# The Impact on Female Sexual Function of a Single-Treatment, Cryogen-Cooled Monopolar Radiofrequency (CMRF) Treatment: A Sub-Analysis of the VIVEVE I Randomized Clinical Trial

Michael Krychman, MD, MPH, Christopher G. Rowan, PhD, Ashley Yacoubian, BS, and Deborah Wilkerson, PhD

## Abstract

**Objective:** A sub-analysis of the VIVEVE I trial aimed to evaluate the impact of CMRF therapy, for the treatment of vaginal laxity, on female sexual desire, arousal, lubrication, orgasm, satisfaction, and pain.

**Methods:** The VIVEVE I clinical trial was prospective, randomized, single-blind, and sham-controlled. Nine clinical study centers in Canada, Italy, Spain, and Japan were included. This sub-analysis included pre-menopausal women (age ≥ 18 years) with vaginal laxity who had ≥ 1 full-term vaginal delivery and a baseline Female Sexual Function Index (FSFI) total score ≤ 26.5. Enrolled subjects were randomized (2:1) to receive CMRF therapy [Active (90 Joules/cm2) vs. Sham (≤ 1 Joule/cm2)] delivered to the vaginal tissue. Independent analyses were conducted to evaluate the change on each of the six domains of sexual function included in the FSFI for Active vs. Sham treated subjects at six months post-intervention.

**Results:** Subjects who received Active treatment showed greater overall FSFI improvement than Sham treated subjects. For each of the six FSFI domains, subjects who received Active treatment had greater improvement than Sham treated subjects. The adjusted mean change (AMC) from baseline to 6 months showed statistically significant improvements, in favor of Active treatment, on the Arousal, Lubrication, and Orgasm domains.

**Conclusions:** This was the first randomized, controlled, clinical study using validated endpoints for the treatment of vaginal laxity using an energy-based device. This sub-analysis of the VIVEVE I trial showed that a single, non-ablative CMRF treatment improves overall sexual function (FSFI total score) and is associated with statistically significant improvements on the individual FSFI domains of sexual arousal, lubrication, and orgasm in women with vaginal laxity and baseline sexual dysfunction.

**Clinical Trial Registration:** clinicaltrials.gov Identifier: **NCT02261974**

# Background

Vaginal laxity secondary to childbirth, aging or other connective tissue influencers, is associated with reduced physical sensation during intercourse and diminished sexual satisfaction.[1-3] This poorly recognized and frequently unreported medical condition[4-6] negatively impacts female sexual function, self-image, and quality of life (QOL).[7-10] A recent study showed 50% of parous women were concerned about vaginal laxity, yet 83% of them failed to discuss their concern with a healthcare professional (HCP).[4] A study of urogynecologists showed vaginal laxity negatively impacts their patients' QOL, sexual function, sexual satisfaction and relationship happiness; they further identified the vaginal introitus as the most frequently cited location of laxity, with symptoms arising from changes in the integrity of both the deep muscle and submucosal tissue.[4]

Non-surgical, cryogen-cooled, monopolar radio frequency (CMRF) therapy provides a novel, outpatient modality to effectively treat vaginal laxity. This dual-mode (heating and cooling) therapy coupled with surface cooling activates fibroblasts to produce new collagen and stimulates remodeling of vaginal tissue without evidence of fibrosis or underlying scarring.[11-23] Preclinical studies of CMRF delivered to the vaginal introitus demonstrated non-fibrotic collagen deposition up to 6 months.[12,13] Two single-arm, pilot studies in women with vaginal laxity showed CMRF therapy was safe and effective at 6 and 12 months post-intervention.[24,25] Prior to the VIVEVE I randomized clinical trial (RCT), there was no comparative effectiveness data (i.e., there were no placebo-controlled trials) to support the safe and effective use of any energy-based therapy for the treatment of vaginal laxity.

The current standard of care for vaginal laxity assessment is the use of self-reported instruments of sexual function, as currently no reliable objective measures exist to accurately define vaginal laxity.[24-27] The Female Sexual Function Index (FSFI) is a widely accepted, global assessment used in female sexual medicine trials that has been validated in many languages and for a variety of patient populations.[27,28] The FSFI is categorized by six domains of sexual function: Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain. The domain scores combine to create a total score (range 1.2 to 36). A total FSFI score ≤26.55 is recognized in the medical literature as indicating sexual dysfunction.[29] In validation studies, the FSFI demonstrated excellent discriminant validity for all domains of sexual function, including the ability to discriminate sexual function and dysfunction.[30]

This sub-analysis of the VIVEVE I trial aimed to evaluate changes in FSFI domains for subjects with a baseline FSFI score ≤26.5 who received CMRF therapy for the treatment of vaginal laxity. This is the first, and only, randomized, placebo-controlled trial with a comparator arm of energy-based therapy for the treatment of vaginal laxity.

# Methods

### Study Design and Research Subjects

The VIVEVE I study was a multi-center, prospective, randomized, single-blind, sham-controlled trial that was conducted between January 2015 and March 2016 at nine centers in Canada, Spain, Italy, and Japan.

Women presenting at the participating study centers with self-reported vaginal laxity were invited to participate in study screening. The VIVEVE I trial included premenopausal females (≥18 years

of age) who had ≥1 full-term vaginal delivery and presented with vaginal laxity during sexual intercourse (classified by a score of ≤ 3 on a Vaginal Laxity Questionnaire). Women were excluded from the trial who: had an abnormal genitopelvic exam; were currently pregnant or breastfeeding; had a history of genital fistula or a thin recto-vaginal septum; had clinically significant pelvic organ prolapse. This sub-analysis was restricted to subjects with sexual dysfunction at baseline (i.e., FSFI total score ≤26.5 at the screening visit).

**Randomization and Intervention**

Study subjects meeting the inclusion/exclusion criteria were randomized 2:1 to receive either Active or Sham treatment. The Active group was treated with a CMRF energy dose of 90 Joules/cm$^2$; the Sham group was treated with ≤ 1 Joule/cm$^2$ (a non-therapeutic energy dose).

RF energy has a long history of use in sensitive tissues, such as mucosal tissue in the vagina, pharynx, cornea, and skin. The patented device used in the VIVEVE I trial delivers dual-mode monopolar RF with cryogen cooling to protect the surface mucosa while enabling heat to reach the deeper underlying tissue layers. CMRF energy stimulates fibroblastic collagen formation and remodeling—thereby providing additional support to the soft tissue support matrix of the introitus.

Randomized subjects received one treatment of up to 110 pulses. A coupling fluid was applied to the vaginal introitus and device hand-piece to ensure safe and effective CMRF transfer. For both treatment arms, a single-use tip (Active or Sham) delivered CMRF therapy circumferentially to the vaginal mucosal surface, avoiding the urethral area, in ~0.5 cm overlapping intervals for 5 complete passes.

All subjects were treated exactly the same throughout the study, regardless of their assigned randomization group; the only exception was that the treatment tip used for the Sham group was specially programmed to deliver ≤1 Joule/cm$^2$. This allowed the subjects to remain blinded to the treatment they received—i.e., whether they received Sham or Active during the procedure.

**Follow-up and Study Exit**

The FSFI questionnaire was administered at the screening visit and at months 1, 3, and 6 post-intervention. Adverse events were also recorded at these study intervals. Study exit occurred after completion of the 6-month follow-up visit, unless the subject requested to leave the study early, or was lost to follow-up.

**FSFI Assessment**

The formally-validated English, Spanish, French, and Italian versions of the FSFI were used in this study. The FSFI includes 19 questions, categorized into six domains, that evaluate a women's recent state of sexual function (i.e., within the past 4 weeks). The minimum and maximum scores for each domain ranged from 0-6 (except for the "Desire" domain, where the minimum score is 1.2). The "Desire" domain includes 2 questions to assess sexual desire or interest. The "Arousal" domain includes 4 questions to assess sexual arousal and excitement during sexual activity or intercourse. The "Lubrication" domain includes 4 questions to assess lubrication and "wetness" during sexual activity or intercourse. The "Orgasm" domain includes 3 questions to assess the ability to reach orgasm or climax during sexual activity or intercourse. The "Satisfaction" domain includes 3 questions to assess satisfaction with their sexual relationship with their partner and overall sex life. The "Pain" domain includes 3 questions to assess pain or discomfort during and following vaginal penetration.

## Statistical Analyses

The VIVEVE I trial was powered to detect statistically significant and clinically important differences between the Active and Sham treatment groups. The sample size was derived using the combined results from two single-arm pilot studies in Japan[24] and the US[25]. Conceptually, power is the probability of detecting a true difference between two treatment groups. The validity of clinical research relies on the ability to distinguish a causative treatment effect from one occurring due to a placebo effect, or chance alone. It is well recognized that "placebo" or "sham" effects can be substantial, especially on subjective endpoints such as assessments of health-related quality of life (e.g., the FSFI used to measure female sexual health in this trial). To obtain a causative treatment effect, the VIVEVE I trial employed the requisite two-arm design (i.e., Active and Sham treatment groups) with adequately powered sample sizes in each treatment group to distinguish a bona fide, causative treatment effect from either a placebo effect or chance alone.

| **Table 1. Baseline Subject Characteristics** | **Active Treatment** | | **Sham Treatment** | |
|---|---|---|---|---|
| Number of subjects | 82 | | 40 | |
| **Demographic Data** | **Mean** | **SD** | **Mean** | **SD** |
| Age | 40.1 | 6.3 | 39.8 | 5.9 |
| Age categories | **N** | **%** | **N** | **%** |
| <35 years | 15 | 18.3% | 9 | 22.5% |
| 35-39 years | 21 | 25.6% | 8 | 20.0% |
| 40-44 years | 27 | 32.9% | 13 | 32.5% |
| ≥45 years | 19 | 23.2% | 10 | 25.0% |
| **Clinical Data** | **Mean** | **SD** | **Mean** | **SD** |
| BMI | 24.7 | 5 | 25.0 | 6.1 |
| BMI categories | **N** | **%** | **N** | **%** |
| BMI <20 | 8 | 9.8% | 5 | 12.5% |
| BMI 20-24 | 42 | 51.2% | 19 | 47.5% |
| BMI 25-29 | 20 | 24.4% | 11 | 27.5% |
| BMI ≥30 | 12 | 14.6% | 5 | 12.5% |
| **Comorbidities** | **N** | **%** | **N** | **%** |
| Ear, nose, or throat condition | 4 | 4.9% | 6 | 15.0% |
| Dermatologic condition | 6 | 7.3% | 2 | 5.0% |
| Pulmonary condition | 1 | 1.2% | 3 | 7.5% |
| Hepatic/biliary condition | 2 | 2.4% | 3 | 7.5% |
| Endocrine condition | 10 | 12.2% | 4 | 10.0% |
| Neurologic condition | 9 | 11.0% | 2 | 5.0% |
| Psychiatric condition | 2 | 2.4% | 1 | 2.5% |
| Hematologic condition | 5 | 6.1% | 5 | 12.5% |
| Allergies | 16 | 19.5% | 8 | 20.0% |
| Gynecologic condition | 16 | 19.5% | 7 | 17.5% |
| **Other Health Status Data** | **N** | **%** | **N** | **%** |
| Prior surgery | 55 | 67.1% | 25 | 62.5% |
| Major illness within 5 years | 9 | 11.0% | 2 | 5.0% |
| Prior sexually transmitted disease | 4 | 4.9% | 1 | 2.5% |
| **Maternal History** | **Mean** | **SD** | **Mean** | **SD** |
| No. of pregnancies | 2.8 | 1.4 | 2.6 | 1.3 |
| No. of full-term deliveries | 2.2 | 0.9 | 2.0 | 0.8 |
| Time since last delivery (years) | 7.9 | 6.3 | 8.0 | 6.0 |
| No. of vaginal deliveries | 2.1 | 1.0 | 1.9 | 0.8 |
| Median birthweight (kg) | 3.2 | 0.6 | 3.4 | 0.5 |

**TABLE 1.** Baseline demographics, clinical characteristics, comorbidities, and maternal history for Active and Sham treated subjects.

The analysis set, for this sub-analysis, included randomized subjects with a baseline FSFI score ≤26.5 who received complete or partial treatment and who completed the baseline and 6 month FSFI efficacy assessment. For the FSFI total score, mean values are described for Active and Sham treated subjects at 1, 3, and 6 months post-intervention. The difference in adjusted mean values (Active vs. Sham) for each FSFI domain were analyzed using analysis of covariance (ANCOVA). All change from baseline (CFB) data were analyzed as observed raw means.

The FSFI domain ANCOVA analyses were compared to a two-sided significance level of 0.05. No adjustments were made for multiplicity. Given the number of comparisons, these sub-analyses were considered exploratory. The assumptions of normality of error distribution (i.e., homoscedasticity) and linearity were assessed for the ANCOVA CFB analyses. Statistical analyses were conducted using STATA version 14 (Stata Corp. College Station, TX).

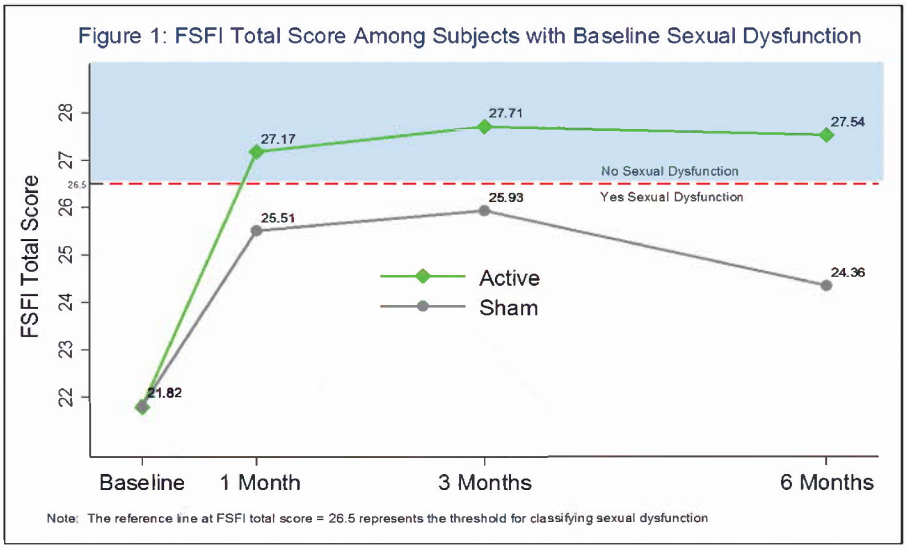


**FIG. 1.** FSFI total score mean values for Active and Sham treated subjects at baseline and at months 1, 3, and 6 post-intervention. The dashed red line at 26.5 indicates the threshold for classifying sexual dysfunction.

# Results

### Participants

Between January 2015 and March 2016, 122 subjects were included in the VIVEVE I clinical study with an FSFI score ≤26.5 at baseline; these subjects were included in this sub-analysis. Eighty-two (82) and 40 subjects were randomized to receive Active or Sham CMRF therapy to the vaginal introitus, respectively. One-hundred-eight subjects (108, 88%) completed the baseline and 6 month FSFI assessment [Active (n=73) and Sham (n=35)]. **Table 1** shows baseline characteristics for subjects in each treatment group.

### FSFI Total Score

Mean FSFI total score values at baseline and months 1, 3, and 6 are presented in **Figure 1.** Baseline values were similar between active and sham treatment groups. Subjects who received Active treatment showed greater overall FSFI improvement than Sham treated subjects. The mean FSFI total score for Active subjects improved from "dysfunctional" to "functional" at 1, 3, and 6 months post-intervention; whereas, the mean FSFI total score for Sham treated subjects did not reach "functional" at any follow-up time-point.

### FSFI Domain Analyses

FSFI domain analyses at 6 months post-intervention are presented in **Table 2**. Baseline values for each FSFI domain were similar for both treatment

groups. For each of the six FSFI domains, subjects who received Active treatment had greater improvement than Sham treated subjects. The adjusted mean change (AMC) from baseline to 6 months showed a statistically significant improvement (at the 0.05 significance level) for Active vs. Sham for the Arousal, Lubrication, and Orgasm domains. There was a borderline significant improvement (p=0.053) for the Desire domain. Among all FSFI domains, the greatest differences between Active and Sham treatment were observed for the Arousal and Orgasm domains.

**Table 2: FSFI Domain Analyses Among Subjects with FSD at Baseline**

| FSFI Domains | Treatment Group | Baseline* Mean | 6 Month Mean | Adjusted† Mean Change | p-value |
|---|---|---|---|---|---|
| **Desire** | Active | 2.92 | 3.72 | 0.82 | 0.053 |
| | Sham | 2.90 | 3.33 | 0.42 | |
| **Arousal** | Active | 3.12 | 4.39 | 1.27 | **0.004** |
| | Sham | 3.30 | 3.80 | 0.62 | |
| **Lubrication** | Active | 3.78 | 5.07 | 1.30 | **0.040** |
| | Sham | 3.90 | 4.59 | 0.77 | |
| **Orgasm** | Active | 3.07 | 4.23 | 1.24 | **0.007** |
| | Sham | 3.18 | 3.53 | 0.51 | |
| **Satisfaction** | Active | 3.65 | 4.60 | 1.04 | 0.124 |
| | Sham | 3.35 | 4.14 | 0.66 | |
| **Pain** | Active | 4.85 | 5.14 | 0.27 | 0.083 |
| | Sham | 4.79 | 4.72 | -0.13 | |

† The adjusted mean change was estimated from individual ANCOVA models (for each domain) which included the baseline domain score and treatment group as independent variables.
* The baseline FSFI assessment was conducted prior to the intervention

**TABLE 2.** Change from baseline analyses (Active vs. Sham) for each Domain of sexual function on the Female Sexual Function Index (FSFI). Statistically significant differences (Active vs. Sham) are depicted by bold p-values.

treated subjects; however, these did not achieve statistical significance. Overall, the CMRF procedure was well-tolerated and showed an excellent 6-month safety profile. No topical anesthetic was required and there were no serious adverse events reported.

The positive efficacy results from this trial support the proposed mechanism of action, as well as safe delivery of minimally invasive CMRF therapy to vaginal tissue. The significant results seen with CMRF may be explained by an effect on the genitopelvic-clitoral complex via enhancement of the structural integrity by enriched fibroblastic deposited connective tissue. This underlying architectural modification may improve neural, hormonal and vascular flow to the underlying structural components including the circumferential crural arms of the clitoral arousal complex, hence enhancing both genital arousal and potentially improving orgasmic intensity, while decreasing orgasmic latency.

## Discussion

Building on two single-arm pilot studies,[24,25] the VIVEVE I trial is the first and only multi-center, randomized, sham-controlled study to evaluate the efficacy of a non-surgical modality for the treatment of vaginal introital laxity. For the FSFI total score and domain sub-analyses, Active CMRF therapy demonstrated superiority over Sham therapy using a validated assessment of sexual function (FSFI) among subjects with baseline sexual dysfunction (FSFI baseline score ≤26.5). The results show statistically significant improvements on the Arousal, Lubrication, and Orgasm domains for Active vs. Sham treatment. Improvements were also observed for the Desire, Satisfaction, and Pain domains for Active vs. Sham

While there was a statistically significant improvement on the Arousal, Lubrication, and Orgasm analyses (in favor of Active treatment), a short-lived Sham effect at months 1 and 3 is worth

noting. The perception of improvement among Sham treated subjects diminished at 6 months and the mean FSFI total score for Sham-treated subjects never achieved "functional" status. This is not surprising, as a significant placebo response has been observed in several female sexual dysfunction trials.[31-33] It also is an established principle in the field of sexual health that an individual's mental perception can have a profound direct and indirect effect on overall sexual function and satisfaction.[34,35] If one has a lowered or negative impression of one's capacity for sexual function, it can directly impact physiological reactivity and subsequent sexual responsiveness.

The Sham effect observed in the VIVEVE I trial underscores the importance of conducting rigorous research investigations with adequate follow-up time and a comparator group to ensure the treatment effect is attributable to the intervention, and is beyond the effects gained from an office visit or counseling with a provider alone.

## Conclusion

This sub-analysis of the VIVEVE I trial showed that a single, non-ablative CMRF treatment improves overall sexual function (FSFI total score) and is associated with statistically significant improvements in the individual FSFI domains of sexual arousal, lubrication, and orgasm in women with vaginal laxity and baseline sexual dysfunction.

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