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CLINICAL ARTICLE

Gynecology

Vaginal erbium laser treatment for stress urinary incontinence: A multicenter randomized sham-controlled clinical trial

Barry A. O'Reilly[1] | Volker Viereck[2] | Christian Phillips[3] | Philip Toozs-Hobson[4] | Annette Kuhn[5] | Stavros Athanasiou[6] | Adolf Lukanović[7] | Brendan Palmer[8] | Darren Dahly[8] | Yair Daykan[9,10] | Linda Cardozo[11]

[1]Department of Urogynecology, Cork University Maternity Hospital, Cork, Ireland

[2]Bladder and Pelvic Floor Center/ Urogynecology, Kantonsspital Frauenfeld, Frauenfeld, Switzerland

[3]Women's Health Unit, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK

[4]Urogynecology Department, Birmingham Women's & Children's NHS Foundation Trust, Birmingham, UK

[5]Women's Clinic/Clinic for Gynecology, Universitätsspital Bern, Bern, Switzerland

[6]Department of Urogynecology and Pelvic Floor Surgery, Alexandra University Hospital, Athens, Greece

[7]Division of Gynecology and Obstetrics, University Clinical Center Ljubljana, Ljubljana, Slovenia

[8]Clinical Research Facility, University College Cork, Cork, Ireland

[9]Department of Obstetrics and Gynecology, Meir Medical Center, Kfar Saba, Israel

[10]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[11]Urogynecology Department, King's College Hospital NHS Foundation Trust, London, UK

Correspondence
Barry A. O'Reilly, Department of Urogynecology, Cork University Maternity Hospital, Cork, Ireland.
Email: barry.oreilly@ucc.ie

Abstract

Objective: To evaluate the efficacy and safety of non-ablative vaginal Er:YAG laser device in stress urinary incontinence (SUI) treatment.

Methods: We conducted a multicenter blinded randomized sham-controlled trial in which women with urodynamic SUI were randomization to active arm using Er:YAG laser therapy, and sham arm using sham handpiece. Patients received two treatments 1 month apart. The primary outcomes measure was 1 h pad weight test measured at 6 months. Secondary outcomes were durability of treatment success at 12 months, and questionnaires for assessment of SUI severity (ICIQ-UI SF), sexual function (PISQ-12) and HRQoL (KHQ), and incidence and severity of device related adverse events and pain (VAS).

Results: A total of 110 participants with SUI were recruited; 73 in the active arm and 37 in the sham arm. Two participants were excluded; one was assigned the wrong treatment and one withdrew their consent. Treatment success was observed in 36% of the sham arm and 59% of the active arm; in the latter, odds of achieving treatment success were more than three-fold higher (OR 3.63, 95% CI: 1.3–11.2, $P=0.02$). HRQoL by KHQ showed significant improvement in the active versus the sham arm (OR 0.36, 95% CI: 0.15–0.87, $P=0.003$). Similarly, subjective patient assessment of general and sexual function improvement with PISQ-12 and PGI-I showed superior effect over sham (OR 2.8, 95% CI: 1.2–7.0, $P=0.02$ and OR 0.13, 95% CI: 0.05–0.36, $P<0.001$, respectively).

Conclusion: Non-ablative vaginal Er:YAG laser therapy significantly improves SUI symptoms versus sham treatment. Er:YAG laser therapy should be considered as a non-surgical treatment option for SUI patients.

This trial was presented at the 14th EUGA Annual Congress, Ljubljana, October 2021 and at ICS Melbourne online, October 2021 (www.ics.org/2021/abstract/218).

Trial Registration: NIH ClinicalTrials.gov—NCT03098992, https://clinicaltrials.gov/ct2/show/NCT03098992.

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KEYWORDS
Er:YAG, laser, non-ablative, pad test, stress urinary incontinence, vaginal

1 | INTRODUCTION

Stress urinary incontinence (SUI), an involuntary leakage of urine on physical effort or exertion, is a common condition affecting 25%–45% of women in their lifetime.[1] Although non-life-threatening, it profoundly impairs health-related quality of life (HRQoL) placing a significant financial burden on women and healthcare systems.[1] Care of women who actively seek help, typically consists of initial advice on lifestyle changes (e.g., diet or weight loss) and conservative treatments (pessaries and pelvic floor muscle training [PFMT]), both requiring a high level of commitment and patient compliance, in order to achieve desired results. However, the available effective surgical procedures are linked to significant downtime and potential complication rates,[1] clearly indicating a need for novel, safer, non-surgical treatment options for SUI.[2]

SUI arises from decreased support of the pelvic floor and vaginal connective tissue around the bladder neck and urethra. The majority of therapeutic approaches are aimed at strengthening different components of the urethral support, either conservatively by PFMT, or surgically, mainly focused on strengthening the suburethra. Non-ablative vaginal erbium laser (VEL; 2940 nm Er:YAG) using the SMOOTH mode technology[3] has been shown to promote the formation of neocollagen in the treated tissue,[4–8] and to restore the tissue structure;[9] resulting in a thickened and strengthened vaginal wall, which offers improved support of the bladder and urethra,[10] and subsequently leads to continence. The positive changes in the structure of the tissue have been used for treatment of SUI,[10–17] vaginal laxity[18–20] and symptoms of genitourinary syndrome of menopause (GSM).[21–23] Indeed, previous trials using the vaginal erbium laser (VEL) technology have shown promising and consistent results on efficacy and safety[24] with a favorable risk–benefit ratio following treatment;[24] notwithstanding the need for higher data quality from parallel-arm randomized controlled trials. We, therefore aimed to compare the effects of active VEL treatment to sham treatment with a longer follow-up period, by assessing the objective and subjective outcomes after 6 months in both arms and 12 months in the active arm, in a European multicenter setting, recruiting participants with urodynamically proven SUI. We chose to use urodynamic diagnosis across all recruiting sites to ensure homogeneity of participants.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multicenter, randomized single-blind sham-controlled trial assessing the efficacy and safety of vaginal erbium laser (VEL) for the treatment of stress urinary incontinence (SUI). Patients were recruited between June 2017 and June 2020.

Inclusion criteria were participants with urodynamic SUI, older than 18 years, that had undergone at least one previous conservative treatment with no significant improvement in urinary incontinence. Participants were recruited and enrolled in the trial from eight specialist urogynecological centers/hospitals.

The participants were given an opportunity to discuss the screening procedures, any risks, benefits, and the screening study requirements with the investigator prior to undergoing screening. Exclusion criteria for participation in the study were pre-existing bladder pathology, pregnancy, obesity class II (body mass index: BMI, calculated as weight in kilograms divided by the square of height in meters) BMI >35 and above, radical pelvic surgery or previous incontinence surgery, urinary tract infection or other active infections of urinary tract or bladder, endometriosis, any form of pelvic organ prolapse greater than POP-Q stage 2, concomitant diagnosis of detrusor overactivity or diagnosis of collagen disorders, for example, benign joint hypermobility/Elhers-Danlos/Marfans, and so on. Participants were also excluded if they had incomplete bladder emptying, vesicovaginal fistula, fecal incontinence or were unwilling or unable to complete follow-up schedule or give informed consent.

2.2 | Procedure

Participants who met the inclusion criteria were invited to voluntarily participate in the trial. Signed informed consent was obtained from those who agreed to participate.

The IncontiLase® protocol for treatment of SUI is a three-step procedure during which the vaginal tissue is irradiated with 2940 nm Er:YAG laser light using specific non-ablative, thermal smooth pulses (Protocol, Fotona, Slovenia). The active arm received an active laser therapy, while the sham arm received treatment using the same laser, but with a sham handpiece, in which the laser beam is physically blocked from reaching the tissue. Post-procedure participant care was equal for both groups.

2.3 | Active arm description (laser treatment)

Two non-ablative Er:YAG IncontiLase® treatments applied at monthly intervals.

The IncontiLase® protocol consists of three steps:

1. Intravaginal laser pulses with a directed angular, patterned laser beam (PS03-GAc, 7 mm, 6 J/cm^2, 2.0 Hz, seven pulses, six positions, one pass per position)
2. Intravaginal laser pulses with a circular full laser beam (R11-GCc, 7 mm, 3 J/cm^2, 2.0 Hz, seven pulses, two passes)

3. Laser pulses of vestibule and introitus with a straight, patterned laser (PS03, 7 mm, 10 J/cm^2, 1.6 Hz, two to three pulses, two to three passes, 10% overlapping)

The total duration of the treatment: 20 min/session.

2.4 | Randomization

A statistical analysis plan (SAP) was performed during the study design. Enrolled participants were randomly allocated into active and sham arms in a 2:1 ratio. The randomization was stratified by center and restricted using a block size of 15. Allocation concealment was achieved by sequentially numbered opaque sealed envelopes. This was a single-blind clinical trial with the participants being blinded to allocation. Data were collected and analyzed by separate research staff who were blinded to the treatment arms.

2.5 | Data collection and outcomes

Clinical and vaginal examination took place at the day of each treatment. At the end of each treatment, pain and adverse events were assessed. Forty-eight hours after each treatment, a telephone follow-up occurred for an adverse event review.

Data were collected for both arms at baseline, 3-month follow-up (FU) visit and after 6-months. The active arm had an additional FU visit after 12-months. The data catalog included a 1-h pad weight test,[25] cough stress test (CST) performed in two positions[26] and questionnaires for assessment of SUI severity, sexual function, and HRQoL. Outcome assessment included leakage quantity, as measured by 1-h pad weight test, leakage frequency as recorded by a 3-day bladder diary, CST, International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form (ICIQ-UI SF),[27] the Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire short form (PISQ-12),[28] the King's Health Questionnaire (KHQ)[29] for the condition-specific HRQoL and Patient Global Impression of Improvement (PGI-I).[30]

The primary outcome measure for efficacy treatment success was defined per FDA guidelines[31] as a standardized 1-h pad weight test[25] at 6 months FU that represented a greater than 50% reduction in the pad weight from the weight recorded at baseline.

The secondary trial endpoints included the CST results; KHQ,[29] ICIQ-SF[27] and PISQ-12[28] scores; participant assessment of pain during treatment using a visual analog score (VAS); and the durability of treatment success in the active group at 12 months FU.

Anticipated adverse events (AEs) were defined a priori and included all general risks associated with practiced minimally invasive treatments of SUI (erythema, infection, bleeding, fever, abrasions, lacerations, injury to adjacent structures, discomfort, transient urinary retention, or inflammation of urethra, cramping or pelvic pain, and vaginal discharge).

2.6 | Statistical and subgroup analyses

All data was collected and transferred in a blinded fashion to independent statisticians at University Collge Cork for complete analysis. Primary and secondary outcomes are described by means and standard deviations (SD) and total ranges when continuous, and by their counts and percentages when categorical. Using a modified intention to treat principle (modified ITT), the primary outcome (FDA defined treatment success/failure at 6 months) was estimated using logistic regression. To explore heterogeneity of treatment effects by objective SUI severity based on baseline 1-h pad weight (mild 0–10 g, moderate 11–50 g, severe <50 g), we estimated an additional model that also included a severity by treatment arm interaction. To further supplement this analysis, we also used a log-linear regression model to estimate the between-arm difference in the log of continuously measured pad weight at 6 months, adjusted for baseline pad weight. Analysis of the 3-day bladder diary was performed using Poisson regression analysis. Pain scores after each treatment were analyzed using linear regression. QoL outcomes (KHQ, ICIQ and PISQ-12) were analyzed using ordinal regression models with a logistic link function (i.e., the proportional odds model) to account for the highly skewed continuous nature of the health-related QoL outcomes. All estimated effects were reported with 95% confidence intervals and two-sided *P* values based a null of no treatment effect. A *P* value less than 0.05 was considered statistically significant.

To account for missing data and its effect on final result, multiple imputation with chained equations[32] was used to estimate the treatment effect under the MAR assumption.[33] Multiple imputation of the primary outcome was based on a logistic regression prediction model with a rich dataset that included trial arm, study center, baseline pad weight, BMI, and other baseline patient characteristics. A total of 100 imputed datasets were created, fitting the primary analysis model (logistic regression of the primary outcome on trial arm with adjustment for study center) to each of them and pooled the results using Rubin's rules.[34] All models presented are reported having been adjusted trial center, and the baseline measurement of the outcome when available. Analyses were conducted using R version 4.1.0 (R Core Team, 2021).[35]

2.7 | Sample size calculation

The sample size calculation was based on the primary efficacy hypothesis. Sample size was estimated using a success estimate of 60% for the active arm (based on published literature describing treatments with similar mechanism of action[36]) and 30% for the sham arm.[37] We used a 2:1 allocation ratio. This yielded an intention-to-treat analysis sample size of 69 active and 35 sham participants for 81% power, a total of 104 participants. To compensate for the expected 15% drop-out rate, a total of 120 participants were expected to be recruited in this trial.

3 | RESULTS

Of 110 participants with SUI recruited between October 2015 and October 2019, overall, 73 were randomized into the active arm and 37 into the sham arm. A consolidating standards of reporting trials (CONSORT) flow diagram of patient recruitment and participation is shown in Figure 1. One participant from the active arm was assigned the wrong treatment, and one withdrew consent. Overall, 71 patients received allocation intervention in the active arm and 37 in the sham group. Both were excluded from further analysis (Figure 1).

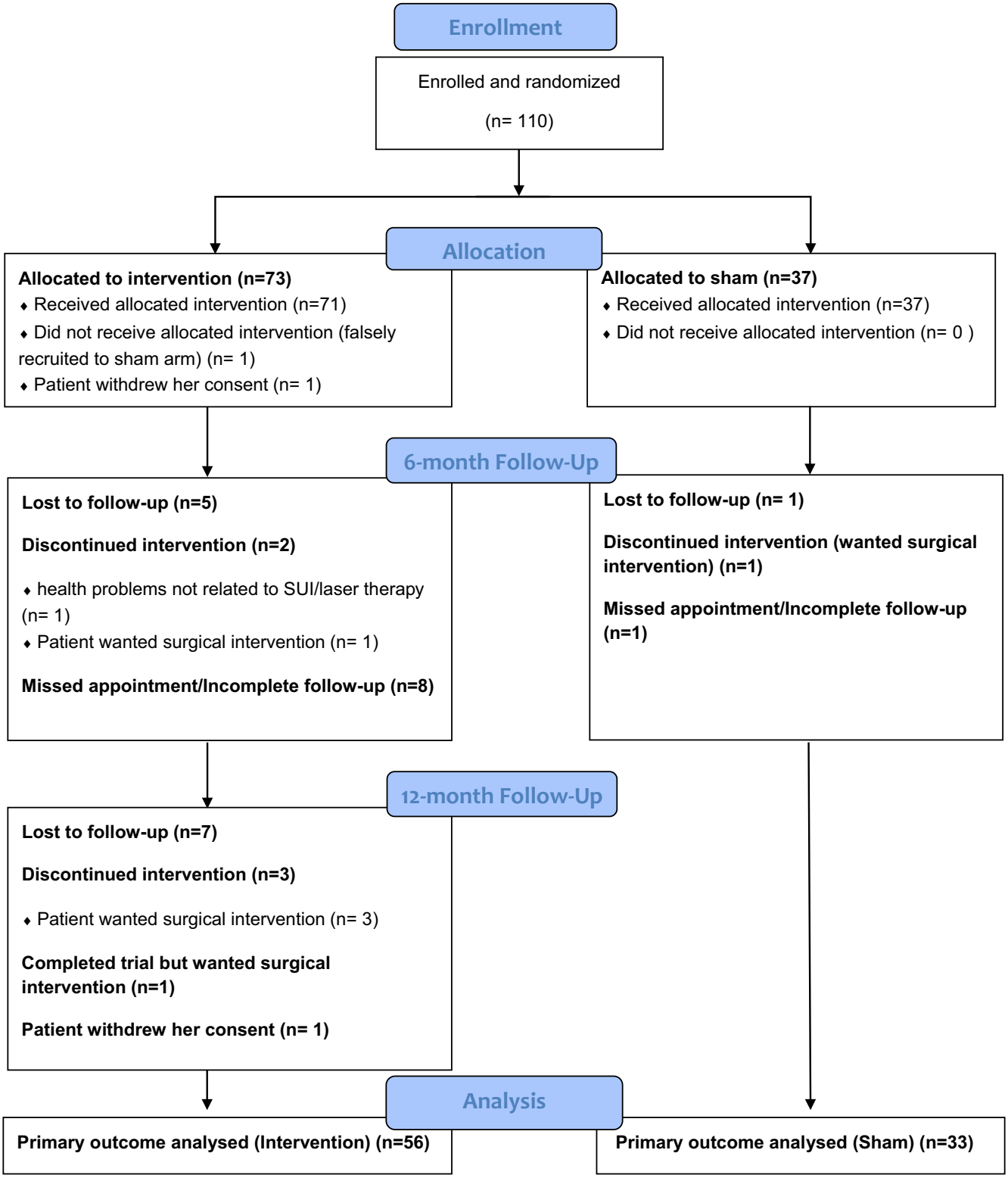

FIGURE 1 Consolidating standards of reporting trials (CONSORT) flow diagram.

A summary of the baseline characteristics of study participants is presented in Table 1. Both groups were similar on baseline characteristics, including baseline pad weight.

3.1 | Primary outcomes

Data on the primary outcome were available for 56 (79%) active arm and 33 (89%) sham arm participants. A total of 19 participants (15 active, 5 sham) were lost to FU or not included in analysis as illustrated in the CONSORT flow diagram.

At the 6 months FU visit, a treatment success (>50% reduction in pad weight from baseline) was observed in 33/56 (59%) of participants in the active arm and 12/33 (36%) of participants in the sham arm (Figure 2). The odds of achieving treatment success were more than three-fold higher in the active arm versus the sham arm (OR 3.63, 95% CI: 1.3–11.19, *P* value = 0.02) (Table 2). The results were similar after adjusting for key prognostic factors (age, BMI, menopause, smoking, number of vaginal deliveries) (OR 4.11, 95% CI: 1.23–16.09, *P* value = 0.03) or exclusion of severe cases (baseline pad weight > 50 g; *n* = 7) (OR 4.55, 95% CI: 1.53–15.29, *P* value = 0.01). Mean pad weights at 6 months FU were 80% lower in the active arm compared to the sham arm (ratio of geometric means 0.20, 95% CI: 0.09–0.47, *P* < 0.001) (Table 2). There was no strong evidence of heterogeneity of treatment effects by baseline SUI objective severity based on the likelihood ratio test of the severity by treatment arm interaction.

To account for missing primary outcome data for 4/37 patients in the sham arm (11%) and 15/71 (21%) in the active arm we performed supplemental analysis to explore associations between the missing data and patient characteristics. Patients with missing outcomes were broadly similar to those with observed values, with the exception of baseline pad weight. For those missing the primary outcome, the median pad weight was 10 (IQR 5, 37) versus 5 (2, 15) for those with observed outcomes. The resulting estimate of the treatment effect was slightly attenuated, with an OR of 3.33 (vs. 3.63 in the complete case analysis reported) but more precise due to the retention of sample with missing values (95% CI: 2.13–5.2 vs. 1.3–11.9 in the complete case analysis).

3.2 | Secondary outcomes

Pain scores were higher in the active versus sham arm following both treatments (treatment 1 difference in means: 3.4 [95% CI: 2.7–4.2], *P* < 0.001; treatment 2: 2.5 [95% CI: 1.8–3.2], *P* < 0.001). The condition-specific HRQoL, as measured by KHQ, showed significantly greater improvement in active arm relative to sham arm (OR = 0.40 [95% CI: 0.17–0.97, *P* = 0.042] (Table 2).

Similarly, the PISQ-12 and PGI-I also showed significantly greater improvement in the active arm (OR = 2.83 (95% CI: 1.16–6.97, *P* = 0.02) and OR = 0.13 (95% CI: 0.05–0.36, *P* = <0.001), respectively [Table 2]). The higher values for PISQ-12 mean greater satisfaction,

TABLE 1 Baseline demographic and clinical characteristics of each arm.

Characteristic	Overall[b]	Study arm	
		Sham, *N* = 37[b]	Active, *N* = 71[b]
Age (years) at time of treatment	47.8 (10.9); 45.0 [26.0, 76.0]; *n* = 107	46.7 (9.8); 45.0 [32.0, 70.0]; *n* = 37	48.4 (11.5); 45.5 [26.0, 76.0]; *n* = 70
BMI (kg/m^2)	24.8 (3.8); 24.0 [18.7, 35.0]; *n* = 106	24.6 (4.3); 23.4 [18.7, 35.0]; *n* = 37	25.0 (3.6); 24.0 [19.0, 33.0]; *n* = 69
Menopausal status	*n* = 107		
Premenopausal	58/107 (54%)	20/36 (56%)	38/71 (54%)
Menopause	49 (46%)	16 (44%)	33 (47%)
Parity	2.5 (1.1); 2.0 [1.0, 7.0]; *n* = 106	2.7 (1.4); 2.0 [1.0, 7.0]; *n* = 37	2.4 (0.9); 2.0 [1.0, 5.0]; *n* = 69
Vaginal deliveries	2.2 (0.9); 2.0 [1.0, 5.0]; *n* = 104	2.2 (0.9); 2.0 [1.0, 5.0]; *n* = 36	2.2 (0.9); 2.0 [1.0, 5.0]; *n* = 68
Hysterectomy	*n* = 107		
Yes	4/107 (3.7%)	1/37 (2.7%)	3/70 (4.3%)
No	103/107 (96%)	36 (97%)	67 (96%)
Bladder capacity (mL)	459.9 (128.2); 480.0 [18.0, 886.0]; *n* = 93	466.2 (101.6); 476.0 [247.0, 717.0]; *n* = 32	456.6 (140.8); 481.0 [18.0, 886.0]; *n* = 61
Baseline pad weight (g)	18.0 (33.0); 6.0 [0.0, 203.0]; *n* = 108	16.8 (32.2); 6.0 [0.1, 173.6]; *n* = 37	18.6 (33.7); 6.0 [0.0, 203.0]; *n* = 71
Leakages (3-day diary)	2.2 (2.0); 1.7 [0.0, 9.0]; *n* = 99	2.0 (1.9); 1.8 [0.0, 7.3]; *n* = 34	2.3 (2.1); 1.7 [0.0, 9.0]; *n* = 65
Recurrent UTI[a]	1/105 (1.0%)	1/37 (2.7%)	0/68 (0%)

Note: Continuous variables are described by their means (SD). Categorical variables are described by the counts in each category and their respective proportions.

Abbreviation: BMI, body mass index (BMI, calculated as weight in kilograms divided by the square height in meters).

[a]Recurrent urinary tract infection (UTI) is clinically defined as a three or more UTIs within 12 months.

[b]Mean (SD); median [range]; *n* = *N*; *n*/*N* (%).

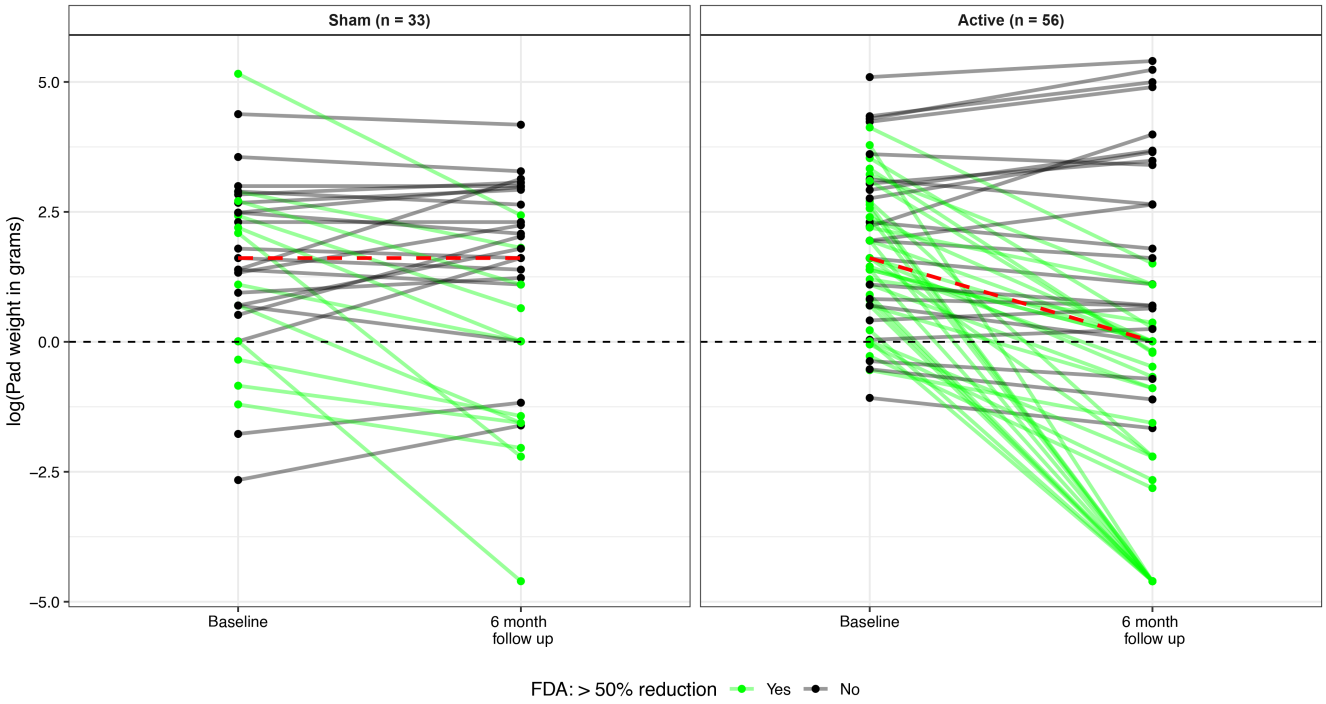

FIGURE 2 Demonstration of treatment success as log transformed pad weight (g) at baseline and at 6 months follow-up in control and active arm. Green line identifies participants who recorded treatment success >50% pad weight reduction from baseline at follow-up, gray lines identify participants without treatment success. Dashed red line identifies the median. Pad weights of zero were recoded to 0.01 for the purposes of supporting the log transformation.

while the lower values for PGI suggest perceived improvement of symptoms.

The analysis of ICIQ scores showed that the odds of a higher value of the ICIQ, meaning worsening of the perception of symptoms' severity, was lower in the active versus the sham arm (OR = 0.46, 95% CI: 0.20–1.04, $P = 0.063$) (Table 2).

The results of the durability of the effect in the active group at 12 months FU was assessed by within-group differences between 6 months FU and 12 months FU ($P = 0.70$ based on McNemar's test for paired binary outcomes). This can be interpreted as the effect being maintained at 12 months FU with a median of 1 g at both 6 months and 12 months, compared to a median of 6 g at baseline (Table 2).

3.3 | Adverse events

A total of 48 participants reported about any kind of AE; however, the AEs were related to the device or intervention in only 23 of them; 17 patients were in the active arm and six were in the sham arm. Altogether these 23 patients reported about 39 incidences of device and intervention related AEs, 28 (72%) were recorded in the active arm and 11 (28%) in the sham arm (Table 3).

All reported AEs were recognized side effects: vaginal discharge, discomfort in vaginal and vulvar area, itching, edema, suspected UTI or vulvitis, discomfort during treatment, and a single incidence of small abrasion at introitus. Most AEs were graded as mild and either required no management or were managed with cranberry capsules, NSAIDs, local anti-inflammatory cream or estrogen cream. One patient with a suspected UTI was treated with antibiotics. All AEs were transient and most frequently resolved in up to 8 days (mean 4.1).

4 | DISCUSSION

The major finding in this multicenter, randomized controlled trial is that VEL treatment demonstrated a statistically significant and clinically relevant superior effect over sham treatment in improving SUI symptoms and no serious AEs were recorded. Two treatment sessions performed with 1 month interval resulted in a 58% treatment success in the active arm and 36% success in the sham arm, as measured by primary outcome measure, the 1-h pad weight test, where a success was defined as >50% reduction in pad weight after 6 months, following the FDA guidelines.[31]

VEL treatment also demonstrated a superior effect over sham treatment in improving the symptoms of SUI, as measured by ICIQ; treatment success measured by PGI-I as well as subjective participant's assessment in improving their sexual function, as measured by PISQ-12 and in improving their health-related QoL, as measured by KHQ.

TABLE 2 Summary of study results.

Characteristic	Study arm		Model estimated effect (95% CI)	*P* value
	Sham, *N* = 37[a]	Active, *N* = 71[a]		
Treatment success at 6 months (primary)	12/33 (36%)	33/56 (59%)	OR 3.6 (1.3– 11.2)[b]	0.018
Pad weight (g) at 6 months	9.0 (12.8); 5.0 [0.0, 65.1]; *n* = 33	17.1 (46.0); 1.0 [0.0, 222.0]; *n* = 56	RGM 0.2 (0.1–0.5)[c]	<0.001
KHQ Part 1 at 6 months	80.0 (28.1); 79.2 [0.0, 125.0]; *n* = 30	63.9 (38.5); 58.3 [0.0, 150.0]; *n* = 55	OR 0.26 (0.1–0.65)[d]	0.004
KHQ Part 2 at 6 months	217.5 (131.3); 216.4 [0.0, 499.7]; *n* = 29	167.1 (142.6); 133.1 [0.0, 672.1]; *n* = 54	OR 0.37 (0.15–0.9)[d]	0.03
KHQ total at 6 months	296.8 (146.1); 319.3 [8.3, 566.3]; *n* = 29	230.0 (173.0); 191.5 [0.0, 797.1]; *n* = 54	OR 0.36 (0.15–0.87)[d]	0.025
PISQ-12 at 6 months	34.3 (6.3); 36.5 [22.0, 46.0]; *n* = 28	37.4 (5.3); 39.0 [22.0, 44.0]; *n* = 44	OR 2.83 (1.16–6.97)[d]	0.023
PGI-1 at 6 months	3.8 (0.8); 4.0 [2.0, 5.0]; *n* = 33	3.1 (1.0); 3.0 [2.0, 6.0]; *n* = 49	OR 0.13 (0.05–0.36)[e]	<0.001
ICIQ-UI SF at 6 months	10.8 (4.6); 10.0 [0.0, 18.0]; *n* = 33	8.8 (4.7); 9.0 [0.0, 20.0]; *n* = 55	OR 0.46 (0.2–1.04)[d]	0.063
Cough test (standing) at 6 months			OR 0.24 (0.08–0.67)[f]	0.008
Dry	12/30 (40%)	42/61 (69%)		
Not dry	18/30 (60%)	19/61 (31%)		
Cough test (lying down) at 6 months			OR 0.27 (0.09–0.78)[f]	0.018
Dry	12/30 (40%)	42/61 (69%)		
Not dry	18/30 (60%)	19/61 (31%)		
Pain VAS 1	0.8 (0.7); 1.0 [0.0, 3.0]; *n* = 37	4.2 (2.4); 4.0 [0.0, 10.0]; *n* = 70	MD 3.4 (2.7–4.2)[g]	<0.001
Pain VAS 2	0.9 (1.3); 1.0 [0.0, 7.0]; *n* = 36	3.4 (2.1); 3.0 [0.0, 9.0]; *n* = 70	MD 2.5 (1.8–3.2)[g]	<0.001

Abbreviations: CI, confidence interval; ICIQ-UI SF, International Consultation on Incontinence Questionnaire–Urinary Incontinence Short Form; KHQ, King's Health Questionnaire; PGI-1, Patient Global Impression of Improvement; PISQ-12, Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire short form; VAS, visual analog score.

[a] *n*/*N* (%); Mean (SD); median [range]; *n* = *N*.

[b] Odds ratio estimated using logistic regression with adjustment for center.

[c] Ratio of geometric means estimated using linear regression of log transformed pad weight with adjustment for center and baseline pad weight.

[d] Odds ratio estimated using original regression with adjustment for center and baseline score.

[e] Odds ratio estimated using original regression with adjustment for center.

[f] Odds ratio estimated using logistic regression with adjustment for center and baseline score.

[g] Mean difference estimated using linear regression with adjustment for center.

TABLE 3 Summary of adverse effect incidences probably or possibly related to device or treatment.

Adverse effect	Observations (*n*)/percentage (%)		Total no. of incidences
	Active	Sham	
(Increased) vaginal discharge	13 (81%)	3 (19%)	16 (41%)
Discomfort in vaginal and vulvar area	9 (56%)	7 (44%)	16 (41%)
Itching	2 (100%)	0	2 (5.1%)
Edema	0	1 (100%)	1 (2.6%)
Suspected UTI or vulvitis	2 (100%)	0	2 (5.1%)
Discomfort during treatment	1 (100%)	0	1 (2.6%)
Abrasion at intoritus	1 (100%)	0	1 (2.6%)
Total per allocation	28 (72%)	11 (28%)	39 (100%)

Abbreviation: UTI, urinary tract infection.

Our primary results confirm VEL as an effective treatment for SUI and is consistent with the previously published data on the VEL treatment of SUI. As such, we have confirmed the previously reported findings of a clinically meaningful improvement (>50% reduction in pad weight) achieved in 60%–79%[10–12,17,21,38,39] of participants with SUI. The reported treatment success in these studies depended on the baseline severity of SUI symptoms, as well as on primary outcome measures, used for evaluation of treatment success (e.g., 1-h pad weight test, ICIQ-UI SF, and so on). As previously observed,[11,12] participants with mild or moderate SUI appeared to have benefited from the VEL treatment to a greater degree as compared to the participants with severe SUI.[11,12] Notwithstanding, as has been previously shown, the treatment effects are dose-responsive thus suggesting participants may have benefited from additional treatment sessions, if these were offered. According to the available data, multiple (>2) treatment sessions result in a sustainable effect lasting 1–2 years.[12,38] Moreover, additional sessions performed every 6 months can further sustain the therapeutic effect.[40] Predictive models[41,42] that have been developed for the non-ablative VEL technology suggest that along with initial SUI severity, BMI, age of the patient, and number of vaginal deliveries are important predictive factors of treatment success.

Our findings on improvement of health related QoL and sexual function (Table 2) corroborate the results of previously conducted trials.[11,17,23] The perception of severity of SUI is highly subjective, which supports the basic requirement of clinical trials in utilizing an array of both objective and subjective outcome measures to assess the efficacy (and safety) of the studied procedure.

Some improvement was noted in the placebo group with 36% of participants in the sham arm demonstrating treatment success, according to the primary outcome measure.[43] In some measure related to the biological variation in symptoms, as well as to a placebo effect of this size, which was anticipated based on previous studies,[11,37,44,45] and has been taken into account in sample size calculation for this clinical trial. The estimation of the magnitude of the placebo effect is not only useful for designing future clinical trials; but also puts in perspective the results of uncontrolled or active-controlled studies;[37,46] in fact, the paradigm of any successful treatment used in clinical practice is to use the placebo effect to maximize its effect on participants receiving active treatment.[47]

In a short-term, single center study the effect of VEL was compared to sham treatment,[11] but in contrast to our trial this study employed only one treatment session, participants were followed up for 3 months and their primary outcome measure was ICIQ-UI SF questionnaire, only. The effects of VEL treatment have also been compared to surgical urethral sling procedures, namely the tension-free vaginal tapes (TVT) and transobturator tape procedures (TOT), in which VEL offered comparable therapeutic results, notably with significantly lower complication rates.[15,16]

The safety findings of this study on VEL treatment are consistent with previously conducted trials.[24] During the 12 month FU, no serious or long-term complications were observed, nor were any new, unanticipated AEs. AEs that were recognized as related to intervention have been labeled as mild or moderate and all had successfully resolved. We noted that patients on the active arm were four times more likely have increased vaginal discharge, but this AE is considered a well-known side effect and self-limited.

The shortcoming of VEL treatment is that its effects appear to be temporary, and repeated treatment after a certain period of time is warranted for sustained treatment effect,[40] with the longevity of the effect size being a function of the number of initial treatment sessions.[12] A study on patient preference has shown that participants are willing to accept a slightly lower probability of cure to avoid substantial postoperative pain and possible complications by undergoing a less invasive procedure.[48,49] This supports our opinion that along with the severity of incontinence symptoms and background medical history, personal choice should determine whether SUI should be managed by conservative measures, surgery or laser therapy in joint decision making.

4.1 | Strengths and limitations

One of the main strengths of this trial was its multicenter design, which minimized any selection bias, due to inclusion of different geographic locations, the possibility of inclusion of a wider range

of population groups, and the ability to compare results among centers, all of which increased the generalizability of the study results. Another important strength of this study was the use of single blinded sham treatment, as a control. This kind of a clinical trial design enables the collection of the highest level of clinical evidence, which specifically in the field of urogynecology is rarely ethically and practically justifiable,[47,50] meaning that only few other available SUI treatment options have been scrutinized to this extent, where we included both objective and patient-reported outcome measures.

The trial's complexity, resulting from a significant number of visits that participants were required to attend, as well as a large number of measures that the participants were required to perform during each of these visits led to a patient fatigue and on some occasions poor compliance with the schedule of FU visits or completion of required tasks pertaining to these visits.

5 | CONCLUSIONS

Active VEL treatment demonstrates a superior effect over sham for treatment of SUI as measured by primary outcome measure, the 1-h pad weight test. VEL appears to be a safe and effective non-surgical treatment option for SUI. As in any intervention, in order to achieve optimal satisfactory results, appropriate patient selection and managing patients expectations are paramount.

AUTHOR CONTRIBUTIONS

Barry A. O'Reilly: Main study conception and design. Assumed responsibility for accuracy and integrity of all aspects of research, data collection and data analysis/interpretation. Involvement in drafting or revising manuscript, statistical analysis and in the approval of final version of manuscript for publication. **Volker Viereck, Christian Phillips, Philip Toozs-Hobson, Stavros Athanasiou, Adolf Lukanović, Annette Kuhn:** Involvement in data collection and data analysis/interpretation. Involvement in drafting and revising manuscript. **Yair Daykan:** Involvement in drafting and revising manuscript. Took part in the approval of final version of manuscript for publication. **Brendan Palmer, Darren Dahly:** Main involvement in data analysis/interpretation and statistics. Involvement in drafting and revising manuscript. **Linda Cardozo:** Involvement in data collection and data analysis/interpretation. Involvement in drafting and revising manuscript. Took part in the approval of final version of manuscript for publication.

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Barry O'Reilly, Cork University Hospital, acted as a study coordinator. Fotona and Hampshire Hospitals NHS Foundation Trust acted as a regulatory cosponsor of the study. Fotona company provided research equipment and has been involved in the development of the Clinical Investigation Protocol (CIP), where the input of the manufacturer was as follows: (a) based on Report of Prior Investigations (ROPI) the manufacturer advised on the number of treatments, (b) provided guidelines and Standard Operating Procedures (SOP) regarding the procedure, where the most important was a list of contraindications, (c) provided training of the PIs and their personnel in safe and proper laser use, so that the treatments were as standardized and reproducible as possible among the research sites. (d) The company and its representatives did not actively participate in patient recruitment, randomization and treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (BOR). The data are not publicly available due to restrictions. The data containing information that could compromise the privacy of research participants.

ORCID

Barry A. O'Reilly https://orcid.org/0000-0003-4031-9414
Yair Daykan https://orcid.org/0000-0002-0447-2414

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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