophy (VVA), genitourinary syndrome of menopause (GSM), irritable bowel syndrome, or Crohn's disease].

c. Untreated medical condition or medication that, in investigator's opinion, may interfere with adequate wound healing response (e.g., congenital connective tissue disease) or the subject's ability to complete the clinical trial requirements.

d. Untreated active malignancy or undergoing treatment (using chemotherapeutic agents, radiation therapy, and/or cytostatic medications) that may interfere with adequate wound healing response or the subject's ability to complete thetrial.

e. Untreated acute or chronic vaginal or vulvar disorder including, but not limited to, vulvovaginal atrophy/GSM; pain, including provoked/generalized vulvodynia, vulvar vestibulitis, dysesthetic vulvodynia, or vulvar dystrophy; current/chronic papulosquamous vulvar dermatoses (e.g., psoriasis, lichen planus, tinea cruris, lichen sclerosis, seborrheic dermatitis, contact/irritant dermatitis, lichen simplex, eczema); bullous dermatoses; systemic diseases with potential involvement of vulva; genital warts; past/current vaginal or vulvar radiotherapy or brachytherapy.

f. Active genital herpes.

g. Active genital/pelvic infection (e.g., gonorrhea, chlamydia).

h. Active yeast infection. If the subject has an active vaginal yeast infection at the Screening or Randomization Visit they may be treated with an antifungal, at the Investigator's discretion, and return within 7 days after completion of vaginal yeast infection treatment. Subjects may return once, within 7 days after treatment completion for a vaginal yeast infection treatment.

E.10 Chronic use of anti-inflammatory drugs, including ibuprofen, aspirin, and steroids (excluding aspirin that is taken for cardiovascular prophylaxis).

E.11 Taking any new medication, including herbal supplements and those taken in teas (< 1 month) that affects urination, or change in the dosage of any medication that affects urination within 1 month of Screening. Dosage should not change for the remainder of the study unless medically necessary.

E.12 Subjects who have started or changed dose of local vaginal hormones <6 weeks before Screening.

E.13 Subjects who have started pelvic floor physical therapy within the last 3 months.

E.14 Undergone previous elective surgical or non-invasive procedure(s) in the vaginal canal (including the Viveve Treatment or any other genital radiofrequency treatment; injectable bulking agent, cosmetic, laser, surgical, and/or genital enhancement procedure). Including previous dilation and cuterage within 12 months of the subject's Pre-Screening Visit.

E.15 Not sterilized (or partner not sterilized/infertile), ***or*** not willing to use an acceptable method of birth control started at least 3 months prior to screening and to be continued throughout the duration of the study [e.g., barrier method, intrauterine device, hormonal therapy (subcutaneous, injectable, or oral contraceptive)]. Rhythm and withdrawal are not considered acceptable forms of contraception.

E.16 Participated in another clinical study (drug or device) within 30 days of screening or is not willing to abstain from participating in other clinical studies for duration oftrial. If participation was in an investigational drug study (i.e., receiving or has received investigational product), subject must wait 30 days, or 5 times the investigational drug half-life, whichever is longer, prior to Screening.

E.17 Subject is employed by Viveve or participating investigative sites.

Efficacy Evaluation

Primary Efficacy Endpoint

- CFB to 6 months post-treatment in 1-hr pad weight.

Exploratory Efficacy Endpoints

- CFB to 3 months post-treatment in 1-hr pad weight.
- CFB to 6 months post-treatment in 24-hr pad weight.
- CFB to 3 and 6 months post-treatment in 3-day bladder voiding diary.
- CFB to 3 and 6 months post-treatment in UDI-6, ICIQ-UI-SF and I-QOL.

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- CFB to 3 and 6 months post-treatment in FSFI total score, in subjects with FSFI total score ≤26.5 at screening.

Safety Evaluation:

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

Statistical Methods

Sample Size

The primary efficacy endpoint for this study is the CFB to 6 months post-treatment in 1-hr pad weight. A clinically meaningful reduction in 1-hr pad weight is defined as >50% (target reduction in active group); a sham (placebo) effect of a 30% reduction is anticipated in the sham group. The sample size for this study will be ~99 randomized subjects, in a 2:1 ratio with ~66 randomized to the active treatment group and ~33 to the sham treatment group. Assumptions include a 2-sided t-test at the 5% level of significance, and a CFB to 6 months post-treatment of >50% in the active group and of 30% in the sham group. Thus, 99 total randomized subjects, in a 2:1 ratio to active: sham treatment groups, will provide approximately 90% power if the common standard deviation in CFB is as large as 28, and will provide approximately 80% power if the common standard deviation in CFB is as large as 33.

An analysis will be performed during the study after ~80 subjects have completed their Month 3 visit. The change from Baseline to 3 months in 1-hr pad weight will be analyzed, to help plan future studies. Viveve team members, subjects, and study site personnel working on the study will remain blinded to individual subject's treatment groups; unblinding of the individual subject's treatment group will only occur at final database lock for Viveve team members, subjects, and study site personnel working on the study. Since this analysis during the study will be analyzing CFB to 3 months post-baseline in 1-hr pad weight, which is not the primary efficacy endpoint for this study, no statistical adjustment is planned for the final significance level ($\alpha = 0.05$) for the primary efficacy endpoint.

Subject Populations

The Full Analysis Set (FAS) includes all randomized subjects and is also known as the intention-to-treat (ITT) population. The FAS will be used for all efficacy analyses.

The Modified ITT (mITT) includes all randomized subjects who are treated and completes the study. The mITT will be used for confirmatory analysis of efficacy endpoints.

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 safety summaries.

Primary Efficacy Analysis

The primary efficacy endpoint for this study is CFB to 6 months post-treatment in 1-hr pad weight. Analysis of covariance (ANCOVA) with treatment group, study site and Baseline 1-hr pad weight as independent variables, will be used to analyze the primary efficacy endpoint. The FAS will be used, with subjects included in their randomized treatment group regardless of the treatment they actually received. The Baseline 1-hr pad weight is defined as the 1-hr pad weight at Screening. Missing values for the 6 month 1-hr pad weight will be imputed using a multiple imputation method that assumes the data are missing at random. Imputed datasets will be analyzed using an ANCOVA model with treatment group, study site, and Baseline 1-hr pad weight as independent variables. Approximately 100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. The adjusted mean change and standard error (SE) will be provided for both treatment groups, along with the difference in adjusted mean change, its 95% confidence interval (CI) and associated p-value. The adjusted mean changes for each study site will also be provided.

A confirmatory analysis of the primary efficacy endpoint will be performed using the FAS and same ANCOVA as the primary analysis, but using only observed case data (no imputation will be performed for missing data). A second confirmatory analysis of the primary efficacy endpoint will be performed using the mITT, using only observed case data.

Exploratory Efficacy Analyses

Exploratory efficacy endpoints include CFB to 3 months post-treatment in 1-hr pad weight; CFB to 6 months

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post-treatment in 24-hr pad weight, CFB to 3 and 6 months post-treatment in 3-day bladder voiding diary; CFB to 3 and 6 months post-treatment in UDI-6, ICIQ-UI-SF and I-QOL; and CFB to 3 and 6 months post-treatment in FSFI total score (in subjects with FSFI total score ≤26.5 at Baseline). For the exploratory efficacy endpoints, a significance level of 0.05 will be used; given the large number of endpoints, the p-values for those endpoints will be considered descriptive.

Each of the continuous endpoints will be analyzed using ANCOVA with treatment group, study site, and the relevant Baseline as independent factors. The FAS population will be used for each analysis (for the FSFI analyses, the FAS subjects with a Baseline FSFI total score ≤26.5 will be used), with subjects included in their randomized treatment group regardless of the treatment they actually received. Baseline for each endpoint is the relevant value from the Screening Visit. For each of the exploratory endpoints, only observed case data will be used (no imputation will be performed for missing data). Output from each ANCOVA will include the adjusted mean change and SE for the active treatment and sham groups, as well as the difference in adjusted mean change, its 95% CI, and p-value. The adjusted mean changes for each study site will also be provided for each ANCOVA.

Confirmatory analyses will be performed for each of the exploratory endpoints, using the mITT with observed case data only (no imputation for missing data will be performed).

For all continuous endpoints (primary and exploratory), the assumption of normality will be assessed. If any endpoint at any timepoint is found to be not normally distributed, the data will either be transformed to make it normal or a nonparametric test will be used instead of the planned ANCOVA.

Safety Evaluation

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 summarized using treatment-emergent AEs (TEAEs; defined as AEs that begin or worsen after the treatment procedure is started). TEAEs and serious AEs (SAEs) will be summarized by system organ class (SOC), severity, and relationship to study treatment for each treatment group. All AEs (TEAE and non-TEAE) will be provided in a listing.

Table 1: Study Table

	Pre-Screen (Day -30 to Day -5)	Screening (Day -14 to Day -1)	Rando-mization (Day 1)	Day 10 Telephone Call (Day 7 to 13)	Month 3 (Day 90 to 110)	Month 6 (Day 165 to 195)
Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**TC**	**Visit 4**	**Visit 5**
Informed Consent	X					
Demographic Data	X					
Inclusion/Exclusion Criteria	X	X	X			
Collection of 3-day bladder voiding diary		X[1]			X[1]	X[1]
Medical/Sexual/ Gynecological History	X					
Concomitant Therapy/Medication Assessment	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X
Vital Signs Assessment (Blood pressure, temp, pulse, respiratory rate)		X	X		X	X
Height & Weight Measurement	X					
Weight Measurement						X
Physical/Pelvic/Neurologic Exam		X				X
Q-tip test for urethral hypermobility		X				
Bladder Stress Test		X				
Urine Pregnancy Test Dipstick		X	X			X
Bacterial Urine Dipstick		X	X			
Viveve Treatment, SUI protocol, (active or sham)			X			
Distribute and train subject on 3-day bladder voiding diary	X		X		X	
Score 3-day bladder voiding diary		X		X		X
1 -Hour Pad Weight Test		X			X	X
Distribute supplies for and train subject on 24-Hour Pad Weight Test	X				X	
24-Hour Pad Weight Test post-test weighing		X				X
Clinical Laboratory Assessments[2]		X				
UDI-6		X			X	X
ICIQ-UI-SF		X			X	X
I-QOL		X			X	X
FSFI		X			X	X

[1] Site will contact subject 4 to 5 days prior to visit to remind the subject to complete the 3-day bladder voiding diary. Subject must complete the 3-day bladder voiding diary on the 3 consecutive days preceeding visit.
[2] Laboratory assessments will include a complete blood count (CBC) and blood urea nitrogen (BUN).

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1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Definitions

Abbreviation/ Term	Definition	Abbreviation/ Term	Definition
ADL	Activities of Daily Living	IDE	Investigational Device Exemption
AE	Adverse Event	IIQ-7	Incontinence Impact Questionnaire
ADE	Adverse Device Effect	IP	Investigational Product
AICD	Automatic Implantable Cardioverter/ Defibrillator	I-QOL	Incontinence Quality of Life
AMC	Adjusted Mean Change	IRB	Institutional Review Board
ANCOVA	Analysis of Covariance	ISO	International Organization for Standardization
ARS	All Randomized Set	ITT	Intent-to-Treat Population
BMI	Body Mass Index	J	Joule
BUN	Blood Urea Nitrogen	LOCF	Last Observation Carried Forward
CBC	Complete Blood Count	MedDRA	Medical Dictionary for Regulatory Activities
CFB	Change from Baseline	NTF	Note to File
CI	Confidence Interval	OTC	Over-the-Counter
CRF	Case Report Form	PHI	Protected Health Information
CRO	Clinical Research Organization	PI	Principal Investigator
CTCAE	Common Terminology Criteria for Adverse Events	PPS	Per-Protocol Analysis Set
DAL	Device Accountability Log	PRO	Patient-Reported Outcome
EC	Ethics Committee	PT	Preferred Term
eCRF	Electronic Case Report Form	RF	Radiofrequency
EDC	Electronic Data Capture	SADE	Serious Adverse Device Effect
FAS	Full Analysis Set	SAE	Serious Adverse Event
FDA	Food and Drug Administration	SD	Standard Deviation
FSFI	Female Sexual Function Index	SE	Standard Error
GCP	Good Clinical Practice	SOC	System Organ Class
GLP	Good Laboratory Practices	SOP	Standard Operating Procedure
GSM	Genitourinary Syndrome of Menopause	SP	Safety Population
HLGT	High-Level Group Term	SUI	Stress Urinary Incontinence
HLT	High-Level Term	TEAE	Treatment-Emergent Adverse Event
IMV	Interim Monitoring Visits	UDI-6	Urogenital Distress Inventory
IB	Investigator's Brochure	USA	United States of America
ICF	Informed Consent Form	USADE	Unanticipated Serious Adverse Device Effect
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	UTI	Urinary Tract Infection
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form	VVA	Vulvovaginal Atrophy

2 INTRODUCTION

2.1 BACKGROUND

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 void 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-invasive 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 deposit collagen, thereby remodeling the tissue without causing scarring.

2.2 NON-CLINICAL STUDY OF THE INVESTIGATIONAL PRODUCT

Early preliminary research was carried out using the sheep vagina as an animal model (IV0311g Final Study Report). To study the effect of the device in the vaginal introitus, the device was tested in a GLP Animal Study between April 2011 and November 2012. Microscopic tissue examinations of sheep vaginal mucosa biopsy specimens were obtained at Week 1, Month 1, Month 3, and/or Month 6 post-treatment to evaluate short- and long-term effects of treatment.

The study findings support a mechanism of action for this RF-based therapy that involves tissue with fibroblast activation and new collagen production. The absence of ulceration, regional necrosis, and diffuse fibrosis over the 6-month follow-up period support an acceptable safety profile for this treatment regimen.

2.3 CLINICAL EXPERIENCE OF THE VIVEVE SYSTEM

Viveve, Inc. conducted three pilot studies in the US, Canada, and Japan, and recently completed a larger post-market study in Canada, Japan, Spain, and Italy on the Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function (Millheiser 2010, Sekiguchi 3013, Krychman 2017, Krychman 2018).

The purpose of these studies was to evaluate the safety and efficacy of the Viveve Procedure for the treatment of the vaginal introitus following childbirth. Data were collected primarily by means of clinical observations and patient-reported outcomes. Several quality of life questionnaires and global response indices were used to assess subject outcomes.

In recent studies, a beneficial side effect was noted, many of the women observed an improvement of their SUI symptoms. As such, a pilot study was conducted to evaluate the potential effectiveness of cryogen-cooled monopolar radiofrequency for temporary relief of SUI symptoms through an investigator-sponsored research program, supported by Viveve, Inc. (submitted for publication). Outcome measures included multiple validated patient-reported questionnaires and a voiding diary. Improvements in patient's SUI symptoms were observed, with a decrease in all of the composite scores for the three incontinence questionnaires used and less leaking episodes as documented in the voiding diary. Additional detailed information is outlined in the Investigator's Brochure (IB).

2.4 RISK/BENEFIT PROFILE OF THE VIVEVE SYSTEM

2.4.1 Risk Profile

Radiofrequency (RF) energy has a long history of use in sensitive tissues, such as mucosal tissue in the vagina, pharynx, cornea, and skin. However, the Viveve System delivers a lower amount of energy than the typical RF devices on the market (average energy of the Viveve System is <50W). In addition, the Viveve System includes a surface cooling feature to protect the treated surface from getting overheated.

A review of the previously published clinical trials, one additional clinical trial that has not yet been published, and the Viveve internal complaint log found no treatment-related Serious Adverse Events (SAEs), and all events were considered transient in nature. Additional detailed information is outlined in the Investigator's Brochure (IB).

To minimize the possibility of impacting the rectum, the investigator(s) will not treat subjects with a thin recto-vaginal septum.

2.4.1.1 Mitigation of Risks

Possible risks of the Viveve treatment, SUI protocol, are mitigated by using qualified clinicians [Medical Doctors (M.D.), Doctors of Osteopathic Medicine (D.O.), Nurse Practioners (NP) or Physician Assistants (PA-C)] who have received training and are experienced in vaginal gynecological procedures. All participating clinicians will be thoroughly trained in the safe use of the Viveve System. No subjects will be given the Viveve treatment, SUI protocol, until training is completed. In addition, risks are mitigated by including only those subjects that meet the study entry criteria.

2.5 POTENTIAL BENEFITS

The potential benefits, based on a recent investigator-initiated study of the Viveve treatment, SUI protocol, suggest an improvement in stress urinary incontinence. This study will characterize the potential benefit.

3 TRIAL OBJECTIVES AND ENDPOINTS

3.1 PROPOSED INTENDED USE

The Viveve Treatment, SUI protocol, is being evaluated for the temporary improvement of SUI.

3.2 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the efficacy of the Viveve treatment, SUI protocol, in improving mild to moderate stress urinary incontinence (SUI), assessed using the change from Baseline (CFB) to 6 months post-treatment in the 1-hr pad weight test.

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this trial is:

- The CFB to 6 months post-treatment in the 1-hr pad weight test.

3.3 SECONDARY OBJECTIVE

The secondary objective of this study include the determination of:

- Safety of the Viveve Treatment from the treatment procedure through 6 months post-treatment.

3.3.1 Safety Endpoints

Safety endpoints for this trial include:

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

3.4 EXPLORATORY OBJECTIVES

The exploratory objectives include the determination of:

- Efficacy in decreasing the 1-hr pad weight at 3 months post-treatment.
- Efficacy in decreasing the 24-hr pad weight at 6 months post-treatment.
- Efficacy to reduce the number of incontinence episodes in the 3-day bladder voiding diary at 3 and 6 months post-treatment.
- Quality of Life benefits as measured by changes from Baseline to 3 and 6 months post-treatment in the UDI-6, ICIQ-UI-SF and I-QOL.

- Efficacy of the Viveve Treatment, SUI protocol, to improve FSFI total score in subjects with FSFI ≤26.5 at Baseline.

3.4.1 Exploratory Endpoints

Exploratory endpoints for this trial include:

- CFB to 3 months post-treatment in 1-hr pad weight.
- CFB to 6 months post-treatment in 24-hr pad weight.
- CFB to 3 and 6 months post-treatment in 3-day bladder voiding diary.
- CFB to 3 and 6 months post-treatment in UDI-6, ICIQ-UI-SF and I-QOL.
- CFB to 3 and 6 months post- treatment in FSFI total score, in subjects with FSFI total score ≤ 26.5 at screening.

3.5 DESCRIPTION OF PRIMARY EFFICACY ENDPOINT

3.5.1 1-hour Pad Weight Test

A 1-hr pad weight test will be used as the primary endpoint and one of the objective measurements of treatment efficacy. Pad weight testing will be conducted using standard techniques. All investigative sites will be trained for consistency. An equivalency of 1 mL of urine to 1 g of pad weight will be used. A pad weight increase of <1 g will be defined as dry to account for subject perspiration. Subject's 1-hr pad weight at Baseline must have a net increase of 5-50 g. A clinically meaningful level of improvement will be defined as a >50% reduction from Baseline in pad weight. A description of the 1-hour pad weight test is provided below (Khrut 2014).

- Sites will use the Sponsor provided bladder scanner to confirm that the subject's bladder is moderately full to full (≥200 mL). If the subject's bladder volume is <200 mL, the site will instruct the subject to drink 500 mL of sodium-free liquid. Approximately fifteen minutes after the subject has drinks the liquid, the site will rescan the subject's bladder. If the bladder volume is ≥200 mL, the site may begin the test. The subject should not void prior to starting the test.
- Subjects will be asked to undergo the following set of activities during the pad weight test:
    1. 0 – 15 min:
        - Subject puts on one standardized, pre-weighed pad without voiding
        - Subject drinks 500 mL of sodium-free liquid in <15 min – then sits or rests
    2. 15 – 45 min:
        - Walking, including stair climbing to one flight up and down
    3. 45 – 60 min:
        - Standing up from sitting (10 times)
        - Coughing vigorously (10 times)
        - The subject should be standing with their legs slightly apart when coughing
        - Instruct the subject not to make any attempts to hold in her urine
        - Running in place (1 min)
        - Bending to pick up an object from the floor (5 times)
        - Washing hands in running water (1 min)

    Per ICS guidelines, this activity may be modified according to the subject's physical fitness. If modified for a subject, this must be documented, and the same set of activities must be done for the individual subject it was modified for at each relevant timepoint.
    - After 60 minutes, the weight of the pad is measured to determine the amount of leakage. Even if all activities are completed before 60 minutes, do not ask the subject to remove the pad until 60 minutes has elapsed.
    - If a moderately full bladder cannot be maintained through the hour (i.e., if the subject must void), the test must be started again.
- Before and after the test, the weight of the pad is measured with a high-precision scale to determine the amount of leakage.
- For inclusion in the study, each subject's 1-hr pad weight at Baseline must have a net increase that ranges from 5-50 g.

3.6 DESCRIPTION OF EXPLORATORY EFFICACY ENDPOINTS

3.6.1 24-hour Pad Weight Test

A 24-hr pad weight test will be used as an exploratory endpoint and one of the objective measurements of treatment efficacy. Pad weight testing will be conducted using standard techniques. All investigative sites will be trained for consistency. An equivalency of 1 mL of urine to 1 g of pad weight will be used. An increase in weight >4 g / 24-hours will be considered a positive test (Staskin 2009). The 24-hr pad weight test records the volume of urine leakage while a woman is performing her normal daily activities.
It is conducted in the following manner:

- The subject will be provided with pre-weighed pads, airtight plastic bags and the 24-Hr Pad Weight Test Guide for Subjects.
- The subject will be asked to capture her urine leakage with these pads for a 24-hr period within 24 hours of the following visit.
- The subject will start the test after she has emptied her bladder, she will place a pre-weighed pad in her underwear.
- During the 24-hr test period, the subject is asked to perform her normal daily activities, changing the pad every 4 to 6 hours.
- Upon changing pads, the subject will immediately place the used pad in an airtight plastic bag to avoid weight loss caused by evaporation.
- It is important provide storage instructions to each subject detailing that the bag must be stored in a room temperature area away from direct sunlight.
- The airtight bag with all pads will be weighed at the research site during the following visit.

3.6.2 Urogenital Distress Inventory-6 (UDI-6)

The Urogenital Distress Inventory (UDI-6) (Continence Program for Women Research Group, Wake Forest University) assesses the degree to which symptoms associated with incontinence are troubling; it was originally developed to complement the IIQ. The UDI-6 was developed in 1995 and derived from the long form version of the Urogenital Distress Inventory (UDI) developed in 1994 (Shumaker 1994, Uebersax 1995, Harvey 2001). The UDI-6 is a symptom inventory specific to lower urinary tract dysfunction and genital prolapse. The format includes 6 items about urinary problems over the previous 3 months (frequent urination, urine leakage related to the feeling of urgency, urine leakage related to physical activity or coughing or sneezing, small amounts of urine leakage (drops), difficulty emptying the bladder, pain or discomfort in the lower abdominal or genital area). Seen Appendix 14.1 for a sample UDI-6 questionnaire.

3.6.3 International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence Short Form (ICIQ-UI-SF)

The ICIQ-UI-SF (Bristol Urological Institute) provides a brief and robust measure to assess the impact of symptoms of incontinence on quality of life and outcome of treatment, see Appendix 14.2 for a sample ICIQ-UI-SF questionnaire. This short and simple questionnaire is also of use to general practitioners and clinicians in both primary and secondary care institutions to screen for incontinence, to obtain a brief yet comprehensive summary of the level, impact and perceived cause of symptoms of incontinence and to facilitate patient-clinician discussions. Its brevity also makes the ICIQ-UI-SF an ideal research tool (Avery 2004).

3.6.4 Incontinence Quality of Life (I-QOL)

The I-QOL will be used to assess the impact of urinary incontinence on quality of life (University of Washington 1996. Revised 2000), see Appendix 14.3 for a sample I-QOL questionnaire. Twenty-two self-administered questions cover three domains: avoidance and limiting behavior, psychosocial impact and social embarrassment. Each question has a 5-point response scale; subjects are asked to rate the extent to which their urinary incontinence is affecting their quality of life (1, extremely; 2, quite a bit; 3, moderately; 4, a little; 5, not at all). The subject is asked to answer each question based on how they feel at the time they are completing the questionnaire (Patrick 1999).

3.6.5 Three-day Bladder Voiding Diary

The main purpose of a bladder diary is to document daily how the subject's bladder functions and to provide an overview of the bladder's functions, habits, and patterns, including the number of leaks; see Appendix 14.4 for a sample diary) . The diary will be used as both an evaluation tool and to later measure a subject's progress. The

subject must complete the diary during the week prior to Visits 2, 4 and 5. Study site personnel should call each subject approximately 1-week prior to each visit to remind the subject to complete the diary.

3.6.6 The Female Sexual Function Index (FSFI)

The FSFI will be used to assess patient-reported sexual function. It is a 19-item validated measure of female sexual function, see Appendix 14.2 for a sample questionnaire. The FSFI consists of six domains: Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain. The recall period is the past 4 weeks.

Psychometric evaluation has been carried out, including studies of reliability, convergent validity, and discriminant validity (Meston 2003, Rosen 2000). The reliability and validity of the FSFI has been supported in several samples of women with mixed sexual dysfunctions (N = 568) and to develop diagnostic cut-off scores for classification of women's sexual dysfunction (Wiegel 2005).

4 INVESTIGATIONAL PLAN

4.1 STUDY DESIGN

This is a randomized, double-blind, sham-controlled clinical trial. This study is designed to demonstrate that the active treatment (i.e., Viveve Treatment, SUI protocol) is superior to the sham treatment for the primary efficacy endpoint, 1-hr pad weight test. Approximately 99 subjects who meet the entry criteria will be randomized 2:1 to either the active or sham treatment group. Randomization will be stratified by study site, with a maximum of 21 subjects randomized at an individual site. The active group will receive a therapeutic dose of 90 J/cm^2 of RF energy and the sham group will receive a sub-treatment dose of ≤1 J/cm^2. Subjects will be followed out to a 6-month post-treatment visit.

4.2 STUDY PROCEDURES BY VISIT

4.2.1 Subject Participation

Subjects presenting at the participating study centers who meet the study inclusion/exclusion criteria will be considered as potential candidates and invited to participate in the study. Subjects will be considered as participating in the study when they have signed an Institutional Review Board-approved consent form from a standpoint of monitoring adverse events.

4.2.2 Pre-screening and Informed Consent Visit

At the Pre-screening visit, prior to collecting any study information or performing any screening procedures, informed consent will be obtained from each subject. The nature of the research protocol, including potential risks and benefits, will be explained to potential subjects by study personnel. When all questions concerning the study have been answered, and the subject voluntarily decides to participate in the study, she will be asked to sign a consent form and will be provided with a copy of the signed form.

Pre-screening may be conducted up to 30 days prior to the randomization visit. The information collected, and activities carried out will include:

- Review and signing of the informed consent
- Demographic/Medical/Sexual/Gynecological history
- Inclusion/Exclusion criteria review
- Height and weight measurement to obtain BMI
- Concomitant therapy or medication assessment
- Distribute and train on 3-day bladder voiding diary
- Request that subject comes to the screening visit with a full bladder

4.2.3 Screening Visit

The Screening Visit will include the following:

- Inclusion/Exclusion criteria review
- Collection and scoring of 3-day bladder voiding diary
- Concomitant therapy and medication assessment
- Adverse event assessment
- Vital signs assessment
- Urine dipstick pregnancy test will be collected, and results recorded
- Urine bacterial dipstick test will be collected, and results recorded
- Physical exam, including pelvic exam

- The Investigator, or designee, should complete an evaluation by both visualization and palpation to exclude any women with morphological or anatomical distortion that may be suggestive of underlying hypertrophic tissue or fibrosis. Women who will be included in the clinical program must have normal perineal anatomy without distortion and no signs or symptoms of underlying abnormalities that would preclude them from the study.
- All pelvic support compartments (anterior, posterior and apical) will be assessed to rule out extraurethral incontinence from a fistula or ectopic ureter (ACOG 2015).
- Pelvic exam should include bimanual exam, including pelvic floor muscle examination with assessment of muscle strength and voluntary muscle relaxation. Subjects with motor and sensory differences, and pelvic organ prolapse must be excluded from the study (ACOG 2015).
- The pelvic exam, including a recto-vaginal exam, will be performed to confirm that the recto-vaginal septum is not too thin and therefore potentially unsuitable for the procedure.
- Investigators will be trained on appropriate measurement to determine if the recto-vaginal septum is thin as follows:
  - A disposable, flexible tape measure will be provided to sites to measure the distance between the 6 o'clock position of the vaginal introitus and the 12 o'clock position of the anus.
  - To avoid complications for subjects with a thin recto-vaginal septum, investigators should exclude any subject with a distance of < 2 cm between the vaginal introitus and the anus.

- Neurological exam
  - The investigator, or designee, should complete a neurologic examination that includes mental status as well as sensory and motor function of the perineum and both lower extremities to rule out neurologic conditions that may impact urinary incontinence (ACOG 2015).
- The Q-tip test
  - The test is performed by inserting a Q-Tip lubricated with anesthetic gel inserted into the urethra and up to the urethrovesical junction. The subject will be asked to cough and strain. If, upon straining, the angle between the Q-tip axis and the horizontal axis exceeds 35°, the test is considered positive (Bergman 1987).
- Bladder stress test (cough stress test)
  - The cough stress test can be performed during the pelvic exam in the supine position. However, if urine leakage is not observed in the supine position the test should be repeated with a full bladder (or at a minimum bladder volume of 300 mL).
  - The exam result is considered positive for SUI if the investigator visualizes fluid loss from the urethra (ACOG Committee 2015).
- Subjects will be asked to fill out the following questionnaires:
  - UDI-6
  - ICIQ-UI-SF
  - I-QOL
  - FSFI
- The 1-hour pad weight test
- The 24-hour pad weight test
- Blood specimen collection for laboratory assessments

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be scheduled for treatment within 14 days of their screening visit. A subject is considered to be enrolled when she is randomized.

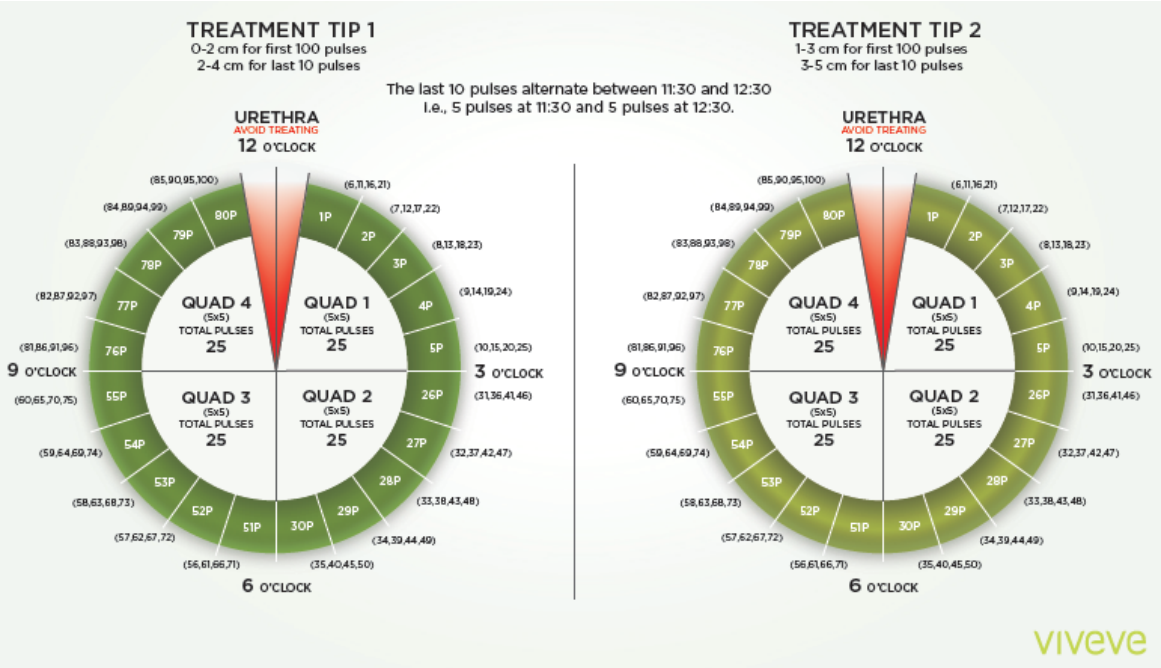
4.2.4 Randomization Visit

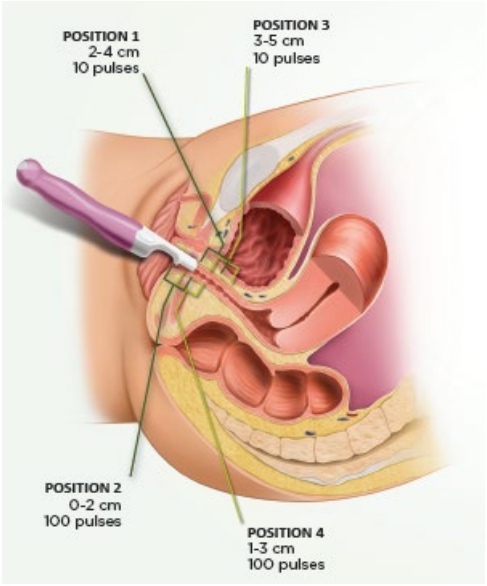
Subjects who meet all inclusion criteria and none of the exclusion criteria at screening will be randomized (stratified by study site) to their assigned treatment.

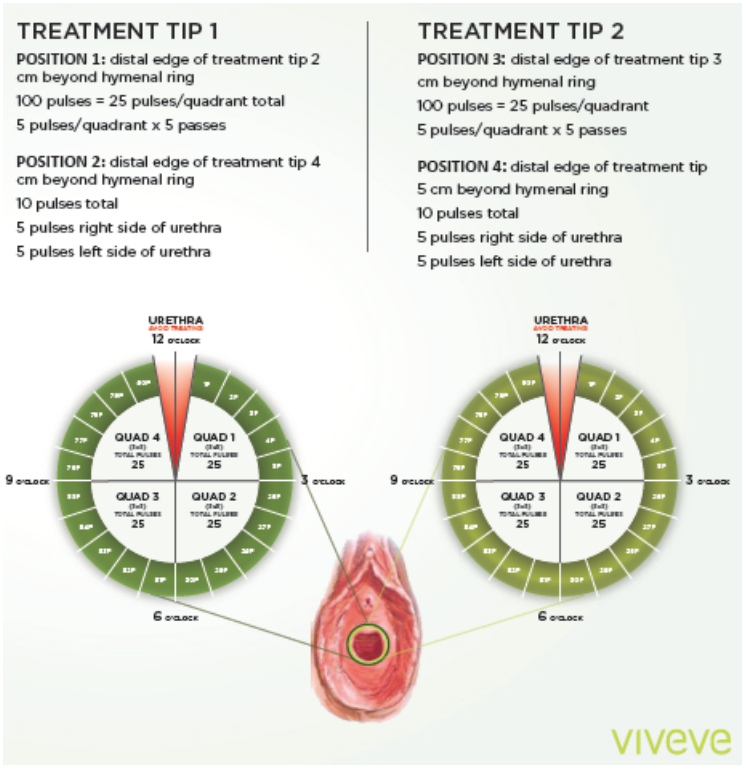
At the Randomization Visit, the following procedures will be performed:

- Inclusion/exclusion criteria review
- Urine pregnancy dipstick test will be collected and results recorded
- Urine bacterial dipstick test will be collected and results recorded
- Adverse event assessment
- Concomitant therapy and medication assessment

- Vital signs assessment
- The randomized subjects will be provided with the Viveve treatment, SUI protocol (by an M.D., D.O, NP, or PA-C) as follows:
    - The subject will be placed on an examination table in a dorsal lithotomy position.
    - A return pad will be attached to the subject and RF generator as per the User's Manual for the Viveve System.
    - The vagina, perineum, and peri-anal area will be cleansed using a sterile saline wipe supplied by Viveve.
    - Viveve coupling fluid will be applied to the entire treatment area and the treatment tip to ensure safe RF transfer and cooling effectiveness.
        - The coupling fluid acts as a conductor and skin protectant and is not a lubricant. No substitutes should be used for the coupling fluid and no lubricants should be used for the Viveve Procedure (e.g., K-Y jelly or surgi-gel may **NOT** be used). Additional coupling fluid will be reapplied throughout the treatment to ensure appropriate transfer of RF energy.
    - Subjects will be treated with either the active treatment tip (delivering 90 J/cm^2 of RF energy), or the sham treatment tip (delivering ≤1 J/cm^2).
    - A total of 220 pulses will be applied during the treatment procedure. The treatment area is divided into quadrants of the vaginal introitus with the area directly beneath the urethra excluded. One hundred and ten (110) pulses are programed on each treatment tip. Two (2) treatment tips per patient will used to administer the Viveve treatment, SUI protocol.
    - First treatment tip:
        - **Position 1:** *0-2 cm beyond hymenal ring (100 pulses)*
            - **Treatment tip placement beyond hymenal ring:** proximal edge 0 cm, distal edge 2 cm
            - The first set of 100 pulses is applied to the area just behind the hymenal ring using the quadrant approach. Each quadrant is treated with five consecutive passes of five locations of pulses for a total of 25 pulses per quadrant. The pulses are applied in a clockwise fashion with an overlap of ~0.5 cm. Once a quadrant is fully treated with 25 pulses the next quadrant is treated until all four quadrants are treated.
        - **Position 2:** *2-4 cm beyond hymenal ring (10 pulses)*
            - **Treatment tip placement beyond hymenal ring:** proximal edge 2 cm, distal edge 4 cm
            - The treatment tip will then be positioned with the proximal edge of the treatment tip window ~2 cm behind the hymenal ring. Five pulses are applied directly to the right of the urethra and five pulses are applied directly to the left of the urethra.
        - The first treatment tip will be removed from the handpiece and replaced by the second treatment tip.
    - Second treatment tip:
        - **Position 3:** *1-3 cm beyond hymenal ring (100 pulses), Position 3 is ~1 cm overlapped with Position 1*
            - **Treatment tip placement beyond hymenal ring:** proximal edge 1 cm, distal edge 3 cm (there should be ~1 cm overlap between Position 1 and Position 3)
            - The second set of 100 pulses is applied in a similar fashion to the first set but at ~1 cm deeper than Position 1. This provides an ~1 cm overlap of treatment pulses.
        - **Position 4:** 3-*5 cm beyond hymenal ring (10 pulses), Position 4 is ~1 cm overlapped with Position 2*
            - **Treatment tip placement beyond hymenal ring:** proximal edge 3 cm, distal edge 5 cm (there should be ~1 cm overlap between Position 2 and Position 4)
            - The fourth depth of treatment is applied in a similar fashion to the second pass but with the proximal edge of the treatment window positioned ~3 cm behind the hymenal ring.







The treatment is completed when a total of 220 pulses have been applied. Subjects receiving <200 pulses will be considered an incomplete treatment, and a protocol deviation will be generated. These subjects will be asked to continue in the study; however, for the formal analyses, these subjects will only be included in the safety analysis, not in the efficacy analysis.

In the event the subject experiences pain or discomfort, the procedure may be stopped temporarily, allowing the subject to relax and adjust.

- The only potential dose adjustment would be if a subject was unable to tolerate the Viveve Treatment, SUI protocol, and treatment had to be stopped prior to the completion of energy administration.

- That subject would still be followed for the remainder of the 6-month post-treatment period for safety evaluation.
- Additionally, an Adverse Event should be recorded.

The treating clinician should have a discussion with the subject about when to resume certain activities based on the subject's medical history and tolerability during the procedure.

The subject will be provided with and trained on the 3-day bladder voiding diary that will be collected at Visit 4 (Month 3).

4.2.5 Telephone Call (Day 10)

The investigator, or designee, will contact each subject via telephone 10 days (± 3 days) after the treatment procedure to assess each subject's health status. During the call, study site staff will assess adverse events and concomitant therapies and medications. The investigator, or designee, will request that the subject comes to Visit 4 with a full bladder.

4.2.6 Visit 4 (Month 3)

The following procedures will be carried out at Visit 4 (Month 3):

- Concomitant therapy and medications assessment
- Adverse events assessment
- Vital signs assessment
- Collection and scoring of 3-day bladder voiding diary
- 1-hr pad weight test
- Subjects will be asked to fill out the following questionnaires:
  - UDI-6
  - ICIQ-UI-SF
  - I-QOL
  - FSFI
- Distribute and re-train subject on 3-day bladder voiding diary
- Request that the subject comes to Visit 5 with a full bladder

4.2.7 Visit 5 (Month 6)

The following procedures will be carried out at Visit 5 (Month 6):

- Concomitant therapy and medications assessment
- Adverse events assessment
- Vital signs assessment
- Collection and scoring of 3-day bladder voiding diary
- Weight measurement
- Physical exam, including pelvic exam
- Urine pregnancy test will be collected and results recorded
- 1-hr pad weight test
- 24-hr pad weight test
- Subjects will be asked to fill out the following questionnaires:
  - UDI-6
  - ICIQ-UI-SF
  - I-QOL
  - FSFI

4.2.8 Adverse Events and Concomitant Therapies and Medications

4.2.8.1 Adverse Events

All adverse events (AEs) will be collected from the date the subject signs the Informed Consent Form. Subjects will be assessed for AEs at each study contact point or visit. Details of the AE, including date of onset/resolution, severity, resultant therapies/medications used to treat, and assessment of relatedness, by the Investigator, to the procedure will be collected from the investigative sites for each AE. Additionally, each AE will be assessed by the medical monitor for relatedness.

4.2.8.2 Concomitant Therapies/Interventions

All concomitant therapies and medications will be tracked for each subject from the date of screening until her exit from the study. Additionally, interventions that she undergoes (e.g., surgeries, additional therapies) throughout her participation in the study will be recorded.

4.2.9 Study Exit/Study Completion

Each subject will be exited from the study after completion of her 6-month follow-up visit (or earlier if the subject withdraws consent prior to the completion of the 6-month follow-up).

5 STUDY POPULATION

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be considered eligible to participate in the study.

5.1 SUBJECT INCLUSION CRITERIA

At the Screening Visit, a subject must meet the following criteria to participate in this study:

- I.1 Able to understand and has voluntarily signed and dated the informed consent form (ICF) prior to initiation of any screening or study-specific procedures.
- I.2 Willing to comply with study requirements and instructions.
- I.3 Documented diagnosis of stress urinary incontinence with urethral hypermobility as determined by Q-tip test. If there are mixed symptoms there must be a predominant stress component as determined by investigator or designee.
- I.4 Pre-menopausal females, ≥ 18 years of age. Premenopausal is defined as a woman who has had menstrual cycles over the previous 12 months. If menstrual cycles cannot be established, premenopausal can be defined as FSH levels <30.0 mIU/mL.
- I.5 Subjects with a BMI of ≤ 35 kg/m².
- I.6 Normal, or abnormal but not clinically significant (as determined by the investigator), physical, pelvic and neurologic exam at the Screening visit.
- I.7 Negative pregnancy test at Screening and Randomization visit.

Subject uses an acceptable form of birth control started ≥3 months prior to screening. Acceptable forms of birth control include: abstinence from heterosexual vaginal intercourse, hysterectomy, double tubal ligation, vasectomy, double barrier contraception, intrauterine device or hormonal contraceptive. Rhythm and withdrawal are not considered acceptable forms of contraception.

- I.8 Patient-reported or documented diagnosis of SUI symptoms for > 6 months.
- I.9 Positive Bladder Stress Test at Screening.
- I.10 1-hr pad weight at Baseline with a 5 to 50 g net increase from the pre-test pad weight.
- I.11 Subjects must complete 3 days in the 3-day voiding diary during the 3 consecutive days prior to the Screening Visit, AND subjects must report a minimum of 1 incontinence episode per day as determined in the 3-day voiding diary.

5.2 SUBJECT EXCLUSION CRITERIA

A subject will be excluded from participating in the study for any of the following reasons:

- E.1 Subjects who are currently breastfeeding or have discontinued breastfeeding fewer than 6 months prior to screening.
- E.2 Subjects who are pregnant or plan to become pregnant during the course of the study.
- E.3 Subjects who have undergone other stress urinary incontinence treatments, excluding behavioral modifications (e.g., Kegel exercises).
- E.4 Urinary Tract Infection (UTI) at the Screening or Randomization Visit based on the results of a urine dipstick. If the subject has a UTI at the Screening or Randomization Visit they may be treated with antibiotics, at the Investigator's discretion, and return within 7 days after UTI treatment completion. Subjects may return once, within 7 days after completion of UTI treatment.
- E.5 Abnormal, clinically significant laboratory results at the Screening Visit (as determined by the Investigator).
- E.6 History of any condition, illness, or surgery that might confound the results of urinary incontinence assessment, including, but not limited to:

a. Prominent (i.e. greater than Stage II as defined by the International Continence Society) pelvic organ prolapse (e.g., cystocele, rectocele) as determined by investigator.
b. Neurological disorders (e.g., multiple sclerosis, Parkinson's disease)
c. History of recurrent Urinary Tract Infections (UTI)
d. Vesicoureteral reflux
e. Bladder stones at time of enrollment or history of recurrent bladder stones
f. History of or current diagnosis of bladder tumors
g. Interstitial cystitis

E.7 Has any implantable electrical device [e.g., implantable pacemaker, automatic implantable cardioverter-defibrillator (AICD)].

E.8 Subjects with conditions that may pose unreasonable risks, including but not limited to:
a. Concurrent infection (e.g., active UTI, cystitis, urethritis)
b. Coagulation abnormalities
c. Abnormal kidney function
a. Uncontrolled diabetes

E.9 Medical or immunological condition, including, but not limited to:
a. Uncontrolled cardiovascular, respiratory, neoplastic, infectious, and/or endocrinological condition that could impact the subject's ability to complete the trial.
b. Untreated chronic abdominal/pelvic pain disorder [including, but not limited to, dyspareunia, vaginismus, endometriosis, vulvovaginal atrophy (VVA), genitourinary syndrome of menopause (GSM), irritable bowel syndrome, or Crohn's disease].
c. Untreated medical condition or medication that, in investigator's opinion, may interfere with adequate wound healing response (e.g., congenital connective tissue disease) or the subject's ability to complete the clinical trial requirements.
d. Untreated active malignancy or undergoing treatment (using chemotherapeutic agents, radiation therapy, and/or cytostatic medications) that may interfere with adequate wound healing response or the subject's ability to complete the trial.
e. Untreated acute or chronic vaginal or vulvar disorder including, but not limited to, vulvovaginal atrophy/GSM; pain, including provoked/generalized vulvodynia, vulvar vestibulitis, dysethetic vulvodynia, or vulvar dystrophy; current/chronic papulosquamous vulvar dermatoses (e.g., psoriasis, lichen planus, tinea cruris, lichen sclerosis, seborrheic dermatitis, contact/irritant dermatitis, lichen simplex, eczema); bullous dermatoses; systemic diseases with potential involvement of vulva; genital warts; past/current vaginal or vulvar radiotherapy or brachytherapy.
f. Active genital herpes.
g. Active genital/pelvic infection (e.g., gonorrhea, chlamydia).
h. Active yeast infection. If the subject has an active yeast infection at the Screening or Randomization Visit they may be treated with an antifungal, at the Investigator's discretion, and return within 7 days after yeast infection treatment completion. Subjects may return once, within 7 days after completion of yeast infection treatment.

E.10 Chronic use of anti-inflammatory drugs, including ibuprofen, aspirin, and steroids (excluding aspirin that is taken for cardiovascular prophylaxis).

E.11 Taking any new medication, including herbal supplements and those taken in teas (< 1 month) that affects urination, or change in the dosage of any medication that affects urination within 1 month of Screening. Dosage should not change for the remainder of the study unless medically necessary.

E.12 Subjects who have started or changed dose of local vaginal hormones <6 weeks before Screening.

E.13 Subjects who have started pelvic floor physical therapy within the last 3 months.

E.14 Undergone previous elective surgical or non-invasive procedure(s) in the vaginal canal (including the Viveve Treatment or any other genital radiofrequency treatment; injectable bulking agent, cosmetic, laser, surgical, and/or genital enhancement procedure). Including previous dilation and cuterage within 12 months of the subject's Pre-Screening Visit.

E.15 Not sterilized (or partner not sterilized/infertile), ***or*** not willing to use an acceptable method of birth control started at least 3 months prior to screening and to be continued throughout the duration of the study [e.g., barrier method, intrauterine device, hormonal therapy (subcutaneous, injectable, or

oral contraceptive)]. Rhythm and withdrawal are not considered acceptable forms of contraception.

E.16 Participated in another clinical study (drug or device) within 30 days of screening, or is not willing to abstain from participating in other clinical studies for duration oftrial. If participation was in an investigational drug study (i.e., receiving or has received investigational product), subject must wait 30 days, or 5 times the investigational drug half-life, whichever is longer, prior to Screening.

E.17 Subject is employed by Viveve or participating investigative sites.

5.3 SUBJECT WITHDRAWAL CRITERIA

A subject may be withdrawn if any of the following occur during the study:

W.1 Subject requests withdrawal from the study

W.2 Subject refuses to comply with required study procedures

W.3 Use of any additional experimental drug or device, or participation in another clinical trial

W.4 The study sponsor terminates the study site or the study

Subject participation in this trial is voluntary. If a subject decides to participate, she is free to withdraw her consent and to discontinue participation in the trial at any time and for any reason without prejudice to her or effect on her medical care by the physician or the institution. Subjects who withdraw consent after enrolling will be followed until time of withdrawal. In all cases of withdrawal, the reasons for withdrawal must be recorded. If more than one reason is cited for termination, study personnel should identify the most significant reason. Subjects who are withdrawn from the study will not be replaced.

At the discretion of the Principal Investigator or trial Sponsor, Subjects may be removed from this trial due to unanticipated circumstances. A Study Exit Form will be completed for all subjects screened, randomized and treated in the study to document the final disposition of the subjects regardless of whether the subject screen-failed and/or withdrew early or not, as well as the reason(s) the subject was excluded or withdrew from the study, if available.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject and document subject outcome. Subjects will only be considered lost to follow-up if study personnel are unable to communicate with the subject by three separate attempts; attempts may be made via email, phone/text, and/or certified letter. A subject who fails to keep appointments or who refuses to provide any end-of-study information will be documented as lost to follow-up. Subjects who withdraw from the study prior to being randomized will be replaced. Any subject who withdraws from the study after randomization will not be replaced.

6 CONCOMITANT MEDICATIONS/THERAPIES

Subjects will be queried regarding concomitant use of medications throughout their participation in the study until the final follow-up visit. All concomitant medication use (both prescription and over-the-counter, including herbal medications and nutritional supplements) should be reported during the study and recorded on the eCRF.

6.1 ALLOWED OVER-THE-COUNTER PRODUCTS AND MEDICATIONS

The following medications will be allowed during the study:

- Vaginal moisturizers and lubricants.
- Pharmacologic agents that may impact urinary incontinence (e.g. oral estrogens, sedative-hypnotics, antidepressants, ACE inhibitors, nonsteroidal anti-inflammatory drugs and calcium channel blockers) are allowed during the study as long as the subject has been on a stable dose for ≥ 1 month prior to the Screening Visit and remains on a stable dose throughout study participation.
- Prescription changes for medications that do not affect urination.
- Oral or implantable birth control.
- Local vaginal hormones are allowed if the subject has been on them for ≥6 weeks before Screening and remains on a stable dose throughout study participation.

6.2 PROHIBITED MEDICATIONS/THERAPIES

Prohibited medications/treatments throughout this study include:

- Chronic use of anti-inflammatory drugs, including ibuprofen, aspirin, and steroids (excluding aspirin that is taken for cardiovascular prophylaxis).

- Taking any new medication, including herbal supplements and those taken in teas (< 1 month) that affects urination, or change in the dosage of any medication that affects urination within 1 month of Screening. Dosage should not change for the remainder of the study unless medically necessary.
- The addition of pelvic floor strengthening interventions. Subjects who have implemented pelvic floor strengthening interventions may be included if there have been no changes within the 3 months prior to screening.

7 LIFESTYLE GUIDELINES

7.1 CONTRACEPTION

Acceptable forms of birth control include: abstinence from heterosexual vaginal intercourse, hysterectomy, double tubal ligation, vasectomy, double barrier contraception, intrauterine device or hormonal contraceptive. Rhythm and withdrawal are not considered acceptable forms of contraception.

7.2 DIETARY RESTRICTIONS

Subjects should refrain from drinking more than 2 cups of caffeinated beverages per day on days of pad weight assessment and during the voiding diary data collection.

7.3 USE OF ALCOHOL, TOBACCO AND DRUGS

Subjects are required to abstain from excessive alcohol consumption the night prior to study visits and during the voiding diary collection period.

The abuse of illicit drugs or alcohol during the study is prohibited.

7.4 RESTRICTIONS ON PHYSICAL ACTIVITY

There are no restrictions on physical activity during the study; however, activity should be noted on the voiding diary.

8 INVESTIGATIONAL PRODUCT (IP) MATERIALS AND MANAGEMENT

8.1 TREATMENT GROUPS

There are two treatment groups in this study:

- Active Treatment Group: The active treatment group will receive a treatment dose of 90 J/cm^2.
- Sham Treatment Group: The sham treatment group will receive a sub-treatment dose of ≤1 J/cm^2.

The two tips look and behave exactly the same from the subjects and investigators (or designee) perspective. All other study procedures for the two treatment groups will remain the same.

8.2 DESCRIPTION OF INVESTIGATIONAL PRODUCT (IP)

The Viveve system is a monopolar radiofrequency system that uses surface cooling and radiofrequency (RF) energy delivery to provide a non-surgical and minimally-invasive approach to generate heat within the submucosal layers of vaginal tissue while keeping the surface cool. During the Viveve treatment, coolant is delivered to the membrane of the Viveve treatment tip. The RF technology creates a reverse thermal gradient, which heats the deeper tissues at a higher temperature while the coolant protects the surface epithelium.

The Viveve Treatment System consists of the following components:

- RF generator to provide the energy, which incorporates the Cooling Module
- Handpiece that couples the cooling and energy to the tissue through the treatment tip
- Footswitch
- Return pad
- Disposable treatment tip

8.3 INVESTIGATIONAL PRODUCT PACKAGING AND LABELING

Treatment tips will be pre-packaged into subject treatment kits and labeled with randomly assigned kit numbers for the purpose of blinding and device accountability. All investigational products will be labeled with the study protocol number, the Sponsor's contact information, and include the following statement: "CAUTION – Investigational Device. Limited by Federal (or United States) Law to Investigational Use. Keep out of reach of children." Additionally, the name and place of business of Viveve, Inc., the quantity of contents, and a description

of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions will be included on IP packaging.

8.4 STORAGE

Investigational product will be kept in a secure location (i.e., limited access area or in a locked cabinet under conditions congruent with the Technical User's Manual) and operated per the Technical User's Manual that is provided with the system. The Principal Investigator or qualified designee agrees not to dispense investigational product from, nor store them at, any site other than the study sites described on the Form FDA 1572.

8.5 INVESTIGATIONAL PRODUCT DISPENSATION

The investigational product shall only be administered to subjects by the Principal Investigator (or designee). Study personnel shall not supply the investigational product to any person not authorized to receive it. f

8.5.1 Stratification and Randomization

Subjects will be randomized in a 2:1 (Active: Sham) ratio. Randomization will be stratified by study site, with a maximum of 21 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.

8.5.2 Blinding/Unblinding

To maintain blinding, the randomization schedule will be generated by a statistician who is not otherwise assigned to work on this study. The randomization code will be stored in a secure location.

The details of maintaining the blind for the study will be captured in the study blinding plan.

The site must always inform Viveve as soon as possible regarding any emergency unblinding of the subject that occurs, and whenever possible, prior to unblinding. If the need for emergency unblinding should arise, the following should occur:

- Only one site member should be designated to know which treatment group the subject was randomized to. The site member should be someone, such as an investigator on the study, who can fully discuss any potential medical concerns with the subject.
- The designated site member who breaks the blind should NOT disclose to anyone else besides the subject (including other site members or any Viveve staff) any reference to which treatment group the subject was assigned.
- The designated site member will document the date, time, and nature of the breaking of the blind in a Note to File (NTF). This NTF will include reference to the subject for whom the blind was broken and detail as fully as possible all information received from and communicated to the subject, but will NOT contain any reference to the treatment assignment. The NTF will be placed in the site regulatory files and a copy will be sent to Viveve.

8.5.3 Dose Adjustments

There will not be any pre-planned dose adjustments for this study. The only potential dose adjustment would be if a subject was unable to tolerate the Viveve Procedure and treatment had to be stopped prior to the completion of energy administration. That subject would still be followed for the remainder of the 6-month post-treatment period.

8.6 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the clinical investigator to ensure that all investigational product received at the site will be inventoried and accounted for throughout the study. The site will record all information on the Device Accountability Log (DAL) maintained in the Site Regulatory Binder. The devices allocated for investigational site use will be recorded in the DAL upon delivery to the study site and will be stored in a secured area until use. No devices will be shipped until IRB/EC approvals to begin the study are received by the Sponsor. Each site will be responsible for tracking the receipt and disposition of all study devices.

The DAL will be updated as each device is used, opened, or returned. The DAL will contain delivery dates of devices to the site, dates used, and returned-to-sponsor dates; the reason for the return; serial numbers of devices

delivered to the site; and the subject ID for all used devices. All unused study devices must be returned to the Sponsor.

Sites should retain the treatment tip boxes following each procedure, and the subject ID and procedure date should be written on the box. During Interim Monitoring Visits (IMVs), monitors will review the tip boxes and compare the lot number, subject ID, kit ID, and date used against the DAL and Procedure CRF to ensure that tip allocation has been appropriately captured. The boxes may be discarded at the end of the IMVs after the monitor has reviewed them.

8.7 INVESTIGATIONAL PRODUCT HANDLING AND DISPOSAL

The Viveve or CRO-assigned study monitors will assist the study site staff in arranging for return of used and unused study supplies.

8.7.1 Disposal of Empty Cryogen Canisters

Sites will be instructed to dispose of empty cryogen containers using an environmental service for disposal and recycling of hazardous material.

8.7.2 Disposal of Used Investigational Product Accessories

All other consumable components of the Viveve System (e.g., return pad, treatment tip, and coupling fluid) are labeled disposable and should be disposed of with standard medical waste following their use. Treatment tips are packaged sterile, do not require cleaning prior to use, and must not be reused. Each bottle of Viveve coupling fluid is for single-subject use only and should not be reused.

9 ASSESSMENT OF SAFETY

9.1 SAFETY PARAMETERS

Safety will be assessed by adverse event (AE) reporting, vital signs, and Screening visit laboratory tests during study participation.

9.1.1 Safety Definitions

Adverse Event (AE): Per ISO 14155, an AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or the comparator (in this study the sham) and events related to the procedure involved. For users or other persons, the definition is restricted to events related to the investigational medical device only.

Adverse Device Effect (ADE): An ADE is an AE related to the use of an investigational medical device, including AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuses of the investigational medical device.

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance including malfunctions, use errors, and inadequate labelling.

Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan.

Serious Adverse Event (SAE): An SAE is an AE that:

- Led to a death,
- Led to a serious deterioration in the health of the subject that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect

Note: A planned hospitalization for pre-existing condition or a procedure required by the protocol without a serious deterioration in health is not considered to be a SAE.

Serious Adverse Device Effect (SADE): An ADE that resulted in any of the consequences/characteristics of a SAE.

Treatment-Emergent Adverse Event (TEAE): An AE that began or worsened after the treatment procedure was initiated. Safety summaries will focus on this population of subjects.

Unanticipated Serious Adverse Device Effect (USADE): SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report or investigator brochure.

9.1.2 Severity

The severity of every AE is assessed based on the following Common Terminology Criteria for Adverse Events (CTCAE), Version 4.3, Published June 14, 2010, U.S. Department of Health and Human Services. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1:** Mild; asymptomatic, or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[3].
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[4].
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

9.1.3 Relationship to Investigational Device

The relationship of an AE to the use of the investigational device will be determined using the following classifications:

- **Related AE:** the type and timing of the AE indicate that the AE is related to use of the investigational device. (Causal relationship is certain.)
- **Possibly Related AE:** the type and timing of the AE suggests that the AE is possibly related to use of the investigational device, although other causes of the AE are more likely. (Causal relationship at least reasonably possible, i.e., relationship can't be ruled out.)
- **Unrelated AE:** the type and timing of the AE indicate that the AE is clearly unrelated to use of the investigational device (Causal relationship can be ruled out.)

In order to provide a consistent assessment of AEs across all study sites, the relationship will be determined by the Principal Investigator at each site as well as the Medical Monitor for the study.

9.1.4 Anticipated vs. Unanticipated

For the purposes of this study, an anticipated AE will be defined as the following:

- Pain or discomfort during procedure related to warmth/heat and/or cold in the designated treated area
- Transient vulvar or vaginal inflammation and/or swelling
- Transient vaginal discharge
- Transient vulvar and/or vaginal erythema/redness
- Transient pelvic pain or pelvic discomfort
- Transient allergic reaction or hypersensitivity in the vulvar and/or vaginal region to any component of the device
- Altered sensation that may be focal or transient, manifested as numbness or tingling in the vulvar and/or vaginal pelvic region
- Excessive vaginal tightness resulting in interference with sexual activity
- Transient damage to the urinary bladder and/or urethra

9.1.5 Outcome Assessment After an AE

An outcome assessment of a subject's status after an adverse event will also be carried out. This assessment will include the following options:

- Not Recovered or Not Resolved,

[3] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[4] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- Recovering or Resolving,
- Recovered or Resolved with Sequelae,
- Recovered or Resolved,
- Death Related to Adverse Event, or
- Unknown.

9.1.6 Adverse Event Classification and Documentation

A brief, free-text description of each AE will be provided by the site in the study database. Events will be coded using definitions in the Medical Dictionary for Regulatory Activities (MedDRA), a clinically-validated international medical terminology dictionary and thesaurus. This medical dictionary is also the AE classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The most recent English language version of MedDRA (Version 19.0, September 2016; or most current version during the conduct of the study) will be used to code each AE with its appropriate Preferred Term (PT), ultimately linking with its associated High-Level Term (HLT), High-Level Group Term (HLGT), and System Organ Class (SOC). Standard coding rules ensure consistent and accurate coding and will be applied in the study database. Auto-coding within the study database may assign the most appropriate pre-determined MedDRA PT of common or anticipated events in the patient population (e.g., urinary tract infection, common cold). If a term is not auto-coded, data management personnel may issue a query directly to the site for clarification; manual coding may be required for some events. Data management and monitoring personnel will review AE entries into the database and query site staff on clarification needed to properly classify each event. In the medical monitor's systematic review of AEs, proper AE and MedDRA term classification will be ensured. If discrepancies are found within any stage of the AE review process, queries will be issued to the site for clarification or correction.

9.2 SAFETY REPORTING

All adverse events (AEs, ADEs, SAEs, SADEs) and device deficiencies will be recorded on the Case Report Form (CRF) from the time the subject signs the Informed Consent Form until the subject is exited from the clinical investigation.

When required by national or local regulations, the Principal Investigator shall also notify the Institutional Review Board/Ethics Committee (IRB/EC) and Regulatory Agencies of all reportable events according to national regulations in acceptable timely conditions, and may also be requested by the IRB/EC to provide annual reports.

9.2.1 Adverse Event (AE) Reporting

An AE is any untoward medical occurrence in a subject participating in a clinical study and which does not necessarily have to have a causal relationship with this treatment or clinical study. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include illnesses, signs, or symptoms, independent of causality, that appear or worsen during the course of the study. Whenever the investigator is confident of the diagnosis, he/she should group together as a single illness all related signs, symptoms, and abnormal laboratory test results (e.g., cough, rhinitis, and sneezing should ordinarily be reported as "upper respiratory tract infection").

Procedures, such as surgery, should not be reported as AEs or SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of AE/SAE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy noted under Comments. In addition, an elective surgery (and any related hospitalization) whether or not there is an existing medical condition should not be reported as an AE (e.g., breast augmentation).

The AE reporting period for this study begins at the time informed consent is signed and ends at the subject's study exit. A pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical form) should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period.
All AEs will be recorded on the AE CRF.

For subjects experiencing AEs that result in study treatment discontinuation, or those experiencing AEs that are present at the end of their participation in the study, the site will attempt to follow-up with the subject until the AE is resolved, attributed to a cause other than study treatment administration, or assessed as chronic or stable.

9.2.2 Serious Adverse Event (SAE) Reporting

Medical and scientific judgment should be exercised in deciding whether an important medical event is serious. Although the event may not be immediately life threatening, fatal, or result in hospitalization, it should be considered serious when it jeopardizes the subject, or requires an intervention to prevent a serious outcome as defined above. Examples of serious medically important events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. The term "inpatient hospitalization" in the definition of "serious" refers to an event in which the subject was admitted to the hospital for one or more days, even if release on the same day; or an emergency room visit, which results in admission to the hospital. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes criteria (e.g., important medical event).

The SAE reporting period begins at the time informed consent is signed and ends at the subject's study exit. SAEs that are considered at least possibly related to the investigational product, or that occur in a pregnancy that began while the subject was using the investigational product, can be reported at any time.

AEs classified as "serious" require expeditious handling and reporting to Viveve to comply with regulatory requirements. Upon occurrence of an SAE as defined above, the investigator must immediately notify Viveve regardless of the relationship of the SAE to the study treatment. The investigator must complete and return the Viveve SAE form within 24 hours. All SAE reports will be filed with regulatory bodies by Viveve according to established regulatory guidelines.

All AEs that are 1) serious, 2) unexpected, and 3) definitely related, possibly related, or of undetermined relationship to the study treatment, will be shared with all investigators. These events must be reported to the Institutional Review Board (IRB)/Ethics Committee (EC) responsible for the study.

The study site will do their best to follow SAEs through resolution or until the investigator attributes the SAEs to a cause other than the investigational product or assesses them as chronic or stable. Follow-up SAE reports should adhere to the same procedures and timelines as initial reports. In addition, any SAE that occurs subsequent to the reporting period that the investigator assesses as possibly related to the investigational product should also be considered for follow-up.

9.2.2.1 SAE Contacts

For this study, SAE contacts are:

SAE Fax Number:	1-408-716-2699
Email:	ClinicalAffairs@viveve.com
Medical Monitor:	Roger Dmochowski, MD
Clinical Project Lead:	Marisol Clemens
SAE Mailing Address:	345 Inverness Drive South, SuiteB-250, Englewood, Colorado 80112

9.3 PREGNANCY REPORTING (WHEN APPLICABLE)

During the course of the study, subjects will be instructed to contact the study site immediately if they suspect they might be pregnant. The Investigator should notify Viveve of any pregnancy within 72 hours, and include the following information in the notification:

- Initial pregnancy notification
- Ultrasound (preferably transvaginal) between 6-12 weeks gestation when possible
- Quantitative βHCG
- Follow-up pregnancy notification as new information becomes available
- Other appropriate follow-up procedures should be considered if indicated

Protocol-required procedures for study discontinuation should be performed unless contraindicated by pregnancy. The Pregnancy Reporting CRF should be completed for any subject who becomes pregnant during her participation in the study. Additionally, the study site will make every reasonable effort to follow, until delivery or termination of the pregnancy, subjects who become pregnant during the course of the study. In the case of induced or spontaneous abortion, the aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

Pregnant subjects will be followed until pregnancy resolution (delivery or otherwise). Adverse events will be collected throughout the subject's participation in the trial.

Pregnancies will NOT be routinely reported as an AE or SAE. However, any pregnancy-related events that meet the definition for an AE or SAE should be reported accordingly. Pregnancy outcomes that are classified as SAEs are:

- Spontaneous abortion, including miscarriage and missed abortion
- Congenital anomaly/birth defect
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs
- Any infant death after 1 month that the Investigator, or qualified designee, assesses as possibly related to the *in utero* exposure to the investigational device

10 STATISTICS

10.1 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint for this study is the CFB to 6 months post-treatment in the 1-hr pad weight. A clinically meaningful reduction in the 1-hr pad weight is >50% (target reduction in the active treatment group); a sham (placebo) effect of a 30% reduction is anticipated in the sham group. The sample size for this study will be ~99 randomized subjects, in a 2:1 ratio with ~66 randomized to the active treatment group and ~33 to the sham treatment group. Assumptions include a 2-sided t-test at the 5% level of significance, and a CFB to 6 months post-treatment of >50% in the active group and of 30% in the sham group. Thus, 99 total randomized subjects, in a 2:1 ratio to active: sham treatment groups, will provide approximately 90% power if the common standard deviation in CFB is as large as 28, and will provide approximately 80% power if the common standard deviation in CFB is as large as 33.

10.2 ANALYSIS POPULATIONS

The Full Analysis Set (FAS) includes all randomized subjects and is also known as the intention-to-treat (ITT) population. The FAS will be used for all efficacy analyses.

The Modified ITT (mITT) includes all randomized subjects who are treated and completes the study. The mITT will be used for confirmatory analysis of efficacy endpoints.

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.

10.3 DISPOSITION AND BASELINE CHARACTERISTICS

Subject disposition will be summarized by treatment group. Baseline characteristics and subject demographics will also be summarized by treatment group.

10.4 INVESTIGATIONAL PRODUCT ADMINISTRATION

Investigational product administration will be summarized 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.

10.5 EFFICACY ANALYSIS

10.5.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint for this study is CFB to 6 months post-treatment in 1-hr pad weight. Analysis of covariance (ANCOVA) with treatment group, study site and Baseline 1-hr pad weight as independent variables, will be used to analyze the primary efficacy endpoint. The FAS will be used, with subjects included in their randomized treatment group regardless of the treatment they actually received. The Baseline 1-hr pad weight is defined as the 1-hr pad weight at the Screening Visit. Missing values for the 6 month 1-hr pad weight will be imputed using a multiple imputation method that assumes the data are missing at random. Imputed datasets will be analyzed using an ANCOVA model with treatment group, study site, and Baseline 1-hr pad weight as independent variables.

Approximately 100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. The adjusted mean change and standard error (SE) will be provided for both treatment groups, along with the difference in adjusted mean change, its 95% confidence interval (CI) and associated p-value. The adjusted mean changes for each study site will also be provided.

A confirmatory analysis of the primary efficacy endpoint will be performed using the FAS and same ANCOVA as the primary analysis, but using only observed case data (no imputation will be performed for missing data). A second confirmatory analysis of the primary efficacy endpoint will be performed using the mITT, using only observed case data.

10.5.2 Exploratory Efficacy Endpoint Analyses

Exploratory efficacy endpoints include CFB to 3 months post-treatment in 1-hr pad weight; CFB to 6 months post-treatment in 24-hr pad weight; CFB to 3 and 6 months post-treatment in 3-day bladder voiding diary; CFB to 3 and 6 months post-treatment in UDI-6, ICIQ-UI-SF and I-QOL; and CFB to 3 and 6 months post-treatment in FSFI total score (in subjects with FSFI total score ≤26.5 at Baseline). For the exploratory efficacy endpoints, a significance level of 0.05 will be used; given the large number of endpoints, the p-values for those endpoints will be considered descriptive.

Each of the continuous endpoints will be analyzed using ANCOVA with treatment group, study site, and the relevant Baseline as independent factors. The FAS population (for the FSFI analyses, the FAS subjects with a Baseline FSFI total score ≤26.5) will be used for each analysis, with subjects included in their randomized treatment group regardless of the treatment they actually received. Baseline for each endpoint is the relevant value from the Screening Visit. For each of the exploratory endpoints, only observed case data will be used (no imputation will be performed for missing data). Output from each ANCOVA will include the adjusted mean change and SE for the active treatment and sham groups, as well as the difference in adjusted mean change, its 95% CI, and p-value. The adjusted mean changes for each study site will also be provided for each ANCOVA.

Confirmatory analyses will be performed for each of the exploratory endpoints, using the mITT with observed case data only (no imputation for missing data will be performed).

For all of the continuous endpoints (primary and exploratory), the assumption of normality will be assessed. If any endpoint at any timepoint is found to be not normally distributed, the data will either be transformed to make it normal or a nonparametric test will be used instead of the planned ANCOVA.

10.6 Safety and Tolerability Analysis

No statistical analyses will be performed on any of the safety data in this study. The SP will be used, with subjects included in the treatment group they actually received regardless of their randomized treatment group. The summarization of AEs will include treatment-emergent AEs (TEAEs, defined as AEs that begin or worsen after the Viveve procedure [sham or active] is initiated). TEAEs and serious AEs (SAEs) will be summarized by system organ class (SOC), severity, and relationship to study treatment for each treatment group. Deaths and withdrawals from the study due to AEs will each be summarized by treatment group. All AEs (TEAE and non-TEAE) will be provided in a listing.

10.7 Mid-study Analysis

A prospective analysis will be performed after ~80 subjects have completed their 3-month visit. For this analysis, the CFB to 3 months post-treatment in 1 hr pad weight will be analyzed. The analysis of this data will allow for planning of future studies for this indication. Since the efficacy endpoint that will be analyzed is exploratory (not the primary efficacy endpoint), no statistical adjustment is needed for the final analysis ($\alpha = 0.05$) of the primary efficacy endpoint. Viveve team members will be unblinded to group treatment summary data during this analysis performed during the study; however, these Viveve team members will be blinded to individual subject treatment group until final database lock at the end of the study. Investigators, study site personnel and subjects will be blinded until final database lock at the end of the study.

When the last subject has completed her 6-month visit, the final database lock will occur for all data for all subjects. At this time, the database will be fully unblinded and all protocol-defined analyses and summaries will occur.

10.8 MULTIPLICITY

In this study, the overall Type 1 error is controlled at 0.05 two-sided for the primary efficacy endpoint. There will be a mid-study analysis, performed on one of the exploratory efficacy endpoints. Since this analysis does not include the primary efficacy endpoint, no statistical adjustment will be made to the final analysis of the primary efficacy endpoint (it will remain 0.05 two-sided for the final analysis). The final analysis of the primary efficacy endpoint will occur when the last subject has completed her 6-month visit.

The exploratory 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 exploratory efficacy endpoints will be considered descriptive.

11 STUDY ADMINISTRATION

11.1 GOOD DOCUMENTATION PRACTICES

If any member of the study staff makes an error on any required study document (e.g., source documents, protocol signature page, Delegation of Authority Log, etc.), he/she should draw a single line through the error and write the corrected response above it. Adjacent to any such change, the study staff member should write his/her initials and the current date. Study staff members should not obscure or "white-out" an incorrect entry. If corrections are made after review and signature by the Investigator, the Investigator will be made aware of the changes and his/her awareness will be documented by initialing and dating the changes.

11.2 ADHERENCE TO THE PROTOCOL

Except for a change that is intended to eliminate an immediate hazard to subjects, the approved protocol shall be conducted as described. Any protocol deviation or violation must be documented. Any protocol-related issue that poses an immediate or significant hazard to subjects must be reported to Viveve immediately. Protocol deviations will be defined by the Viveve SOP, CLN-015 Protocol Deviation SOP.

All protocol modifications and amendments must be approved and prepared by Viveve. If the modification is an Administrative Change Letter, the Investigator must submit it to the IRB/EC(s) for their information. If the modification is an amendment, the Investigator will sign it. The Investigator must submit the Amendment to the IRB/EC(s) for review and approval or favorable opinion prior to implementation. Documentation of approval, signed by the chairperson or designee of the IRB/EC(s), must be sent to Viveve.

If an amendment substantially alters the study design or increases the potential risk to the subject:

- The consent form must be reviewed and submitted to the IRB/EC(s) for review and approval or favorable opinion;
- The revised form must be used to obtain consent from subjects currently randomized into the study if they are affected by the amendment; and
- The new form must be used to obtain consent from new subjects prior to screening.

The Principal Investigator may not implement any deviation or change to the protocol without the agreement of Viveve and prior review/favorable opinion of the IRB/EC(s), except where necessary to eliminate an immediate hazard to a subject or when the change involves only a logistical or administrative aspect of the study (e.g., change of telephone numbers, ancillary personnel). Any deviation from the protocol must be documented and explained in written communication to Viveve and, where applicable, to the IRB/EC(s). Where applicable, the protocol designates study responsibilities to the “Investigator”. Those tasks may be performed by the Principal Investigator or qualified designee.

11.3 REGULATORY COMPLIANCE

This clinical study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), and the applicable regulatory requirements. It is the responsibility of each participating Principal Investigator to conduct this study in conformance with all national/local standards, regulations, and guidelines, and to ensure that prior to undergoing any study-related procedures, all screened subjects have voluntarily and willingly signed and received a copy of the Informed Consent Form and have been given the opportunity to ask any questions regarding the trial.

11.4 CLINICAL INVESTIGATION SITE SELECTION AND TRAINING

Only qualified clinicians will be invited to participate as Principal Investigators in this study. Interested Principal Investigators will be considered on the basis of their existing or referred subject population, sufficient facility, and

staff capable of conducting the study, and their experience in research. The Principal Investigator and all relevant study site personnel will undergo training by Viveve personnel in the use of the investigational device and other study-specific procedures prior to performance of the trial operative procedures.

11.5 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All representatives of Viveve with direct access to subjects' medical records will take reasonable precautions within the constraints of applicable regulatory requirements to maintain the confidentiality of the subjects' identity.

11.5.1 Study Monitoring

Representatives of Viveve must be allowed to visit all study site locations to review study records and compare them with source documents directly, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

Appropriate monitoring and fulfillment of the applicable requirements in 21 CFR 812.46, ICH E6(R2):2016 and ISO 14155:2011 are the responsibility of the study sponsor. Viveve, Inc. will appoint adequately trained and experienced personnel, either Viveve employees or a Clinical Research Organization (CRO), to conduct monitoring activities and ensure the study is conducted in accordance with the study protocol, all applicable laws and regulations, associated IRBs, and the research agreement. Monitors will ensure the maintenance of adequate and accurate clinical records. CRFs will be reviewed against source documents as appropriate, for which purpose the clinical monitor will require access to subject medical records and other primary source documentation. Procedures for monitoring are detailed in the "Clinical Monitoring Plan" for this study protocol.

Prior to study implementation, both the screening and treatment initiation visits will be conducted at each center. Approval to begin screening is pending receipt of the following documents:

- Signed original Clinical Trial Agreement
- Signed all approved protocols
- IRB/EC-approved version of the Informed Consent document
- IRB/EC approval letter
- Documentation that the Principal Investigator did not participate in the IRB approval process (e.g., IRB/EC Roster, Assurance Number, or Statement of Compliance)
- Training documentation
- Curriculum vitae for the Principal Investigator and key study site personnel
- Financial disclosures

The Sponsor, or designee, will determine frequency and timing of periodic monitoring visits for each center based on screening and/or randomization rate, volume, study compliance, and findings from previous visits. Each center that is screening subjects will be monitored at least every 6 months. During a monitoring visit, the monitor may evaluate the center's compliance with regulatory and protocol requirements, verify data recorded on eCRFs to available source documents, verify investigational device disposition and the device tracking log, and sign a monitoring visit log.

When necessary, queries will be raised using the EDC system and answered by the trained study staff providing the reason for change. Full data traceability is assured by the EDC system. New and previous findings and recommended corrective and preventative actions, if they exist, will be communicated with the study staff during the visit, and will also be addressed in a final letter that will be sent to the Principal Investigator after the visit.

The sponsor will be responsible for overseeing monitoring activities, as specified in the Monitoring Plan. All Principal Investigators and relevant site personnel must be available to Sponsor personnel during Sponsor monitoring visits.

The Sponsor may use centralized monitoring during this study. Centralized monitoring is a remote evaluation carried out by the Sponsor (designee) at a location other than the site(s) at which the clinical investigation is being conducted. Centralized monitoring can be used to achieve the following:

- Conduct activities such as: standard checks of range, consistency, and completeness of data and checks for unusual distribution of data, such as too little variance

- Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring)
- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at the site
- Verify source data remotely, provided that both source data and CRFs can be accessed remotely
- Conduct aggregate statistical analyses of study data to identify subject data that are outliers relative to others and to evaluate individual subject data for plausibility and completeness
- Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify early corrective actions needed for characteristics correlated with poor performance or noncompliance

11.5.2 Audits and Inspections

Viveve auditors and government inspectors may evaluate the study and must be allowed access to CRFs, source documents, and other study files. Viveve audit reports will be kept confidential.

The Investigator should promptly notify Viveve of any inspections scheduled by any regulatory authorities, and promptly forward copies of inspection reports.

11.6 Study Closure/Termination

The study may be stopped, if in the opinion of Viveve, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Principal Investigator by Viveve. When terminating the study, Viveve and the Principal Investigator will ensure that adequate consideration is given to the protection of the study subjects' interests. Examples of sufficient reasonable cause include:

- Failure to screen subjects,
- Protocol violations,
- Inaccurate or incomplete data collection or recording,
- Unsafe or unethical practices, and
- Any subject safety considerations.

The Principal Investigator is then required to notify the Institutional Review Board/Ethics Committee of the trial termination and to submit to Sponsor in a timely manner all requested Subject and trial data.
Study closure visits will be conducted at all clinical sites in order to review record retention requirements, device disposition requirements, etc., with site personnel. A trial monitor will ensure that all trial files have been appropriately completed and all data have been entered into the EDC system and all queries are resolved. The trial files will then be inventoried and placed in an archiving box for their conservation. Return of investigational devices and related equipment to the Sponsor will be arranged and disposal of any other study supply will be performed. Appropriate inventories will be completed and closed.

11.7 Quality Control and Quality Assurance

Quality assurance measurements are designed to ensure that complete, timely, and accurate data are submitted, that protocol requirements are followed, and that complications and/or AEs are immediately identified. Quality assurance audits may be carried out during the conduct of the study.

11.8 Ethics

11.8.1 Institutional Review Board (IRB)/Ethics Committee (EC) Review

Prior to study initiation and when amended, the protocol, the informed consent form, and any applicable advertisement for subject recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility. Written notification of this approval will be submitted by the Investigator to Viveve.

Site personnel must provide reports of the progress or completion, termination, or discontinuation of the study to the IRB/EC(s) at appropriate intervals; at least yearly for all studies, or more frequently if required by applicable regulations and guidelines or institutional procedures.

11.8.2 Written Informed Consent

The principles of informed consent are described in United States FDA Regulations 21 CFR Part 50 and ISO 14155:2011, the Declaration of Helsinki, and local regulations. The informed consent form approved by the IRB/EC must include all elements required by Health Canada, FDA, state and local regulations, as well as any additional elements relevant to a specific study situation, including a statement that Viveve (and its designated representatives) and regulatory authorities have access to subject records. Viveve shall review all informed consents approved by the IRB/EC prior to implementation.

The study will be explained to each prospective candidate and the subject must give consent by signing and dating the approved informed consent form. A copy of the signed consent form will be given to the Subject, and the original signed consent form will remain at the study site. The consenting process will be documented by the Principal Investigator or designee in the study records. There will be documentation that consent was obtained before initiation of any study-specific procedures.

11.8.3 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be traced back to the source data. A subject identification log will be maintained at each study site in the regulatory site binder.

Study data may be made available to third parties, e.g., study sponsor, government regulatory agencies, study monitoring personnel, provided the data are treated confidentially and that the subjects have given their approval by signing the informed consent form and their privacy is protected. The identity of a subject will never be disclosed in the event that study data are published.

A site(s) should maintain subject privacy in accordance to federal regulations (45 CFR Parts 160 and 164), local regulations, and institutional (if applicable) requirements.

11.9 Data Handling and Recordkeeping

11.9.1 Electronic Case Report Form (eCRF) Completion

Queries can be raised through the EDC system by monitors, data management personnel, or other Sponsor-designated personnel. The Principal Investigator or his/her authorized designee are responsible to answer these queries using the appropriate functions in the EDC system. Full traceability for each data point will be assured by the functions of the EDC system including who, when, and why a data point was changed.

11.9.2 Database Management and Quality Control

Data will be collected through a secure, internet based, electronic data capture (EDC) system. The EDC system will be used to record all subject information collected in the study for the purpose of secure data tracking and centralized data monitoring (“remote monitoring”).

Study personnel at the clinical site will perform primary data collection by entering the data into the electronic case report forms (eCRF) using a standard internet browser. Study personnel will each be assigned a unique user name and password to access the eCRFs. Each user access to the system is tracked, so that all data operations can be monitored and verified.

The designated site personnel, using his/her personal login information, shall approve each page of the case report form in the EDC system by applying their electronic signature.

The monitor, using his/her personal login information, shall verify all data points against the source documents and issue electronic queries for the authorized clinical site personnel to respond.

An eCRF shall be considered complete when all data are completed, verified by the monitor, outstanding queries resolved, and signed off by the principal investigator, or designee.

11.9.3 Regulatory Documentation

Documentation responsibilities of the Principal Investigator before or during the study include the following:

- Maintain a fully executed Clinical Trial Agreement and Non-Disclosure Agreement.

- Maintain Investigator Agreement along with a copy of a Curriculum Vitae for each investigator listed on this form.
- Provide monitoring personnel with a list of all other persons whose participation materially affects the study (ancillary personnel). Must also include their training and/or title and the role they will assume in the study.
- Inform monitoring personnel if, during the study, additional sub-investigators will be added to the study. The site should revise the Investigator Agreement to reflect the addition of any sub-investigator(s).

If any changes to study site personnel are made during the study, the Delegation of Authority Log will be updated.

11.9.4 Principal Investigator Reports

The Principal Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 4 below. These are also subject to regulatory authority inspection and the retention requirements described above for the Investigator Records.

Table 3: Required Investigator Reports

Report	Submit to	Description
Unanticipated Serious Adverse Device Effect (UADE)	Sponsor and IRB	The Principal Investigator must submit to the Sponsor and reviewing IRB a report of any USADE as soon as possible but not less than 10 working days after the Investigator first learns of the effect.
SAE	Sponsor	The Principal Investigator must submit to the Sponsor report of any SAE within 24 hours of when the Investigator first learns of the event.
Withdrawal of IRB Approval	Sponsor	The Principal Investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	Sponsor, Monitor, and IRB	The Principal Investigator must submit this report at regular intervals, but not less than once per year or as per national/local requirements to the IRB, sponsor, and monitor.
Deviation from Protocol in Emergency	Sponsor and IRB	Deviation from the study protocol that are made to protect the life or physical well-being of a subject in an emergency situation must be reported within 5 working days after the emergency occurred.
Deviation from Protocol that affects the scientific soundness of the study plan or the rights, safety or welfare of human subjects	Sponsor	Deviations whether or not beyond the Principal Investigator's control (e.g. inadvertent errors, product failure, or inability to perform required procedures due to subject illness) will be reported in the CRFs.
Failure to obtain informed consent	Sponsor and IRB	If a study device was used without obtaining informed consent, the Principal Investigator must notify the Sponsor and IRB within 5 working days of the use of the device.
Final Report	Sponsor and IRB	If required by the national/local regulations, the Principal Investigator must submit this report to the Sponsor and IRB within 3 months after the termination or completion of the study or after the Investigator's participation in the study is complete.

11.9.5 Protocol Deviations

A protocol deviation is an event in which the Principal investigator or site personnel did not conduct the study in accordance with the protocol or the Research Study Agreement or the instructions for use pertaining to the investigational device. Protocol deviations are discouraged unless deemed necessary to protect the life or physical well-being of a subject in an emergency. Other deviations beyond the investigator's control (e.g., inadvertent errors, product failure, or inability to perform required procedures due to subject illness) must also be reported. All protocol deviations are to be reported to the sponsor, along with the justification or reason for the deviation, in the appropriate section of the CRF. Protocol deviations will be defined as major and minor per the protocol deviation guidelines.

11.9.6 Retention of Records

The Principal Investigator will maintain all study records according to ICH-GCP/ISO 14155 and any other applicable regulatory requirement(s). The site shall retain study-related correspondence, subject signed consent forms, investigational product disposition records, CRFs (or electronic files), and source documents for all subjects

randomized for a minimum of two (2) years following the approval of a marketing application, or for the period required by the Institution in which the study will be conducted, whichever is longer. If a marketing application is not submitted or the submitted application is not approved, the Investigator shall retain all study-related records as outlined above for two years after shipment and delivery of the investigational product is discontinued and the appropriate regulatory bodies are notified. Site personnel must contact Viveve prior to destroying any records associated with the study.

If the site withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee [e.g., another Investigator, IRB/EC, or Viveve home office (de-identified of subject PHI only)]. Notice of such transfer will be given in writing to Viveve.

11.10 Subject Recruitment

Any advertisements that will be used in subject recruitment will be reviewed and approved by Viveve prior to submission to the IRB/EC. Any further changes suggested by the IRB/EC will also be reviewed and approved by Viveve prior to implementation.

11.11 Study Supplies

The Investigator will be provided with the following supplies:

- Viveve system
- Viveve system handpiece
- Cryogen for the Viveve system
- Viveve treatment tips
- Viveve coupling fluid
- Return pads
- Urine pregnancy dipstick tests
- Urine bacterial dipstick tests
- Lab kits
- Saline wipes
- Disposable, flexible measuring tapes
- Bladder scanner
- External pads to absorb urine leakage
- High-precision scales (for weighing pads for the pad-weight test)
- Q-tips
- Analgesic gel
- Study-specific laptops for EDC entry and randomization code generation

11.12 New Safety Information

The Sponsor will provide the Principal Investigators with any relevant information regarding device-related SAEs and will address safety issues as appropriate, either with additional safety measures or with a premature termination of the trial, as may apply.

Additionally, per sections 4.8.2 and 4.8.10(p) of the ICH Harmonized Tripartite Guideline for Good Clinical Practice, Principal Investigators must be able to provide on-going information to study subjects regarding safety and their participation in the study. In addition, Principal Investigators are required to communicate any new relevant safety information that may change a subject's willingness to participate in the clinical study. Informed Consent must be renewed in such cases, if pertinent.

11.13 Use of Information and Publication

All information not previously published concerning the test product and Viveve is considered confidential and is the sole property of Viveve. Site personnel agree to use this information only in connection with this study and will not use it for other purposes without written permission from Viveve.

It is agreed that before publication Viveve will be given the opportunity to review and comment upon any manuscript that contains data derived from this study.

11.14 FINANCING AND INSURANCE

The study is fully financed by Viveve and is insured. Upon request, a certificate of insurance can be provided. This clinical investigation insurance policy will cover medical treatment expenses for any injury that is directly a result of treatment in accordance with the protocol, that occurred while the subject was involved in this study.

12 SIGNATURE OF INVESTIGATOR

Protocol No. VI-17-01

I have reviewed this protocol for the study entitled:

LIBERATE International
VI-17-01
Evaluation of the Safety and Efficacy of the Viveve Treatment for Stress Urinary Incontinence

Prepared for:

Viveve Inc.
345 Inverness Drive South, Suite B-250
Englewood, Colorado 80112
(720) 696-8100

I agree to conduct this study according to the requirements described in the protocol.

Principal Investigator Name (print or type):	
Principal Investigator Signature:	
Date:	
Site Number:	
Site Address:	

13 REFERENCES

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14 APPENDICES

14.1 UROGENITAL DISTRESS INVENTORY-6 (UDI-6)

Do you experience, and, if so, how much are you bothered by:

	Not at All	Slightly	Moderately	Greatly
1. Frequent urination	0	1	2	3
2. Leakage related to feeling of urgency	0	1	2	3
3. Leakage related to activity, coughing, or sneezing	0	1	2	3
4. Small amounts of leakage (drops)	0	1	2	3
5. Difficulty emptying bladder	0	1	2	3
6. Pain or discomfort in lower abdominal or genital area	0	1	2	3

14.2 INTERNATIONAL CONSULTATION ON INCONTINENCE MODULAR QUESTIONNAIRE-URINARY INCONTINENCE SHORT FORM (ICIQ-UI-SF)

Many people leak urine some of the time. We are trying to find out how many people leak urine, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth: _____DD MONTH YEAR
2. Are you (check one) □ Female or □ Male?

FREQUENCY OF URINARY INCONTINENCE

3. How often do you leak urine? *(Mark one box)*

Never	☐	0
About once a week or less often	☐	1
Two or three times a week	☐	2
About once a day	☐	3
Several times a day	☐	4
All the time	☐	5

AMOUNT OF LEAKAGE

4. We would like to know how much urine <u>you think</u> leaks.
How much urine do you <u>usually</u> leak (whether you wear protection or not)? *(Mark one box)*

None	☐	0
A small amount	☐	2
A moderate amount	☐	4
A large amount	☐	6

OVERALL IMPACT OF URINARY INCONTINENCE

5. Overall, how much does urine interfere with your everyday life?
Please circle a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

Not at All ***A Great Deal***

SELF-DIAGNOSTIC

6. When does urine leak? *(Please mark all that apply to you)*

Never – urine does not leak	☐
Leaks before you get to the toilet	☐
Leaks when you cough or sneeze	☐
Leaks when you are asleep	☐
Leaks when you are physically active/exercising	☐
Leaks when you have finished urinating and are dressed	☐
Leaks for no obvious reason	☐
Leaks all the time	☐

14.3 INCONTINENCE QUALITY OF LIFE QUESTIONNAIRE (I-QOL)

SAMPLE: Incontinence Quality of Life (I-QOL) Questionnaire

Below, you will find some statements that have been made by people who have urinary incontinence (leaking urine when you don't want to). Please choose the response that applies best to you right now and circle the number of your answer. If you are unsure about how to answer a question, please give the best answer you can. **There are no right or wrong answers.**

Your Feelings (Please circle the number of your answer)

		Extremely	Quite a Bit	Moderately	A Little	Not at All
1	I worry about not being able to get to the toilet on time.	1	2	3	4	5
2	I worry about coughing or sneezing because of my urinary problems or incontinence.	1	2	3	4	5
3	I have to be careful standing up after I've been sitting down because of my urinary problems or incontinence.	1	2	3	4	5
4	I worry about where toilets are in new places.	1	2	3	4	5
5	I feel depressed because of my urinary problems or incontinence.	1	2	3	4	5
6	Because of my urinary problems or incontinence, I don't feel free to leave my home for long periods of time.	1	2	3	4	5
7	I feel frustrated because my urinary problems or incontinence prevents me from doing what I want.	1	2	3	4	5
8	I worry about others smelling urine on me.	1	2	3	4	5
9	My urinary problems or incontinence is always on my mind.	1	2	3	4	5
10	It's important for me to make frequent trips to the toilet.	1	2	3	4	5
11	Because of my urinary problems or incontinence, it's important to plan every detail in advance.	1	2	3	4	5
12	I worry about my urinary problems or incontinence getting worse as I grow older.	1	2	3	4	5
13	I have a hard time getting a good night of sleep because of my urinary problems or incontinence.	1	2	3	4	5
14	I worry about being embarrassed or humiliated because of my urinary problems or incontinence.	1	2	3	4	5
15	My urinary problems or incontinence makes me feel like I'm not a healthy person.	1	2	3	4	5
16	My urinary problems or incontinence makes me feel helpless.	1	2	3	4	5
17	I get less enjoyment out of life because of my urinary problems or incontinence.	1	2	3	4	5
18	I worry about wetting myself.	1	2	3	4	5
19	I feel like I have no control over my bladder.	1	2	3	4	5
20	I have to watch what or how much I drink because of my urinary problems or incontinence.	1	2	3	4	5
21	My urinary problems or incontinence limit my choice of clothing.	1	2	3	4	5
22	I worry about having sex because of my urinary problems or incontinence.	1	2	3	4	5

14.4 3-Day Bladder Voiding Diary

The subject will complete 3-day bladder voiding during the 3 days prior to each visit.

3-DAY, DAILY VOIDING DIARY

Please complete this diary during the **three** consecutive days prior to your next visit. The goal of this form is capture trips to the bathroom, as well as number of leaks each day, fluid intake and number of pads used. Each day should capture 24 hours of urine output, fluid intake and pads used. On the **front** of the form, please record all trips to the bathroom and incidents of leaking that you experience each day. On the **back** of the form, please record your fluid intake throughout the day and the number of pads used each day. Use additional pages as necessary.

DATE:			
Voiding Type	**Approximate Time**	**Amount**	**Activity at Time of Leak (or write N/A for trip to bathroom)**
Check one	**AM or PM**	**How much urine? (circle one)**	**Sneezing, exercising, having sex, lifting, etc.**
✓ Urine Leak ☐ Trip to Bathroom	6:30AM	sm (med circled) lg	**Running**
☐ Urine Leak ✓ Trip to Bathroom	**7:00 AM**	(sm circled) med lg	**N/A**
☐ Urine Leak ☐ Trip to Bathroom		sm med lg	
☐ Urine Leak ☐ Trip to Bathroom		sm med lg	
☐ Urine Leak ☐ Trip to Bathroom		sm med lg	
☐ Urine Leak ☐ Trip to Bathroom		sm med lg	
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☐ Urine Leak ☐ Trip to Bathroom		sm med lg	
☐ Urine Leak ☐ Trip to Bathroom		sm med lg	
☐ Urine Leak ☐ Trip to Bathroom		sm med lg	

Date:		
Fluid type	**Approximate Time**	**Approximate Amount in milliliters**
Water, coffee, milk	**AM or PM**	**mL**
Water	6:00AM	237 mL

Pad Usage
Total number of pads used today _____

14.5 FSFI: FEMALE SEXUAL FUNCTION INDEX

These 19 questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions, the following definitions apply:

- Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.
- Sexual intercourse is defined as penile penetration (entry) of the vagina.
- Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

Check only one box per question.

	FSFI: Questions	Responses
Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex		
1	Over the past 4 weeks, how often did you feel sexual desire or interest?	5 - Almost always or always 4 - Most times (more than half the time) 3 - Sometimes (about half the time) 2 - A few times (less than half the time) 1 - Almost never or never
2	Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?	5 - Very high 4 - High 3 - Moderate 2 - Low 1 - Very low or none at all
Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.		
3	Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?	0 - No sexual activity 5 - Almost always or always 4 - Most times (more than half the time) 3 - Sometimes (about half the time) 2 - A few times (less than half the time) 1 - Almost never or never
4	Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?	0 - No sexual activity 5 - Very high 4 - High 3 - Moderate 2 - Low 1 - Very low or none at all
5	Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?	0 - No sexual activity 5 - Very high confidence 4 - High confidence 3 - Moderate confidence 2 - Low confidence 1 - Very low or no confidence
6	Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?	0 - No sexual activity 5 - Almost always or always 4 - Most times (more than half the time) 3 - Sometimes (about half the time) 2 - A few times (less than half the time) 1 - Almost never or never
Lubrication		
7	Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?	0 - No sexual activity 5 - Almost always or always 4 - Most times (more than half the time) 3 - Sometimes (about half the time) 2 - A few times (less than half the time) 1 - Almost never or never
8	Over the past 4 weeks how difficult was it to become lubricated ("wet") during sexual activity or intercourse?	0 - No sexual activity 1 - Extremely difficult or impossible 2 - Very difficult 3 - Difficult 4 - Slightly difficult 5 - Not difficult
9	Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0 - No sexual activity 5 - Almost always or always 4 - Most times (more than half the time) 3 - Sometimes (about half the time) 2 - A few times (less than half the time) 1 - Almost never or never

	FSFI: Questions	Responses
10	Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0 - No sexual activity 1 - Extremely difficult or impossible 2 - Very difficult 3 - Difficult 4 - Slightly difficult 5 - Not difficult
Orgasm		
11	Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?	0 - No sexual activity 5 - Almost always or always 4 - Most times (more than half the time) 3 - Sometimes (about half the time) 2 - A few times (less than half the time) 1 - Almost never or never
12	Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?	0 - No sexual activity 1 - Extremely difficult or impossible 2 - Very difficult 3 - Difficult 4 - Slightly difficult 5 - Not difficult
13	Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	0 - No sexual activity 5 - Very satisfied 4 - Moderately satisfied 3 - About equally satisfied and dissatisfied 2 - Moderately dissatisfied 1 - Very dissatisfied
Satisfaction		
14	Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?	0 - No sexual activity 5 - Very satisfied 4 - Moderately satisfied 3 - About equally satisfied and dissatisfied 2 - Moderately dissatisfied 1 - Very dissatisfied
15	Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?	5 - Very satisfied 4 - Moderately satisfied 3 - About equally satisfied and dissatisfied 2 - Moderately dissatisfied 1 - Very dissatisfied
16	Over the past 4 weeks, how satisfied have you been with your overall sexual life?	5 - Very satisfied 4 - Moderately satisfied 3 - About equally satisfied and dissatisfied 2 - Moderately dissatisfied 1 - Very dissatisfied
Pain		
17	Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?	0 - Did not attempt intercourse 1 - Almost always or always 2 - Most times (more than half the time) 3 - Sometimes (about half the time) 4 - A few times (less than half the time) 5 - Almost never or never
18	Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?	0 - Did not attempt intercourse 1 - Almost always or always 2 - Most times (more than half the time) 3 - Sometimes (about half the time) 4 - A few times (less than half the time) 5 - Almost never or never
19	Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?	0 - Did not attempt intercourse 1 - Very high 2 - High 3 - Moderate 4 - Low 5 - Very low or none at all