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Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function: The VIVEVE I Randomized Controlled Trial

Michael Krychman, MD,[1] Christopher G. Rowan, PhD,[2] Bruce B. Allan, MD, PhD, FRCS(C),[3] Leonard DeRogatis, PhD,[4] Scott Durbin, MPH,[5] Ashley Yacoubian, BSc,[5] and Deborah Wilkerson, PhD[5]

ABSTRACT

Introduction: Vaginal laxity is a highly prevalent and undertreated medical condition.

Aim: To evaluate the efficacy and safety of surface-cooled, monopolar radiofrequency (RFc) therapy for the treatment of vaginal laxity in the VIVEVE I trial.

Methods: The VIVEVE I trial was a prospective, randomized, single-blinded, and sham-controlled study. Nine study centers in Canada, Italy, Spain, and Japan participated. Women presenting with vaginal laxity were screened and informed consent was obtained. Major study inclusion criteria were premenopausal status, age at least 18 years, at least one full-term vaginal delivery, and normal genito-pelvic examination results. Enrolled subjects were randomized (2:1) to receive RFc therapy (Active [90 J/cm^2] vs Sham [1 J/cm^2], respectively) delivered to the vaginal tissue.

Main Outcome Measures: The primary efficacy outcome was the proportion of randomized subjects reporting "no vaginal laxity" (Active vs Sham) at 6 months postintervention, which was assessed using the Vaginal Laxity Questionnaire. Treatment-emergent adverse events were evaluated in all treated subjects. Secondary efficacy end points included change on the Female Sexual Function Index (FSFI) and the revised Female Sexual Distress Scale (FSDS-R).

Results: No vaginal laxity was achieved by 43.5% and 19.6% ($P = .002$) in the Active and Sham groups, respectively. Differences in FSFI and FSDS-R total scores (Active vs Sham) were 1.8 ($P = .031$) and −2.42 ($P = .056$), respectively, in favor of Active treatment. Treatment-emergent adverse events were reported by 11.1% and 12.3% of subjects in the Active and Sham arms, respectively.

Conclusion: The VIVEVE I trial is the first randomized, controlled, blinded, clinical study of RFc for the treatment of vaginal laxity. A single treatment of RFc therapy was found to be safe and associated with both improved vaginal laxity and improved sexual function. The results from this trial support the use of a novel non-surgical therapy for vaginal laxity, a prevalent and undertreated condition. **Krychman M, Rowan CG, Allan BB, et al. Effect of Single-Treatment, Surface-Cooled Radiofrequency Therapy on Vaginal Laxity and Female Sexual Function: The VIVEVE I Randomized Controlled Trial. J Sex Med 2017;14:215−225.**

Key Words: Vaginal Laxity; Vaginal Looseness; Radiofrequency Therapy; Surface Cooled; Non-Surgical; Sexual Function

INTRODUCTION

Vaginal introital laxity or vaginal looseness is a poorly recognized and ill-defined condition that occurs in many women after pregnancy and vaginal childbirth. Trauma to the genito-pelvic musculature and stretching of the vaginal introitus during pregnancy and vaginal delivery can lead to permanent changes that can be worsened by multiparity, delivery of a large fetus, use of forceps, and age-related changes of vaginal connective tissue.[1,2] Long-term laxity of the vaginal introitus is differentiated from pelvic organ prolapse (POP), which primarily involves the collapse of

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[1]Southern California Center for Sexual Health and Survivorship Medicine, Newport Beach, CA, USA;

[2]Collaborative Healthcare Research and Data Analytics (COHRDATA), LLC Santa Monica, CA, USA;

[3]Allan Centre, Calgary, AB, Canada;

[4]Maryland Center for Sexual Health, Lutherville, MD, USA;

[5]Viveve Medical, Inc, Sunnyvale, CA, USA

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internal genito-pelvic structures, whereas vaginal introital laxity (vaginal laxity) refers to looseness of the vaginal opening.

Vaginal laxity is associated with loss of physical sensation and decreased sexual satisfaction.[2,3] This poorly recognized, and frequently unreported, medical condition[4–6] negatively affects female sexual function, body image, and quality of life.[7–9] A recent study reported that 50% of parous women were concerned with vaginal laxity, yet 83% failed to discuss their concern with a health care professional.[4] Fifty-seven percent of urogynecologists viewed vaginal laxity as negatively affecting their patients' quality of life, sexual function, and relationship happiness. They further identified the vaginal introitus as the most frequently cited location of laxity, with symptoms arising from muscle and tissue changes.[4]

Therapeutic options for vaginal laxity include procedures and therapies targeted at the vaginal introitus and canal. The goal of these procedures is to restore sexual function. External cosmetic and gynecologic procedures of the vulva (eg, labioplasty) are performed primarily for esthetic enhancement, rather than to restore sexual function, and are not the focus of this research initiative. Restorative options for vaginal laxity include surgical procedures, physical therapy, and radiofrequency (RF) therapy.

Identifying an objective assessment of vaginal laxity remains elusive. A reliable correlation between vaginal length and introital caliber with sexual function has yet to be established.[10–14] Prior research of objective assessments such as introital diameter, genital hiatus, and vagina length have reported a poor correlation with women's perception of vaginal laxity and sexual function. The current standard of vaginal laxity assessment is the use of self-reported instruments.[1,15–17]

Surgical procedures (eg, vaginoplasty) intended to restore sexual function associated with vaginal laxity have been performed in women with decreased vaginal sensation, vaginal laxity, or a perception of a "wide vagina." These procedures, although controversial, involve reconstructive techniques aimed to decrease the caliber of the vaginal canal and introitus and can be conducted concomitantly with POP repair. Some studies of vaginoplasty repairs have reported improvements in sexual function.[10,18–20] However, the effectiveness of surgical approaches to restore vaginal tightness should be balanced by the risk involved in any surgery performed on vaginal tissue. Postsurgical recovery is substantial and includes the risk of scar formation and nerve damage, leading to fibrosis, dysesthesia, and dypareunia.[20]

Pelvic floor muscle training and Kegel exercises are recognized therapies for vaginal laxity.[4] However, the heterogeneity of effectiveness evidence currently provides inconclusive scientific support for these therapies.[21,22] There is no scientific evidence to support the safe and effective use of over-the-counter products (eg, topical vaginal tightening products) for the treatment of vaginal laxity.

Non-surgical, monopolar RF therapy with cryogen surface cooling (RFc) provides a minimally invasive, outpatient modality to treat vaginal laxity. This hyperthermic therapy, originally developed to remodel epidermal tissue and treat stress urinary incontinence, activates fibroblasts to produce new collagen and stimulates remodeling of vaginal tissue without evidence of fibrosis or scarring.[23–31] Preclinical studies of RFc therapy delivered to the vaginal introitus reported non-fibrotic collagen deposition up to 6 months posttreatment.[23,24] Two published, single-arm pilot studies in women with vaginal laxity showed RFc therapy was safe and effective.[1,16] Before the data reported in this publication, there were no comparative effectiveness studies (ie, there were no controlled trials with a sham comparator arm) to support the safe and effective use of any RF therapy for the treatment of vaginal laxity.

The VIveve treatment of the Vaginal Introitus to EValuate Effectiveness (VIVEVE I) trial was the first randomized controlled trial of RFc therapy for the treatment of vaginal laxity. The VIVEVE I trial aimed to determine the efficacy and safety of RFc therapy for women with vaginal laxity. The trial was designed to demonstrate that Active treatment was superior to Sham treatment for the primary efficacy end point.

METHODS

Study Design and Research Subjects

The VIVEVE I was a multicenter, prospective, randomized, single-blinded, sham-controlled trial conducted at nine centers in Canada, Spain, Italy, and Japan. The VIVEVE I trial was registered at clinicaltrials.gov (NCT02261974). Subjects were recruited from January 1, 2015 through November, 1 2015.

Women presenting at the participating study centers with self-reported vaginal laxity were invited to participate in study screening. Written informed consent was obtained before screening. Local ethics committees or institutional review boards for each study center approved the overarching trial protocol, which adhered to the Declaration of Helsinki. The same assessments and procedures were carried out for all subjects, regardless of any site-specific required modifications (ie, one additional inclusion criterion and a reordering of efficacy assessments).

Study screening included collection of demographic data, medical and sexual history, physical and genito-pelvic examination, medication history, complete blood cell count and metabolic panel, Papanicolaou test results, and current and past pregnancy status. Women were screened using a detailed comprehensive interview to exclude those with severe psychiatric diagnoses (eg, body dysmorphic syndrome). Sexual function, sexual distress, and vaginal laxity questionnaires were administered in each subject's local language. Theses questionnaires required each subject to self-report on her vaginal laxity and sexual function and did not focus on her sexual partner's assessment.

The trial included premenopausal women (≥18 years of age) experiencing vaginal laxity during sexual intercourse who had at least one full-term vaginal delivery. Vaginal laxity was classified

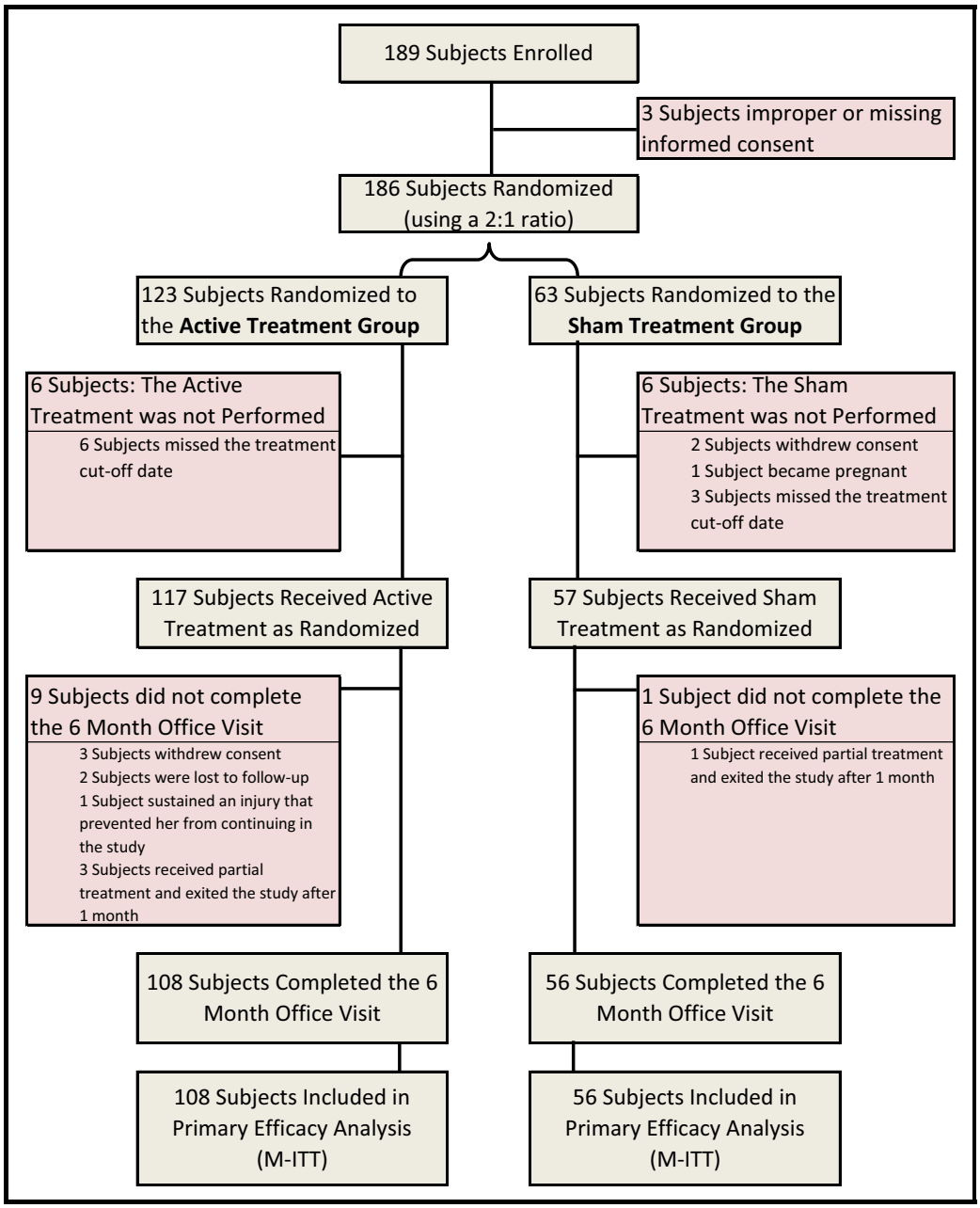

Figure 1. Subject disposition. M-ITT = modified intent-to-treat analysis. Figure 1 is available in color at www.jsm.jsexmed.org.

by a score no higher than 3 on the Vaginal Laxity Questionnaire (VLQ). Excluded from the trial were women who had an abnormal genito-pelvic examination result; were currently pregnant or breastfeeding; had a history of genital fistula or a thin rectovaginal septum; had clinically significant POP; or had a current sexual disorder (genito-pelvic pain, sexual aversion, or dyspareunia). The complete inclusion and exclusion criteria are presented in eTable 1.

Randomization

Study subjects meeting all inclusion and exclusion criteria were randomized 2:1, using a stratified blocked randomization scheme, to receive Active or Sham treatment. Each block contained three or six subjects. The randomization design and random number generator were developed using PROC PLAN in SAS Analytic Pro 9.3 (SAS Institute, Cary, NC, USA). Additional details of the randomization scheme and specifications are presented in eTable 2.

The Active treatment group was randomized to receive an RFc energy dose of 90 J/cm^2; the Sham treatment group was randomized to receive 1 J/cm^2 (a subtherapeutic RFc energy dose). All subjects were treated exactly the same throughout the study, regardless of their assigned randomization group, with the only exception being that the treatment tip used for the Sham group

was specially programmed to deliver only 1 J/cm^2. This allowed the subjects to remain blinded to the treatment they received during the study. Subjects remained blinded to treatment group allocation until study exit.

Intervention

RF energy has a long history of use in sensitive tissues, such as mucosal tissue in the vagina, pharynx, cornea, and skin. This technology and its vaginal use have been previously described.[1,16] The patented device used in this study delivers monopolar RF energy with cryogen surface cooling to generate low-temperature heat. When this therapy is applied to vaginal tissue, the surface mucosa is simultaneously cooled while non-ablative heat is delivered into deeper underlying layers (3–5 mm). RFc energy stimulates collagen formation and remodeling, thereby providing additional support to the soft tissue of the introitus. The treatment has been classified as a low-risk procedure, and the average energy delivered (ie, <50 W) is lower than from other typical RF devices.

Randomized subjects were treated once with the system. An inert coupling fluid was applied to the vaginal introitus and device handpiece to ensure safe and effective RFc transfer. For the two treatment arms, a single-use tip (Active or Sham) delivered RFc therapy circumferentially to the vaginal introitus mucosal surface while avoiding the urethral area. The vaginal introitus was treated with RFc pulses at approximately 0.5 cm in overlapping intervals. The process was repeated until the entire vaginal introitus, except the urethra, was treated five times with up to 110 total pulses. No analgesia or anesthesia was administered before, during, or after the procedure.

All subjects in the Active and Sham treatment groups received the same follow-up and care and, hence, 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 programmed to deliver no more than 1 J/cm^2. This allowed subjects to remain blinded to the treatment they received during the procedure.

Follow-Up and Study Exit

For subjects in both treatment groups, follow-up was conducted postintervention at 72 hours, 10 days, and 1, 2, 3, and 6 months. Telephone contact was made (by study site personnel) at 72 hours and at 2 months to assess sexual activity and concomitant medications and record adverse events (AEs). Clinic visits were scheduled at 10 days and at 1, 3, and 6 months to conduct additional assessments. All clinic visits included a pregnancy test and assessment of AEs and concomitant medications. Clinic visits at 1, 3, and 6 months included sexual history; sexual function, activity, and distress questionnaires; and the VLQ. A pelvic examination was carried out at the 10-day and 1- and 3-month office visits.

Study exit occurred after completion of the 6-month follow-up visit (or sooner if the subject withdrew consent before completion of the 6-month follow-up visit or was removed from the study for another reason).

Table 1. Baseline subject characteristics and maternal history

Baseline subject characteristics	Active treatment	Sham treatment
Subjects, n	123	63
Demographic data		
Age (y), mean (SD)	40.8 (6.0)	40.8 (5.7)
Age categories, n (%)		
<35	19 (15.4)	10 (15.9)
35–39	31 (25.2)	12 (19.0)
40–44	43 (35.0)	23 (36.5)
≥45	30 (24.4)	18 (28.6)
Clinical data		
BMI (kg/m^2), mean (SD)	24.6 (4.8)	24.4 (5.3)
BMI categories, n (%)		
<20	13 (10.6)	5 (7.9)
20–24	58 (47.2)	37 (58.7)
25–29	36 (29.3)	14 (22.2)
≥30	16 (13.0)	7 (11.1)
Comorbidities, n (%)		
Hypertension	7 (5.7)	2 (3.2)
Ear, nose, or throat condition	6 (4.9)	7 (11.1)
Dermatologic condition	9 (7.3)	4 (6.3)
Pulmonary condition	2 (1.6)	4 (6.3)
Hepatic or biliary condition	3 (2.4)	4 (6.3)
Endocrine condition	12 (9.8)	5 (7.9)
Neurologic condition	10 (8.1)	3 (4.8)
Psychiatric condition	3 (2.4)	3 (4.8)
Hematologic condition	8 (6.5)	5 (7.9)
Allergies	20 (16.3)	13 (20.6)
Gynecologic condition	19 (15.4)	7 (11.1)
Other health status data, n (%)		
Prior surgery	82 (66.7)	41 (65.1)
Major illness within 5 y	12 (9.8)	3 (4.8)
Prior sexually transmitted disease	7 (5.7)	2 (3.2)
Maternal history, mean (SD)		
Pregnancies (n)	2.7 (1.4)	2.7 (1.3)
Full-term deliveries (n)	2.2 (1.0)	2.2 (0.9)
Time since last delivery (y)	8.0 (6.3)	8.1 (5.5)
Vaginal deliveries (n)	2.1 (1.0)	2.0 (0.9)
Median birthweight (kg)	3.3 (0.7)	3.4 (0.5)

BMI = body mass index.

Safety Assessments

AE information was collected through subject interviews throughout the study duration. All AEs occurring from the initiation of the treatment procedure through the end of the study were recorded by the principal investigator or other appropriate site personnel. For all AEs, the description, date of onset, severity, duration, and relation to treatment were recorded. AEs were followed during the study until the event subsided or, in case of permanent impairment, until the event stabilized

Table 2. VLQ, FSFI, and FSDS-R summary statistics at each time point

	Baseline			Month 1			Month 3			Month 6		
Study assessment	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
VLQ score												
Active	123	2.4	0.9	110	4.0	1.5	110	4.2	1.6	108	4.2	1.8
Sham	63	2.4	0.9	57	3.7	1.5	57	3.9	1.6	56	3.5	1.4
FSFI total score												
Active	123	24.4	5.1	110	28.2	4.0	110	28.8	4.4	108	28.5	4.9
Sham	63	24.9	5.5	57	27.7	5.4	57	28.2	5.1	55	27.0	6.8
FSDS-R total score												
Active	122	19.4	12.0	110	13.5	10.3	110	12.8	10.3	108	13.1	10.5
Sham	63	17.3	12.3	57	14.0	10.0	57	13.3	10.4	56	14.3	9.6

FSDS-R = Revised Female Sexual Distress Scale; FSFI = Female Sexual Function Index; VLQ = Vaginal Laxity Questionnaire.

and the overall clinical outcome was ascertained. The relation of AEs to the test device was, in the judgment of the principal investigator and study medical monitor, determined using the following classifications: related, possibly related, unknown, and unrelated. AE severity was assessed based on the Common Terminology Criteria for Adverse Events 4.3 (US Department of Health and Human Services, June 14, 2010). AEs were classified and coded using the English version of MedDRA 18.1 (MedDRA MSSO, McLean, VA, USA). The percentage of subjects experiencing a treatment-emergent AE (TEAE)—defined as any AE that began or worsened after initiation of the treatment procedure through 6 months after treatment—are described by treatment group in this report.

Efficacy Assessments

Efficacy assessments were administered at screening (baseline) and at 1, 3, and 6 months postintervention. The primary efficacy end point was assessed using the VLQ. The VLQ, a self-reported assessment of vaginal laxity on a seven-point Likert scale, has been used in other clinical studies of RFc treatment.[1,16] The VLQ consists of one question: *How would you rate your current level of vaginal laxity or looseness during intercourse?* Response values include *very loose* (score = 1), *moderately loose* (score = 2), *slightly loose* (score = 3), *neither loose nor tight* (score = 4), *slightly tight* (score = 5), *moderately tight* (score = 6), or *very tight* (score = 7). Subjects were included in the trial who self-reported vaginal laxity or looseness during intercourse (ie, VLQ score $\leq$ 3). For the primary efficacy end point, "no vaginal laxity" was classified as a VLQ score of at least 5 (ie, $\geq$ 5).

Secondary efficacy assessments of sexual function and distress were evaluated using the Female Sexual Function Index (FSFI) and the revised Female Sexual Distress Scale (FSDS-R). The FSFI, a 19-question instrument, is a validated global assessment of current female sexual function.[17] The FSFI is categorized by six domains of female sexual function: desire, arousal, lubrication, orgasm, satisfaction, and pain. The domain scores combine to create a total score (range = 2–36). An FSFI total score less than or equal to 26.5 is recognized in the medical literature as indicating female sexual dysfunction (FSD).[32] The FSDS-R instrument was used to assess psychological distress associated with FSD.[15] The FSDS-R is a 12-item questionnaire in which higher scores indicate greater sexual distress. The VLQ, FSFI, and FSDS-R have been used in clinical studies of RFc for the treatment of vaginal laxity.[1,16]

The formally validated English, Spanish, French, and Italian versions of the FSFI and FSDS-R were used in this study. The VLQ was translated into Japanese, Spanish, French, and Italian by a certified professional translation service.

Statistical Analysis

This trial was designed to demonstrate that Active treatment was superior to Sham treatment for the primary efficacy end point (ie, proportion of subjects reporting "no vaginal laxity" as assessed by the VLQ at 6 months). The sample size was driven by the desire to obtain 90% power to detect a difference in proportions using a two-group χ^2 test. Based on the combined results from two single-arm pilot studies in Japan[16] and the United States,[1] the proportion of RFc-treated subjects reporting no vaginal laxity at 6 months after intervention was 0.44. An estimate of 0.15 for the proportion of sham-treated subjects reporting no vaginal laxity at 6 months required minimum samples of 75 and 38 subjects (total = 113) in the Active and Sham groups, respectively, to sufficiently power the primary efficacy end point.

Secondary efficacy end points were assessed at 6 months using baseline-adjusted logistic regression (for the end point of no vaginal laxity) and analysis of covariance (ANCOVA) for change from baseline (CFB) on the VLQ score, FSFI total score, and FSDS-R total score. In the baseline-adjusted logistic regression and ANCOVA analyses, treatment group and baseline score were included as independent variables. An analysis of the FSFI total score was conducted in subjects with sexual dysfunction at baseline (ie, baseline FSFI total score $\leq$ 26.5). CFB data were analyzed as observed raw means.

Minimal clinically important differences (MCIDs) were determined using receiver operating characteristics and

Table 3. "No vaginal laxity" analyses at each follow-up time point

Time point	Treatment	n	No laxity, n′ (%)	*P* value by χ^2 test	Adjusted OR*	95% CI	*P* value
Month 1	Active	110	42 (38.2)	.284	1.46	0.73–2.94	.285
	Sham	57	17 (29.8)				
Month 3	Active	110	52 (47.3)	.084	1.86	0.93–3.71	.079
	Sham	57	19 (33.3)				
Month 6†	Active	108	47 (43.5)	.002	3.39	1.54–7.45	.002
	Sham	56	11 (19.6)				

n′ = number of subjects who achieved "no laxity" at each time point; OR = odds ratio.
*Adjusted OR was estimated from multivariable logistic regression analysis.
†The primary efficacy end point was evaluated at 6 months after treatment.

cumulative distribution function methodology. The MCID was estimated using anchor-based methodology, which relates the magnitude of change on the efficacy assessments to an independent measurement (anchor) reflecting the extent of a subject's perceived treatment benefit. Anchoring methodology and receiver operating characteristics were used to establish the MCID at 6 months for the secondary efficacy CFB end points (ie, VLQ score, FSFI total score, and FSDS-R total score). The percentage of subjects who achieved the MCID, for each assessment independently, were analyzed using a χ^2 test of independence of two proportions. In addition, MCID odds ratios (ORs) were generated using a logistic regression model adjusted for the baseline value and treatment group.

The trial used a modified intent-to-treat analysis. With the exception of the FSFI sensitivity analyses in subjects with baseline FSD, efficacy analyses were performed on the full analysis set, defined as randomized subjects who received complete or partial treatment and who completed the baseline and 6-month efficacy assessments. Given this approach, no imputation procedures were implemented. TEAEs were evaluated on the safety analysis set, defined as all subjects who received complete or partial treatment (Active and Sham groups). TEAE data were analyzed from the treatment date through study exit using descriptive statistics; no hypothesis testing was conducted.

Statistical analyses were conducted using STATA 14 (STATA Corp, College Station, TX, USA). The overall type I error was controlled at 0.05 (two-sided) for the primary efficacy end point (no vaginal laxity). All secondary efficacy end points were compared with a significance level of 0.05 (two-sided). No adjustments were made for multiplicity for the secondary end points. Given the number of comparisons, secondary end points were considered exploratory. The assumptions of normality of error distribution (ie, homoscedasticity) and linearity were assessed for the ANCOVA CFB analyses.

RESULTS

Participants

From January 2015 through March 2016, 254 subjects were screened for study enrollment. One hundred eighty-nine subjects were enrolled and 186 were randomized (Active n = 123; Sham n = 63). Figure 1 shows the disposition for randomized subjects. Of randomized subjects, 174 received RFc therapy to the vaginal introitus (Active n = 117; Sham n = 57). The numbers of subjects who completed the baseline and 6-month assessments for the primary efficacy end point were 108 (88%) and 56 (89%) for the Active and Sham groups, respectively. The mean age and number of full-term pregnancies were 40.8 and 2.2, respectively, for all randomized subjects. Baseline characteristics and maternal history were comparable between treatment groups (Table 1). The distribution of randomized subjects by study site is presented in eTable 3.

Efficacy (Primary and Secondary End Points)

Summary statistics for the VLQ score, FSFI total score, and FSDS-R total score at baseline and 1, 3, and 6 months are presented in Table 2. Baseline values were similar for the two treatment groups. For all assessments, subjects who received Active treatment showed greater improvement.

The primary efficacy analysis is presented in Table 3. The percentage of subjects in the Active group reporting no vaginal laxity (VLQ score $\geq$ 5) at 6 months after treatment was 43.5% (47 of 108) compared with 19.6% (11 of 56) in the Sham group (P = .002 by χ^2 test). The adjusted OR (OR = 3.39; 95% CI =1.54–7.45) showed the likelihood of no vaginal laxity at 6 months was more than three times greater for subjects who received Active rather than Sham treatment. At 1 and 3 months after treatment, the percentage of subjects with no vaginal laxity was greater for the Active treatment group but did not reach statistical significance until 6 months after treatment.

Secondary efficacy analyses at 6 months after treatment are presented in Table 4. Subjects who received Active treatment had significantly greater improvement regarding their perception of vaginal laxity or looseness (VLQ assessment) compared with subjects who received Sham treatment (P = .004). The adjusted mean changes (AMCs) from baseline to 6 months were 1.80 and 1.07 on the seven-point scale for the Active and Sham groups, respectively (adjusted difference = 0.73; 95% CI = 0.23–1.20). Similarly, subjects in the Active treatment group reported significantly greater improvement on the FSFI total score. The AMCs on the FSFI total score were 4.16 and 2.36 for the Active and Sham groups, respectively (adjusted difference = 1.80; 95% CI = 0.17–3.43).

Table 4. Analysis of covariance results: change from baseline to 6 months postintervention (Active vs Sham)

Assessment	Treatment	n	Adjusted* mean change (SE)	Adjusted* difference	95% CI	*P* value
VLQ score	Active	108	1.80 (0.15)	0.73	0.23–1.20	.004
	Sham	56	1.07 (0.20)			
FSFI total score	Active	108	4.16 (0.48)	1.80	0.17–3.43	.031
	Sham	55	2.36 (0.67)			
FSDS-R total score	Active	107	−6.55 (0.74)	−2.42	−4.91 to 0.0	.056
	Sham	56	−4.13 (1.02)			

FSDS-R = revised Female Sexual Distress Scale; FSFI = Female Sexual Function Index; SE = standard error; VLQ = Vaginal Laxity Questionnaire.
*Adjusted mean change and adjusted difference were estimated from analysis of covariance models that included baseline score and treatment group as independent variables.

Statistically significant improvements for subjects who received Active treatment also were observed for the arousal and lubrication domains of the FSFI (data not shown). The analysis of the FSFI total score performed on the two-thirds (108 of 163) of randomized subjects with sexual dysfunction (FSFI total score $\leq$ 26.5) at baseline showed even greater improvement on the FSFI total score for the Active vs Sham group (eTable 4). Results on the sexual distress scale (FSDS-R total score) showed a borderline significant finding of less distress for the Active group (AMC = −6.55) compared with the Sham group (AMC = −4.13).

The MCID analyses at 6 months postintervention are presented in Table 5. These analyses evaluated the difference in the proportion of Active vs Sham subjects who experienced what they perceived to be a clinically meaningful treatment benefit (eTable 5) relative to change on each assessment. The MCID for the VLQ assessment was an improvement of at least two points (on the seven-point scale). Fifty-seven subjects (52.8%) in the Active group and 17 (30.4%) in the Sham group achieved an improvement of at least two points on the VLQ assessment (P = .006 by χ^2 test). The MCID OR (95% CI) showed subjects in the Active group were more than 2.6 times as likely to achieve a clinically meaningful treatment benefit regarding their perception of vaginal laxity or looseness compared with subjects in the Sham group (OR = 2.63; 95% CI = 1.31–5.27).

The MCID for the FSFI total score was an improvement of at least 4.8 points. Forty-six subjects (42.6%) in the Active group and 14 (30.4%) in the Sham group achieved an improvement of at least 4.8 points on the FSFI total score (P = .036 by χ^2 test). The MCID OR (95% CI) showed that subjects in the Active group were more than 2.4 times as likely to achieve a clinically meaningful treatment benefit regarding overall sexual function than those in the Sham group (OR = 2.46; 95% CI = 1.06–5.72).

The MCID for the FSDS-R total score was an improvement of 5.9 points. Fifty-eight subjects (54.2%) in the Active group and 19 (33.9%) in the Sham group achieved at least this degree of improvement (P = .014 by χ^2 test). The MCID OR (95% CI) showed subjects in the Active group were more than twice as likely to achieve a clinically meaningful treatment benefit regarding decreased sexual distress than those in the Sham group (OR = 2.33; 95% CI = 1.07–5.07).

Safety

TEAEs are presented in Table 6, eTable 6, and eTable 7. The study was not powered to enable definitive conclusions regarding safety. In the safety analysis set (N = 174; Active n = 117; Sham n = 57), there were 38 (32.5%) and 20 (35.1%) subjects in the Active and Sham groups, respectively, who reported at least one TEAE. Overall, the frequency, severity, and relatedness of TEAEs were mild, resolved spontaneously, and were similar in the two treatment groups.

TEAEs that were classified as related (including unknown and possibly related) to the treatment procedure were reported by 13

Table 5. MCID: analyses at 6-month time point (Active vs Sham)

Assessment	Treatment	MCID value*	n	≥MCID, n′ (%)	*P* value by χ^2 test	MCID OR†	95% CI	*P* value
VLQ score	Active	2.0	108	57 (52.8)	.006	2.63	1.3–5.2	.006
	Sham		56	17 (30.4)				
FSFI total score	Active	4.8	108	46 (42.6)	.032	2.46	1.0–5.7	.036
	Sham		55	14 (25.5)				
FSDS-R total score	Active	−5.9	107	58 (54.2)	.014	2.33	1.0–5.0	.033
	Sham		56	19 (33.9)				

FSDS-R = revised Female Sexual Distress Scale; FSFI = Female Sexual Function Index; MCID = minimal clinically important difference; n′ = number of subjects who achieved the MCID; OR = odds ratio; VLQ = Vaginal Laxity Questionnaire.
*The MCID value was determined for each assessment at the 6-month time point. This value represents the smallest change (6-month value minus baseline value) that a subject would identify as clinically important.
†MCID ORs were estimated using multivariable logistic regression with treatment group and baseline score as independent variables.

Table 6. TEAEs: safety analysis set*

	Active treatment (n = 117)	Sham treatment (n = 57)
Total TEAEs, n (%)	57	29
Subjects with TEAE	38 (32.5)	20 (35.1)
Subjects with related TEAE	13 (11.1)	7 (12.3)
Subjects with serious TEAE	0 (0.0)	1 (1.8)
Subjects with serious TEAE of death	0 (0.0)	0 (0.0)
Subjects with TEAEs, n′ (%′ [n′/n″])		
TEAEs by greatest severity		
Grade 1: mild	14 (36.8)	8 (40.0)
Grade 2: moderate	24 (63.2)	11 (55.0)
Grade 3: severe	0 (0.0)	1 (5.0)
Grade 4: life threatening	0 (0.0)	0 (0.0)
Grade 5: death related to TEAE	0 (0.0)	0 (0.0)
Strongest relation to device or procedure†		
Unrelated	25 (65.8)	13 (65.0)
Unknown or undetermined	1 (2.6)	1 (5.0)
Possibly related	10 (26.3)	5 (25.0)
Related	2 (5.3)	1 (5.0)
Strongest action taken		
No action taken	34 (89.5)	17 (85.0)
Treatment procedure interrupted	0 (0.0)	0 (0.0)
Treatment procedure discontinued	1 (2.6)	0 (0.0)
Not applicable	3 (7.9)	3 (15.0)

% = n/N × 100, where N = number of subjects in safety analysis set and n = number of observations in category; %′ = n′/n″, where n″ = number of subjects in safety analysis set with TEAE and n′ = number of observations in category; TEAE = treatment-emergent adverse event.

*TEAEs that began or worsened in severity after treatment. The safety analysis set consists of all subjects who were randomized and who received complete or partial treatment. For the subjects with a TEAE, subjects are counted only once for highest severity, once for strongest relation to the procedure or device, and once for the strongest action taken, regardless of the number of adverse events reported by the subject.

†TEAEs were counted as "not related" only if the relation was recorded by the site investigator or the Viveve Medical Monitor as "Unrelated". TEAEs were counted as "Related" if relationship was recorded as "Possibly Related", "Related", "Unknown/Undetermined", or if relationship was missing.

subjects (11.1%) in the Active group and 7 (12.3%) in the Sham group. The most frequently reported related TEAE was vaginal discharge (MedDRA system organ class code 10038604), which occurred in three subjects (2.6%) in the Active group and two (3.5%) in the Sham group. Related TEAEs by system organ class and preferred term are presented in eTable 6. No subjects (0.0%) in the Active group and only one (1.8%) in the Sham group had a serious AE. No medically necessary action was taken to resolve the TEAE for 34 of 38 subjects (89.5%) in the Active group and 17 of 20 subjects (85.0%) in the Sham group. Only one subject in the Active group reported pain or discomfort during treatment to an extent that warranted discontinuation of the procedure (eTable 7). The subject underwent surveillance for 3 months; no additional AE was reported and no additional action was necessary.

DISCUSSION

Building on two single-arm pilot studies,[1,16] the VIVEVE I trial is the first multicenter, randomized, sham-controlled study to evaluate the efficacy and safety of RFc therapy for the treatment of vaginal introital laxity. The study results showed statistically significant improvements of self-reported vaginal laxity (VLQ), overall sexual function (FSFI), and decreased sexual distress (FSDS-R). Active RFc therapy demonstrated statistically significant and clinically meaningfully superiority over Sham therapy using validated assessments of sexual function (FSFI) and sexual distress (FSDS-R). Furthermore, the MCID analyses showed RFc therapy delivered a statistically significant and clinically meaningful treatment benefit for vaginal laxity (VLQ), overall sexual function (FSFI), and sexual distress (FSDS-R). The FSFI total score analysis for subjects with baseline sexual dysfunction showed the treatment effect was even greater in this population.

Outpatient RFc therapy to the vaginal introitus was well tolerated and showed an excellent 6-month safety profile, with no substantial difference in AE reporting between the Active and Sham groups. The positive efficacy and safety results from this trial support the proposed mechanism of action and safe delivery of minimally invasive RFc therapy for the treatment of vaginal laxity. Improvements on the VLQ score, FSFI total score, and FSDS-R total score for the Active group in this trial were similar in magnitude to improvements on the same assessments in the two single-arm pilot studies of RFc therapy.[1,16] Currently, there are no other published comparative efficacy and effectiveness studies (ie, studies with an inactive or reference comparator group) in the literature or on clinicaltrials.gov of any energy-based therapy for the treatment of vaginal laxity to further contextualize the efficacy or safety results of this trial.

Few studies of vaginal tightening surgical procedures using validated sexual function assessments (eg, FSFI or FSDS-R) have been published. Abedi et al[20] reported results from a single-arm study of selective vaginal tightening surgery in women with vaginal laxity. Six months after surgery, the mean FSFI total score was 26.92 (SD = 3.41), representing a mean improvement of 2.73. Compared with the results of the VIVEVE I trial, the functional improvement in the study by Abedi et al was greater than the improvement observed in the Sham group but less than the improvement in the Active group. Single-arm studies of surgical POP repair in women with FSD reported non-significant improvement (before vs after surgery) on the FSFI and FDSD-R

total scores, which were similar in magnitude to the statistically significant improvement reported in this trial.[33,34]

The present study had several limitations. Despite the favorable AE profile in the VIVEVE I trial, it was not powered to detect rare AEs. Moreover, no control for multiplicity of secondary end points was applied; therefore, caution must be exercised when interpreting these results. Furthermore, the increased magnitude of the effect in subjects with baseline sexual dysfunction, as assessed by the FSFI questionnaire, suggests the overall improvement on FSFI total score might be attenuated. Further research is warranted to fully elucidate this finding. Two sites contributed more than half the randomized subjects (eTable 3). Although the results at each of the two sites were consistent with the overall safety and efficacy findings, a more even distribution of research subjects at each site is warranted in future studies to mitigate the potential for bias or effect modification and to increase external validity.

The primary efficacy end point (ie, no vaginal laxity at 6 months) was powered to detect a difference between Active and Sham treatment with an estimated Sham treatment effect of 15%. The observed Sham treatment effects in the VIVEVE I trial were 30%, 33%, and 20% at 1, 3, and 6 months post-intervention, respectively (Table 3). Although there was a statistically significant difference in the VIVEVE I trial at 6 months, the Sham effect exceeded expectations—especially at 1 and 3 months. To adequately power and design future research initiatives, investigators must take into account the possibility of a substantial "sham effect" for sexual function studies; this underscores the importance of placebo- or sham-controlled trials to ensure the observed treatment effect is causally associated with the investigational product.

An additional limitation was the use of single-blinding rather than double-blinding. Early system and study design made blinding of the treatment arm difficult to achieve while providing a valid "sham" effect. Although subjects were unaware of treatment assignment for the entire study duration, the site investigator was aware of treatment assignment. Despite this limitation, similar baseline characteristics and a similar study dropout rate empirically suggest bias was not introduced by investigator channeling or differential study conduct by treatment assignment throughout the entire duration of the trial and follow-up. The robust "sham" effect in the first 3 months further suggests study validity was not compromised by single-blinding. To mitigate investigator channeling bias, subjects assigned to the Sham group were permitted to receive Active RFc therapy at study completion.

Despite the high prevalence of vaginal laxity in the general population, comparative efficacy evidence of therapeutics to improve sexual function in women with vaginal laxity is remarkably scant. The VIVEVE I trial is the only high-quality, fully powered, randomized, multicenter, sham-controlled clinical trial to evaluate changes in vaginal laxity and sexual function in women with vaginal laxity. Data from the VIVEVE I trial showed that RFc delivered to the vaginal introitus was associated with statistically significant and clinically important improvements of vaginal laxity or looseness and overall sexual function and decreased sexual distress compared with Sham treatment. The RFc procedure was well tolerated and associated with a favorable safety profile through 6 months after intervention. The findings from the VIVEVE I trial provide evidence for the clinical use and further evaluation of this novel, non-surgical outpatient modality for a highly prevalent and undertreated condition. These trial results underscore the importance of conducting rigorous research using a comparator arm (placebo or sham) with adequate follow-up time to permit the estimation of a valid treatment effect.

Corresponding Author: Michael Krychman, MD, Southern California Center for Sexual Health and Survivorship Medicine, 1501 Superior Avenue, Suite 201, Newport Beach, CA 92663, USA. Tel: 949-764-9300; E-mail: mkrychman@icloud.com

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Michael Krychman; Bruce B. Allan; Leonard DeRogatis; Scott Durbin; Deborah Wilkerson

(b) Acquisition of Data
Michael Krychman; Bruce B. Allan; Ashley Yacoubian; Deborah Wilkerson

(c) Analysis and Interpretation of Data
Michael Krychman; Christopher G. Rowan; Bruce B. Allan; Leonard DeRogatis; Scott Durbin; Ashley Yacoubian; Deborah Wilkerson

Category 2

(a) Drafting the Article
Michael Krychman; Christopher G. Rowan; Deborah Wilkerson

(b) Revising It for Intellectual Content
Michael Krychman; Christopher G. Rowan; Bruce B. Allan; Leonard DeRogatis; Scott Durbin; Deborah Wilkerson

Category 3

(a) Final Approval of the Completed Article
Michael Krychman; Christopher G. Rowan; Bruce B. Allan; Leonard DeRogatis; Scott Durbin; Ashley Yacoubian; Deborah Wilkerson

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jsxm.2016.11.322.