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Twelve-Month Efficacy and Safety Data for the "Stress Incontinence Control, Efficacy and Safety Study": A Phase III, Multicenter, Prospective, Randomized, Controlled Study Treating Female Stress Urinary Incontinence Using the Vesair Intravesical Balloon

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Objectives: The "Stress Incontinence Control, Efficacy and Safety Study" (SUCCESS) is a phase III study of the Vesair Balloon in women with stress urinary incontinence who had failed conservative therapy, and either failed surgery, were not candidates for surgery, or chose not to have surgery. The safety and efficacy of the balloon at 12 months is reported for those participants in the treatment arm who elected to continue with the SUCCESS trial beyond the primary end point at 3 months.

Methods: The SUCCESS trial is a multicenter, prospective, single-blinded, randomized, sham-controlled study. Participants were randomized on a 2.33:1 basis to either Vesair Balloon placement or placebo. The primary efficacy end point was a composite of both a greater than 50% reduction from baseline on 1-hour provocative pad weight test and an at least 10-point improvement in symptoms on the Incontinence Quality of Life questionnaire assessed at the 3-month study visit. Patients in the treatment arm who opted to continue in the trial were followed up prospectively up to 12 months.

Results: A total of 221 participants were randomized, including 157 in the treatment arm and 64 in the control arm. Sixty-seven participants in the treatment arm (42.7% of participants enrolled) were evaluated at 12 months, with 56.3% achieving the composite end point and 78.7% having greater than 50% reduction in pad weight from baseline in a per-protocol analysis. In an intent-to-treat analysis treating all participants who did not continue with the balloon as failures, 24% of the participants achieved the composite end point and 33.6% had a greater than 50% reduction in pad weight from baseline. Treatment-related adverse events in this group included dysuria (40.1%), gross hematuria (36.9%), and urinary tract infection (26.1%).

Conclusions: In this phase III trial, symptom relief was maintained for those participants who continued therapy for 12 months. The balloon was found to be safe with no device- or procedure-related serious adverse events reported. Additional studies are warranted to determine which patient populations are more tolerant of the balloon and to assess the efficacy and safety of its longer-term use. Additional screening methods, including screening patients for balloon tolerability, are warranted to reduce participant withdrawals.

Key Words: urinary stress incontinence, intravesical balloon, pressure attenuation

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The Vesair Balloon is a free-floating intravesical device constructed of a thin polyurethane film inflated with 30 mL of air (Fig. 1). Although most treatments for female stress urinary incontinence (SUI) focus on the bladder outlet to either increase urethral resistance or reduce hypermobility with slings, sphincters, or bulking agents,[1,2] the balloon floats at the bladder dome, and away from the outlet, and produces its favorable effects via a novel mechanism.

In the "closed" hydraulic system of a normal urinary bladder, external pressures transmit directly to urine within the bladder lumen. Urine in the bladder is relatively incompressible; therefore, the pressure within the bladder increases when the surrounding abdominal pressure increases. In a susceptible patient, this intravesical pressure increase subsequently results in urinary incontinence by overcoming urethral closure pressures.[2] Once indwelling, the Vesair Balloon acts in accordance with Boyle's law, which states that the pressure of a gas is inversely proportional to the volume.[3,4] In other words, the balloon will be compressed during transient increases in intravesical pressure, such as a cough or sneeze, thereby attenuating the pressure fluctuation similar to a "shock absorber."

The Vesair Balloon has been evaluated previously in several studies. The mechanism of action was evaluated in an in vitro acrylic bladder model.[5] An in vivo urodynamic study was performed, evaluating Valsalva leak point pressure (VLPP) in 5 women, both before and 24 hours after placing a balloon.[6] In all 5 participants, the required abdominal pressure for leakage to occur increased. Safety and efficacy of this novel intervention was then evaluated in a 166-patient randomized controlled study (RCT) of a smaller balloon at 6 months.[7] After changes were made to the balloon, as well as delivery and removal instrumentation, the SOLECT trial evaluated the safety and efficacy in 63 participants in Europe at 3 months.[8] The current "Stress Incontinence Control, Efficacy and Safety Study" (SUCCESS) is a phase III trial of the Vesair Balloon for female SUI in a larger patient population in the United States,

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TABLE 1. Inclusion and Exclusion Criteria

Inclusion criteria
- Women aged ≥18 y with SUI for at least 12 mo and failed noninvasive treatment (behavior modification, bladder training exercises, pelvic muscle rehabilitation, biofeedback, electrical stimulation or drug therapy) while incontinent
- Positive provocative pad weight test of ≥5 g and confirmed visually during stress maneuvers
- Free of local genital skin infection, impassable urethral strictures, trauma, or necrosis
- Alert, oriented, mentally competent, and capable of determining their need to void by sensing and responding to an urge to void
- Available for a minimum study duration of 12 mo and a maximum study duration of up to 36 mo
- A baseline I-QOL score of ≤70.0

Exclusion criteria
- Pregnant or planning pregnancy during the next 12 mo
- History of urosepsis, urethral inflammation, urethral edema, UTI, or asymptomatic bacteriuria within the past 3 mo
- Recurrent UTIs (≥2 in the past 12 mo)
- Urinary incontinence due to ISD
- Prior surgical procedure for incontinence within the past 6 mo (including suburethral sling placement and/or removal) or history of an artificial urinary sphincter
- Cystocele stage ≥3 on POP-Q classification
- Undergoing or anticipating a course of pelvic radiation therapy or with severe pelvic fibrosis from previous radiation therapy
- Nonambulatory, bedridden, or unable to complete test exercises
- Presence of gross hematuria and/or blood clots in the urine
- Presence of local genital skin infection or urethral abnormalities that would interfere with device placement, such as an impassable urethral stricture, urethral trauma or necrosis, urethral abscess, fistula, or diverticulum
- History of interstitial or follicular cystitis
- VLPP <60 cm H_2O
- Persistent post–void residual urine >100 mL
- Maximum urinary flow rate <5 mL/s with a minimum voided volume of 150 mL
- History of recent alcoholism or illicit drug abuse within the last year
- Immunologically suppressed or immunocompromised
- Evidence of involuntary detrusor contractions and/or discomfort during bladder filling
- Life expectancy of <3 y
- Symptoms of mixed urinary incontinence where urge incontinence is the predominant factor, as confirmed by basic evaluation of patient medical history, including a focused incontinence history
- Urinary incontinence of neurogenic etiology
- History of any neurological disease that could impact bladder function including Parkinson disease, multiple sclerosis, or post–stroke sequelae
- Hypersensitivity to cystoscopy or other urethral manipulations
- Uncontrolled diabetes (persistent A1C levels >9%)
- History of any invasive malignancy (except non–melanoma skin cancer), unless the following apply:
  - The cancer was not in the bladder.
  - The cancer was stage II or less.
  - The cancer was treated with curative intent and there have been no clinical signs or symptoms of the malignancy for at least 2 y.
- History of recurrent (>1) kidney stones, or one within the past 5 y
- Currently taking medications other than anticholinergics that may affect SUI symptoms (such as duloxetine or imipramine)
- Undergoing biofeedback, or has undergone biofeedback within the past 3 mo
- Taking other pharmacologic agents that may have a significant effect on bladder function (excluding estrogen and progesterone in menopausal women) unless on the therapy for at least 3 mo and intending to continue the medication throughout the trial
- Morbid obesity, defined as BMI ≥40.

BMI, body mass index; POP-Q, pelvic organ prolapse quantification.

and 3-month data have been reported previously.[9] This article reports the safety and efficacy of the balloon for those participants who chose to continue with the therapy for 12 months.

METHODS

The SUCCESS trial is a multicenter, prospective, single blinded, randomized, sham-controlled study of the investigational Vesair Balloon for the treatment of female SUI. This study received institutional review board approval and was conducted under a US Food and Drug Administration (FDA)–approved Investigation Device Exemption (G110162). Participant enrollment occurred at 20 investigational sites across the United States. All participants signed a written informed consent before study enrollment.

To establish baseline characteristics and determine study eligibility, all potential participants completed comprehensive incontinence testing before enrollment, including the following: history and physical examination, urinalysis, 1-hour provocative pad weight test, urodynamic evaluation, 7-day voiding diary, questionnaires (Incontinence Quality of Life Scale [I-QOL], International Consultation

on Incontinence Modular Questionnaire: Female Sexual Matters associated with Lower Urinary Tract Symptoms (ICIQ-FLUTSsex); International Consultation on Incontinence Modular Questionnaire: Urinary Incontinence Short Form (ICIQ-SF); Medical, Epidemiologic, and Social Aspects of Aging [MESA]), and cystoscopy. The study population included female adults 18 years or older with SUI symptoms for at least 12 months in duration as evidenced by visual confirmation during stress maneuvers and self-report of incontinence on a voiding diary. Participants must have failed noninvasive incontinence treatments and lacked complicating factors, such as urge predominant symptoms, recurrent urinary tract infections (UTIs), or urethral anatomic anomalies. In addition, all participants had incontinence severity sufficient to produce at least 5 g of leakage on an in-office provocative 1-hour pad weight test. Complete inclusion and exclusion criteria are provided in Table 1. Hypermobility and hypermobility with intrinsic sphincter deficiency (ISD) were determined using the investigator's opinion after review of urodynamic results and patient-reported symptoms. Stress predominate mixed incontinence was determined using the investigator's opinion after evaluating the urodynamic results, MESA, and patient-reported symptoms.

Vesair Balloon placement and removal in this study was performed in an identical manner to what has previously been described.[8] After sterile prep and preprocedural antibiotics, a proprietary urethral access sheath was placed and the bladder surveyed using cystoscopy. The 19F catheter delivery system, preloaded with an uninflated balloon in the tip, was then placed through the sheath. Once within the bladder lumen, the balloon was inflated with 0.7 mL of liquid perfluorocarbon and 30 mL of air via 2 attached syringes and released into the bladder. Balloon removal, when indicated, was accomplished using optical forceps, a custom grasper similarly placed through the Guardian Urethral Sheath. The balloon was pierced with the grasper and removed intact under direct visualization. Sham balloon insertion procedures for participants in the control arm were identical, with the exception of actual balloon deployment.

Eligible and consenting participants were randomly assigned to either the treatment arm or the control arm, and randomization was stratified by clinical site. All participants were blinded to their randomization until the 3-month study visit. The investigator performing the procedure was necessarily unblinded to participant randomization; however, a blinded third-party evaluator performed all efficacy assessments through 3 months.

Participants randomized to the treatment arm received the Vesair Balloon on day 0 and were followed up for 12 months, with assessments at 1, 3, 6, and 12 months. All participants in the treatment arm had their balloons exchanged at 12 months or sooner if clinically indicated. Data collection at each scheduled follow-up visit included documentation of any adverse events (AEs) or change in medical history, a 7-day voiding diary, participant questionnaires (Patient Global Impression of Improvement [PGI-I], I-QOL, ICIQ-FLUTSsex, ICIQ-SF, MESA), and urinalysis if symptomatic. At the 3-month visit, participants also underwent cystoscopy to document appropriate balloon integrity and positioning, and lack of bladder pathology.

Participants in the control arm underwent a sham procedure on day 0 without a Vesair Balloon placed. After completion of efficacy evaluations through the initial 3 months without the Vesair Balloon, control group participants were unblinded and were offered a Vesair Balloon placement at the 3-month visit. Follow-up assessments for the control group were completed at 1, 3, 4, 6, and 12 months. Data collected at each study visit for control group patients were identical to that in the treatment group. Participants were paid $50 per hour for time spent during follow-on visits (Table 2).

Based on the FDA's guidance for clinical studies of SUI,[9] the primary efficacy end point for this study was a composite of both a greater than 50% reduction from baseline on 1-hour provocative pad weight test and an at least ≥10-point improvement in symptoms on the I-QOL questionnaire assessed at the 3-month study visit. Secondary efficacy end points included greater than 50% reduction in pad weight, at least 10-point improvement on I-QOL, proportion of participants reporting improvement on the PGI-I questionnaire, and proportion of participants achieving at least 50% improvement in incontinence episode frequency from baseline at 12 months. The primary safety end point was the incidence of treatment-related (device- or procedure-related) mild, moderate, or severe AEs observed.

Power analysis was performed to determine sample size requirements based on the primary efficacy end point. On the basis of previously published data,[9] conservative estimates for proportion of participants achieving the composite end point in the treatment and control groups were set at 36% and 15%, respectively. Using a 2-sided Fisher exact test between 2 independent proportions and a 2:1 randomization scheme, 174 participants (116 treatment, 58 control) were required to achieve an 80% power with a 0.05 level of significance. To offset for those lost to clinical follow-up, the goal sample size was increased to 220 participants, skewing the randomization scheme to 2.33:1 (157 treatment, 64 control) to account for a higher propensity of treatment participant withdrawal due to tolerability. One additional participant

TABLE 2. Schedule of Visits

Intervention or Test	Preenrollment Visit	Study Entry	1-mo Visit	3-mo Visit	4-mo Visit (Control Only)	6-mo Visit	12-mo Visit
History and physical examination	X					X	
Laboratory urinalysis (including culture and sensitivity, if the urinalysis result is positive)	X	X	*	X	*	*	X
Urodynamic evaluation, including VLPP	X						
1-h provocative pad weight test	X		X	X	X	X	X
PGI-I			X	X	X	X	X
7-d voiding diaries	X		X	X	X	X	X
I-QOL evaluation	X		X	X	X	X	X
Cystoscopic/bladder evaluation		X		X			X
Device or sham insertion		X		X (control)			X
Device removal							X

*Laboratory urinalysis is only performed if the patient is symptomatic.

was enrolled beyond the sample size goal, because of a reporting error at one site, bringing the total to 221 participants in the study.

Statistical analysis was performed on SAS software, version 9.4. For the 3-month end points, missing data were imputed on the basis of the last observation carried forward when the data were missing secondary to participant withdrawal due to a device-related AE. All other missing data were imputed using a multiple-imputation model with 20 imputations performed for each missing piece of data as is current standard practice. To evaluate the 12-month end points, only participants who chose to continue with the study beyond the 3-month primary end point and had evaluable data beyond 6 months were included in the intent-to-treat analysis with no imputation being performed.

RESULTS

Participant enrollment and randomization is depicted visually in Figure 2. Baseline characteristics of the 157 participants in the treatment arm are seen in Table 3. Mean age of the entire cohort was 50.0 years, with an average body mass index of 29.2 kg/m^2. Most participants (74.5%) had pure stress incontinence, with the remainder experiencing stress-predominant mixed urinary incontinence with mean symptom duration before randomization of 107.2 months.

Evaluable results were obtained from 67 participants in the treatment arm who remained in the study beyond 6 months (42.7% of participants enrolled), herein referred to as the "12-month cohort." The composite end point was defined as the number of participants who had both a greater than 50% reduction on the provocative pad weight test and an at least 10-point increase in their I-QOL scores. At 3 months, 55.2% of the participants in the 12-month cohort met the composite end point and 56.3% met the end point at 12 months (Table 4). Improvements were also observed in other end points, analyzed on an intent-to-treat basis. For example, the percentage of participants with a greater than 50% reduction in their provocative pad weight increased from 67.7% at 3 months to 78.7% at 12 months. Furthermore, 44.6% of participants were "dry" on their provocative pad weight test (dry is defined as ≤2-g posttest pad weight) at 3 months compared with 59% at 12 months. An improvement in symptoms was reported on the participant's PGI-I questionnaire, with 65.7% of participants in the 12-month cohort reporting improvement (including "a little better," "much better," and "very much better") at 3 months and 71.6% at 12 months. Mean reduction in absorbent pad usage was 1.3 pads/d at 3 months and 1.1 pads/d at 12 months. Additional improvements were demonstrated in participants with a 10-point or greater improvement in I-QOL scores (score, 0–100), mean change in I-QOL scores, participants with at least a 50% reduction in incontinence episode frequency, and mean reduction in incontinence leaks per day (see Table 4).

FIGURE 1. Vesair Balloon.

In an analysis of the patients in the treatment arm who remained in the study at 12 months, 71.9% of the patients with a baseline pad weight of greater than 20 g achieved a 50% reduction in pad weight, and 86.2% of the patients with a baseline pad weight between 5 and 20 g met the end point. In those patients from the control arm who had the Vesair Balloon placed at 3 months and remained in the study at 12 months, 50% of the patients with a baseline pad weight of greater than 20 g achieved a 50% reduction in pad weight, and 71.4% of the patients with a baseline pad weight between 5 and 20 g met the end point.

No device- or procedure-related serious AEs or unanticipated AEs were reported, and no cases of urinary retention were observed. Adverse events in this study are reported as a cumulative incidence with all AEs recorded even if the symptom was transitory. A complete list of "treatment-related" (device- or procedure-related) AEs with an incidence of greater than 1% for those participants in the treatment arm is seen in Table 5. One hundred thirty-three participants in the treatment arm (85.9%) had at least 1 treatment-related AE. In the 12-month cohort, 42 participants (66.7%) had at least 1 treatment-related AE. The most common AEs reported in the 12-month cohort were gross hematuria (36.9%), UTI (25.4%), and dysuria (17.5%). Urinary tract infections were defined as participants with positive urine cultures (>10,000 colony-forming units) or when participants were treated empirically at the clinical site and had resolution of symptoms. A dipstick urinalysis was performed with a clean catch specimen at enrollment, and any time cystoscopy was performed or the participants presented with symptoms. If the urinalysis result was positive, a catheter specimen was obtained when possible and cultured to confirm the UTI. All treatment-related AEs completely resolved with the balloon indwelling or after removal of the balloon.

In a separate efficacy analysis of the participants in the control arm, evaluable results were obtained from 30 participants who remained in the study at 12 months (46.9% of the control arm participants enrolled). At the 12-month study visit, the control arm participants had the balloon indwelling for a total of 9 months. At the 12-month visit, 46.4% of the participants met the composite end point, 60.7% of the participants had a greater than 50% reduction in their provocative pad weight from baseline, 50% of the patients reported an improvement in symptoms on the PGI-I questionnaire, 66.7% of participants had a 10-point or greater improvement in I-QOL scores (score, 0–100), and 64.3% of the participants reported at least a 50% reduction in incontinence episode frequency. A complete list of "treatment-related" (device- or procedure-related) AEs with an incidence of greater than 1% for those participants in the control arm is seen in Table 5.

Two hundred sixty-six balloons were deployed across the total population during the entire 12-month study period. One hundred seventy-five participants received 1 balloon, 44 received 2 balloons, 1 received 3 balloons, and 1 did not receive a balloon. In the treatment arm (n = 157), 123 patients had a single balloon insertion, 33 had an exchange, and 1 had 2 balloon exchanges. Twenty of the exchanges occurred between months 0 and 3, and 15 occurred between months 3 and 12. For those participants in the treatment arm who remained at 12 months (n = 67), 45 had a single balloon, 21 had 1 exchange, and 1 had 2 exchanges. Ten of the exchanges occurred between months 0 and 3, and 13

occurred between months 3 and 12. In the control arm (n = 64), 44 participants received a single balloon, 11 had an exchange, and 1 did not receive a balloon. Six of the exchanges occurred between months 0 and 3, and 5 occurred between months 3 and 12. For those participants in the control arm who remained at 12 months (n = 30), 21 had a single balloon and 9 had 1 exchange. Four of the exchanges occurred between months 0 and 3, and 5 occurred between months 3 and 12. Exchanges occurred at the discretion of the investigator because of premature deflation of the balloon or in an effort to resolve an AE. Adverse events that were concurrent

TABLE 3. Baseline Characteristics

Participant Baseline Characteristics	Treatment (n = 157)	Patients Enrolled in the Treatment Group With Balloon at 12 mo(n = 67)
Mean age, y	50	51.5
Mean BMI, kg/m^2	29.1	29.5
Length of symptoms, mo	107.2	112.6
SUI type		
Stress only	74.5%	70.1%
Mixed, stress predominant	25.5%	29.1%
Cause of SUI		
Hypermobility	93.6%	92.5%
ISD and hypermobility, predominant hypermobility	6.4%	7.5%
Menopausal status		
Premenopausal	38.2%	34.3%
Perimenopausal	12.7%	7.5%
Postmenopausal	49.0%	58.2%
No. live births, mean	1.8	1.9
No. vaginal deliveries, mean	1.6	1.7
Other symptoms reported		
Frequency	48.4%	55.2%
Urge incontinence	33.1%	31.3%
Poor stream	12.1%	10.0%
Nocturia	24.2%	29.9%
Urgency	40.8%	38.8%
Straining	7.6%	10.5%
Hesitancy	10.2%	13.4%
Dysuria	2.60%	1.5%
Mean VLPP, cm H_2O	117.5	119.3
Prior treatments		
Pelvic surgery (any)	48.4%	53.7%
Failed sling procedure	14.80%	17.9%
Failed kegel exercises	90.5%	86.6%
Failed biofeedback	7.60%	9.0%
Failed electrical stimulation	4.35%	1.5%
Currently on estrogen replacement	12.7%	11.9%
Current tobacco user	8.3%	9.0%
Mean packs/d	0.6	0.7
Current alcohol user	49.7%	49.3%
Mean drinks/wk	3.5	3.4
Mean baseline measures		
Pad weight, g	47.0	57.7
I-QOL	42.8	42.8
Leaks per day	5.2	6.1
ICIQ-FLUTSsex	3.9	4.1
ICIQ-SF	13.6	13.8
MESA (stress)	74.1	77.9
MESA (urge)	40.0	39.6
PUF (symptom)	5.5	5.3
Sensitization inventory	27.3	27.4
Pads/d	1.9	2.3

BMI, body mass index; PUF, Pelvic Pain, Urgency, and Frequency Questionnaire.

TABLE 4. End Points at 3 and 12 Months (ITT Analysis*)

	All Participants Enrolled in Treatment Arm	Participants Enrolled in Treatment Arm With Balloon at 12 mo	
	At 3 mo	At 3 mo	At 12 mo
Composite end points	n = 157	n = 67	n = 64†
>50% decrease in pad weight and ≥10-point improvement in I-QOL, %	42.1	55.20	56.30
>75% decrease in pad weight and ≥10-point improvement in I-QOL, %	34.6	47.8	54.7
Pad weight end points	n = 157	n = 65	n = 67
>50% reduction in pad weight, %	55.9	67.7	78.7
>75% reduction in pad weight, %	43.9	58.5	68.9
Dry (≤2 g), %	38.4	44.6	59.0
Dry (≤1 g), %	28.6	36.9	39.3
Mean reduction	16.3	32.9	42.1
Median reduction	7.3	14.3	13.5
Mean % reduction	−37.2	18.9	61.1
Median % reduction	68.5	85.2	87.3
I-QOL end points	n = 157	n = 67	n = 67
≥10-point increase in I-QOL, %	58.2	70.2	70.2
Mean improvement	19.1	25.0	26.3
Median improvement	15.9	23.3	22.7
Mean % improvement	97.5	125.6	125.4
Median % improvement	36.1	46.7	51
Incontinence episode frequency end points	n = 157	n = 66	n = 67
≥50% reduction in episode frequency, %	55.2	65.2	57.9
Mean reduction	2.22	3.4	2.0
Median reduction	1.43	2.4	2.0
Mean % reduction	32.9	46.0	35.1
Median % reduction	54.5	64.5	70.4
Dry (0/leaks per day) 21.1%, %	6.5	5.3	21.1
Mean increase, voids/d	0.9	−0.1	0.4
Mean reduction, pads/d	1.0	1.3	1.1
PGI-I	n = 157	n = 67	n = 67
Patients improved, %	58.0	65.7	71.6
ICIQ-FLUTSsex	n = 112	n = 65	n = 67
Mean improvement	1.5	0.71	0.96
ICIQ-SF	n = 114	n = 62	n = 63
Mean improvement	3.8	5.1	5.5
Median % improvement	20.8	31.2	34.1
MESA (urge)	n = 114	n = 66	n = 67
Mean improvement	7.2	10.9	8.3
MESA (stress)	n = 114	n = 67	n = 67
Mean improvement	20.3	23.3	24.4

*ITT analysis: 3-month data include all participants enrolled in the treatment arm, with imputation; 12-month data include all participants in the treatment arm, with data available after the 6-month visit.

†Three patients did not complete the pad test and had a greater than 10-pt increase in I-QOL.

ITT, intent-to-treat; pt, point.

with balloon removal are listed in Table 6, including all patients in the treatment arm and those patients in the treatment arm who remained in the study at 12 months.

Forty-one participants (26%) in the treatment arm discontinued within the first 3 months of the study: 40 participants because of lack of tolerability of the balloon and 1 participant who was lost to follow-up. Forty-nine participants (31%) in the treatment arm discontinued between months 3 and 12: 36 because of AEs including dysuria, bladder irritation, suprapubic discomfort, UTI, and urgency; 9 because of unsatisfactory treatment effect, 2 because of the time commitment of follow-up visits, 1 because of physician decision, and 1 who was unwilling to undergo follow-up cystoscopy. One participant in the control group discontinued within the first 3 months of the study. Thirty-three participants (61%) in the control arm discontinued between months 3 and 12: 27 because of AEs including dysuria, bladder irritation,

TABLE 5. AEs at Months 0 to 12

	All Patients Enrolled in the Treatment Group (n = 157)		Patients Enrolled in the Treatment Group at 12 mo (n = 67)		Patients Enrolled in the Control Group at 12 mo (9 mo with balloon; n = 30)	
	No.	% of Patients	No.	% of Patients	No.	% of Patients
Any AE	133	85.9	46	68.7	24	38.1
Dysuria	63	40.1	13	19.4	8	12.7
Hematuria (gross)	58	36.9	19	28.4	6	9.5
Suprapubic discomfort	48	30.6	9	13.4	7	11.1
Uncomplicated UTI	41	26.1	19	28.4	7	11.1
Urgency	34	21.7	7	10.4	9	14.3
Urge incontinence	26	16.6	8	11.9	5	7.9
Hematuria (microscopic)	20	12.7	11	16.4	4	6.3
Frequency	18	11.5	4	6.0	4	6.3
Other*	13	8.3	4	6.0	4	4.8
Balloon deflation	12	7.6	4	6.0	2	3.2
Cystitis	12	7.6	2	3.0	2	3.2
Vaginal irritation	5	3.2	3	4.50	0	0.0
Bacteriuria (asymptomatic)	4	2.5	2	3.0	0	0.0
Hesitancy	4	2.5	0	0.0	1	1.6
Post–void dribbling	4	2.5	1	1.5	2	3.2
Bladder pressure/spasm	3	1.9	0	0.0	0	0.0
Bladder stone	3	1.9	1	1.5	0	0.0
Nocturia	2	1.3	1	1.5	1	1.6

*Abdominal pain, abdominal pressure, sensation of retention, incomplete bladder emptying, and pain at end of void.

suprapubic discomfort, UTI and urgency and 6 because of unsatisfactory treatment effect. In an intent-to-treat analysis treating all participants who did not continue with the balloon as failures, 24% of the participants achieved the composite end point and 33.6% had a greater than 50% reduction in pad weight from baseline.

DISCUSSION

Female SUI is a growing clinical problem, with a predicted 167 million women affected worldwide by 2018.[10] Despite the availability of multiple surgical incontinence treatments, there remains a large unmet need for minimally invasive options. The Vesair

TABLE 6. AEs Concurrent With Balloon Removal at Months 0–12 By Treatment Group

	All Patients Enrolled in the Treatment Group (n = 157)			Patients Enrolled in the Treatment Group at 12 mo (n = 67)		
	Removals	Events	% of Events	Removals	Events	% of Events
Dysuria	39	65	60.0	3	15	20.0
Suprapubic discomfort	30	48	62.5	3	8	37.5
Hematuria (gross)	25	64	39.1	3	22	13.6
Urgency	24	36	66.7	2	7	28.6
Uncomplicated UTI	17	62	27.4	4	30	13.3
Urge incontinence	17	25	68.0	5	8	62.5
Frequency	9	19	47.4	1	6	16.7
Balloon deflation	9	12	75.0	1	4	25.0
Other*	8	12	66.7	1	5	20.0
Cystitis	8	11	72.7	1	2	50.0
Hematuria (microscopic)	5	18	27.8	1	11	9.1
Hesitancy	3	4	75.0			
Post–void dribbling	3	4	75.0			
Bladder pressure/spasm	3	3	100.0			
Vaginal irritation	1	5	20.0			
Bladder stone	1	3	33.3			
Nocturia	1	2	50.0			

*Abdominal pain, abdominal pressure, sensation of retention, incomplete bladder emptying, pain at end of void, spasm, vaginal burning, and urethral sheath left in the vagina.

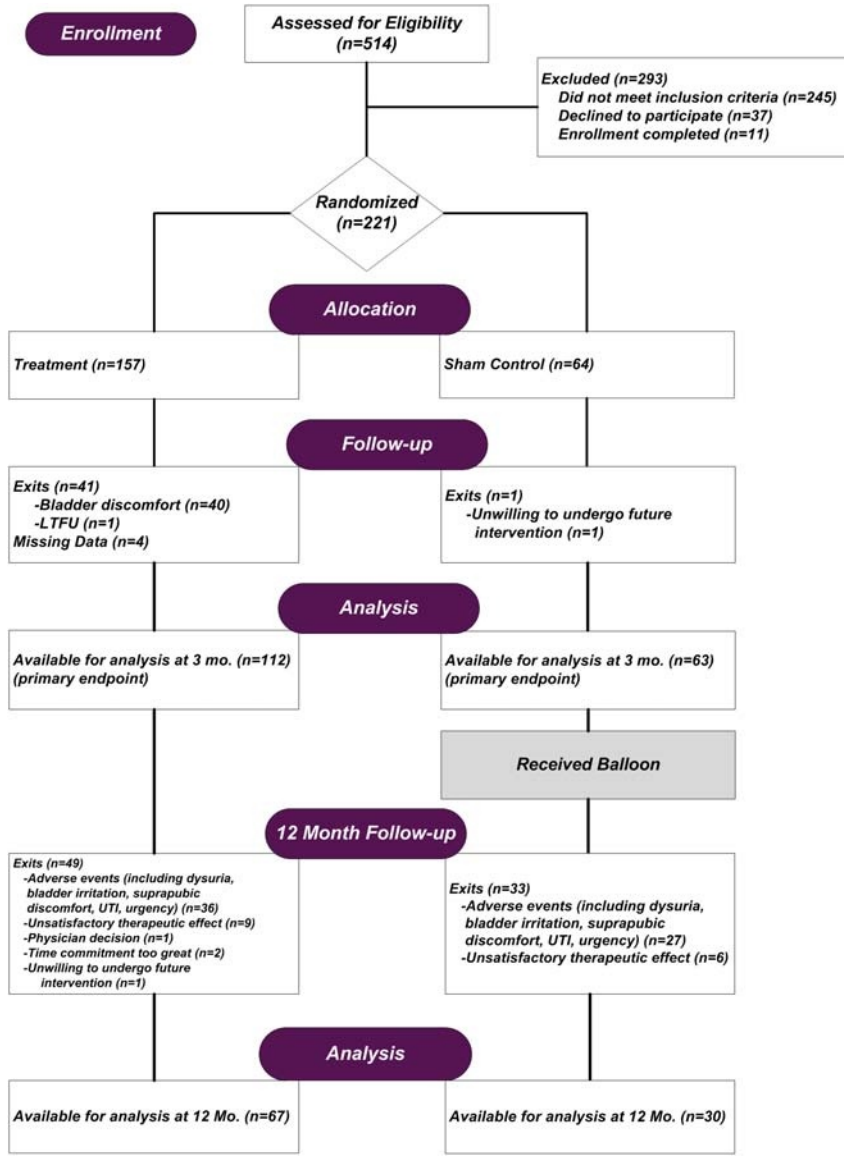

FIGURE 2. CONSORT flow diagram of the SUCCESS study. CONSORT, CONsolidated Standards of Reporting Trials.

Balloon is a novel minimally invasive treatment modality for female SUI. The current SUCCESS trial is a phase III prospective RCT for this device with the largest cohort of participants to date.

Three-month efficacy end points demonstrated clinically and statistically significant improvements in incontinence in treated participants when compared with sham control, not only in the primary composite end point but also in the clinically significant secondary end points. Treated participants experienced significantly more reduction in urinary incontinence episode frequency and more often reported improvement on PGI-I.

In the 12-month cohort, comparison of the primary end point and the secondary end points demonstrates the durability of the treatment for those participants who tolerate the balloon.

In an intent-to-treat analysis treating all participants who did not continue with the balloon as failures, 24% of the participants achieved the composite end point and 33.6% had a greater than 50% reduction in pad weight from baseline. These efficacy results were negatively impacted by less than 50% of the participants remaining in each arm in the study at 12 months. In addition to the typical reasons participants withdrew from the study, participants had the balloon removed for reasons related to tolerability. Although some participants did not feel the balloon in place, others felt the balloon in the bladder, particularly when the bladder was empty at the end of voiding. Select participants accommodated the sensation, with the benefit from the therapy outweighing the sensation, whereas others could not and requested balloon removal. All symptoms were mitigated upon removal of the balloon. Balloon modifications may be needed to reduce or eliminate this sensation, and additional screening methods could be developed in future studies. Given the relative ease of balloon placement and removal, balloon insertion for 30 days as a screening method to determine which patients can tolerate the balloon should be considered.

No treatment-related serious AEs were reported in this study, and most of the reported AEs were transient rather than persistent symptoms (Table 5). Growing clinical experience with this device

led us to consider that there may be a proportion of patients who simply cannot tolerate an indwelling Vesair Balloon. Comparing the AE rates between the full-treatment arm and the 12-month cohort, the AE rates in this "balloon-tolerant" group of participants were noticeably less than those in the overall cohort. One of the unique features of the Vesair Balloon as a treatment modality, especially when interpreting AEs, is ease of reversibility. All AEs resolved upon balloon removal.

Compared with midurethral slings, the Vesair Balloon is a less invasive treatment option for female SUI. Similarly, urethral bulking agents have been suggested as an alternative to midurethral sling placement for those women who either cannot or choose not to undergo sling placement. However, the long-term results after bulking agent injection have been modest. A Cochrane Database review of bulking in 2012 failed to demonstrate any consistent improvement in urinary incontinence over placebo.[11] In addition, some of the injectable agents seemed to have safety concerns either at the injection site or systemically leading to trial termination. A systemic review of polydimethylsiloxane injection for treating female SUI has also been completed.[12] It found a relatively sparse number of RCTs, with most studies being small observational cohorts. In addition, measures of success were variable and often subjective rather than objective. The review found short-term "cure" rates of 43% declining to 37% with longer follow-up. Adverse events were primarily urinary retention (7%), dysuria (50%), and hematuria (45%).

The Vesair Balloon for female SUI is comparable to urethral bulking agents in both outcomes and AEs. It also has the advantage of a longer-lasting result, being easily reversible in those participants who do not derive a benefit or do not tolerate balloon placement. Although slings remain the surgical criterion standard in many centers, not all women desire one or are appropriate candidates for sling placement; the Vesair Balloon offers a safe alternative to these participants. Furthermore, it is possible that patients with residual stress incontinence after sling placement who desire further improvement may benefit from balloon placement rather than repeat surgery or injection of a bulking agent. In addition, the reversibility of the procedure allows the Vesair Balloon to be considered as a potential treatment option for women who wish to have children in the future.

The primary weakness of the study is the inability to blind the providers performing the study procedures. Efficacy evaluations are performed by a blinded third party to mitigate any potential bias. Additional weaknesses of the study include the lack of reproducibility of the pad weight test, the high placebo and Hawthorne effect inherent in the I-QOL questionnaire, and the inability to keep all treatment patients blinded because some patients "feel" the balloon in their bladder. The quantity of visits and evaluations were a burden for patients.

The trial has several strengths. It is the largest prospective RCT to date using the Vesair Balloon for female SUI. This trial documents significant improvements in subjective and objective measures of incontinence outcomes and follows current FDA guidance for SUI study methodology. The study included rigorous follow-up with several subjective and objective outcome end points, allowing for analysis to evaluate the appropriate clinically relevant end points in future studies.

The data reported herein were only from those participants in the treatment arm who remained in the study beyond 6 months—it did not include all participants enrolled in the study. Additional studies of those participants who did not tolerate the balloon will help further screen out patients who are not appropriate candidates for this therapy. Additional studies are also warranted to evaluate the use of an intravesical balloon in combination with existing therapies directed at urethral function to better improve outcomes.

CONCLUSIONS

This randomized, sham-controlled trial evaluated efficacy and safety outcomes for a novel intravesical pressure-attenuation system designed to reduce or eliminate symptoms of SUI for participants who were not candidates for surgery, had failed surgery, or chose not to have surgery. In this trial, for those participants who tolerated the balloon and met 3-month primary and secondary end points both objectively and subjectively, symptom relief continued for the duration of treatment (12 months). For those participants who did not tolerate the therapy or had an unsatisfactory treatment effect, the balloon was simply removed, permitting the patient to pursue alternative treatment options. The pressure-attenuation system was safe and caused no urinary retention. Additional larger studies are warranted to better understand which patient populations better tolerate the balloon and to assess the efficacy and safety of its use beyond 12 months. Additional balloon development is needed to improve balloon tolerability, and additional screening methods are needed in future studies.

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