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Percutaneous tibial nerve stimulation vs sham for fecal incontinence in women: NeurOmodulaTion for Accidental Bowel Leakage Randomized Clinical Trial

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Abstract

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AUTHOR CONTRIBUTIONS

Halina M. Zyczynski, Holly E. Richter, Vivian W. Sung, Emily S. Lukacz, Lily A. Arya, David D. Rahn, Anthony G. Visco, Donna Mazloomdoost and Marie Gantz made substantial contributions to trial design, acquisition, and interpretation of the data; authorship of the manuscript. They have each reviewed and approved the final version submit to AJG. Benjamin Carper contributed to analysis and interpretation of data, authorship of the manuscript. He has reviewed and approve the final version of the manuscript submitted to AJG.

BC and MG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Objective: To determine whether PTNS is superior to sham stimulation for treatment of fecal incontinence in women refractory to first-line treatments.

METHODS: Women ≥18 years with ≥3 months of moderate to severe fecal incontinence that persisted after a 4-week run-in were randomized 2:1 (PTNS:Sham) to 12-weekly 30-minute sessions in this multicenter, single-masked, controlled superiority trial. The primary outcome was change from baseline fecal incontinence severity measured by St Mark's score after 12 weeks treatment (range 0–24; minimal important difference, 3–5 points). Secondary outcomes included electronic bowel diary events and quality of life. Groups were compared using an adjusted general linear mixed model.

Results: Of 199 women entering run-in, 166 (of 170 eligible) were randomized, (111 PTNS, 55 sham); mean (SD) age, 63.6 (11.6) years; baseline St. Mark's score, 17.4 (2.7); recording 6.6 (5.5) fecal incontinence episodes per week. There was no difference in improvement from baseline St. Mark's scores in the PTNS group compared to the sham group (−5.3 vs. −3.9 points, adjusted difference [95% confidence interval] −1.3 [−2.8, 0.2]). Groups did not differ in reduction in weekly fecal incontinence episodes (−2.1 vs. −1.9 episodes, adjusted difference [95% confidence interval] −0.26 [−1.85, 1.33]). Condition-specific QOL measures did not indicate a benefit of PTNS over sham. Serious adverse events occurred in 4% of each group.

Conclusions: Though symptom reduction after 12 weeks of PTNS met a threshold of clinical importance it did not differ from sham. These data do not support use of PTNS as conducted, for treatment of fecal incontinence in women.

Keywords

Fecal incontinence; Accidental bowel leakage; Percutaneous tibial nerve stimulation; posterior tibial nerve stimulation; neuromodulation; sham electrical stimulation; randomized clinical trial

Introduction

Fecal incontinence (FI), also known as anal incontinence and accidental bowel leakage (ABL), is common; reported by 2% to 20% of community dwelling women[1–3], 40% of whom report severe negative impact on quality of life. Effective, non-invasive therapies are limited[4, 5]. Neuromodulation has emerged as a promising third tier therapy. Sacral neuromodulation, approved for both urgency urinary incontinence and fecal incontinence, is safe and reversible but requires surgical intervention at substantial cost[6]. Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive, office-based, low risk neuromodulation modality currently approved in the US for urgency urinary incontinence. Promising response rates of 63–82% in small, predominantly observational studies of FI[7] have supported device marketing approval for FI in the European Union. The National Institute for Health and Care Excellence (NICE)[8] includes PTNS among treatment options for FI though acknowledges the need for further research to inform to efficacy and target populations. A multicenter pragmatic, randomized trial of PTNS versus sham reported no group difference in a diary-based primary outcome of ≥50% reduction in weekly FI episodes[9] though PTNS did result in significantly greater reduction in total weekly FI and urgency associated FI episodes. Posthoc analyses excluding subjects with obstructed defecation symptoms, a subset known to be refractory to FI therapy[10] found a significant clinical effect of PTNS[11]. These findings

support the need for additional controlled efficacy trials of PTNS in a well characterized population.

The aim of this randomized clinical trial was to determine if 12 weeks of treatment with PTNS is more effective than sham stimulation in reducing FI severity, as measured by change from baseline in St. Mark's score, in women refractory to first-line therapies. Secondary aims included comparing changes from baseline in bowel diary measures, self-reported functional outcomes, and quality of life.

METHODS

Study Design and Oversight

This was a multicenter, single-masked, randomized, superiority trial conducted at 9 US clinical sites of the National Institutes of Health Pelvic Floor Disorders Network under approval of a Data and Safety Monitoring Board and the University of Pittsburgh institutional review board (NCT 03278613). All participants provided written informed consent. Study methods have been published[12], and the protocol and statistical analysis plan appear in supplementary materials. Enrollment began February 9, 2018, and follow-up closed March 9, 2020 upon analysis of data from all subjects who completed initial treatment in the randomized trial (Part 1). (Supplemental Digital Content Figure 1. Study Flow Diagram)

Participants

Women ≥18 years with moderate to severe ABL symptoms for ≥3 months, defined as a baseline St. Mark's score ≥12 points, and inadequate symptom control from supervised pelvic muscle training and constipating medications, were eligible to enroll into a 4-week run-in. Women were excluded for self-report of uncontrolled diarrhea or severe constipation as the predominant stool type in the preceding 3 months based on Bristol stool scale,[13] anatomic compromise of the anus or rectum (unrepaired rectovaginal fistula or 4th degree obstetrical laceration, rectal prolapse, congenital anorectal malformation, colon resection), and known contraindications for PTNS.[12]

Intervention

The study included a 4-week run-in prior to randomization to 12 weekly stimulation sessions (Part 1). Treatment responders defined as those reporting ≥4-point reduction in St. Mark's score underwent a second randomization to 'as needed' or scheduled maintenance sessions (Part 2) for an additional 9 months beyond treatment initiation. The protocol specified that if Part 1 did not demonstrate superiority of PTNS over sham, Part 2 would be discontinued.

During the run-in, participants received standardized verbal and written information on causes and treatments for FI including dietary and lifestyle modifications[14]. They also completed two 7-day bowel diaries in weeks 1 and 4. Women were eligible for randomization to Part 1 if they provided two complete diaries (defined as having recorded events on ≥10 of 14 days with minimum of 3 consecutive days per week) and reported a St. Mark's score of ≥12 points at the end of the run-in.

Part 1 randomization assignment was 2:1 PTNS:sham, using randomly permuted blocks, stratified by site and type of run-in diary completed (eDiary or paper). Stimulation was delivered to a single lower extremity in 12 weekly 30-minute sessions. PTNS employed the ES-130 pulse generator (ITO, Tokyo, Japan) programed to be consistent with the Stoller Afferent Nerve Stimulator (SANS) (UroSurge, Coralville, Iowa, USA), (US Patent No.: US 6,493,588) to deliver a threshold current to a needle electrode to induce toe twitch and, or sensation[15, 16]. The validated sham intervention employed a Streitberger retractable placebo acupuncture needle and surface electrodes positioned on the top and bottom of the fifth metatarsal, each connected to a transcutaneous electrical nerve stimulator (TENS) that created a sensory effect without delivering a therapeutic effect[17]. Procedures are detailed in the protocol (Supplementary material) and methods paper [12]. Adherence to the study protocol was defined as completing 10 of 12 sessions within a 14-week window.

Outcome Measures

The primary outcome was change from baseline St. Mark's Score measured after 12 weekly treatments. The St. Mark's Score is a 7 item, validated patient-reported outcome (PRO).[18–20] Higher scores (range 0–24 points) indicate greater symptom severity, and the minimal important difference (MID) is 3–5 points[20]. The St. Mark's Score was assessed at baseline, and after the 4th, 8th, and 12th weekly session.

Secondary outcomes included bowel movement and stool leakage episodes per week qualified by urgency and stool consistency recorded for 14-days on the PFDN Bowel eDiary phone application[21] at baseline, and with start dates at the 6th and 12th stimulation session. In the absence of a single superior measure for ABL, a robust panel of PRO measures were collected assessing FI symptom severity, quality of life,[22, 23] co-existent bowel and bladder symptoms,[24] constipation symptoms,[25] global impression of improvement, behavior adaptations for pelvic floor disorders[26] and sexual function[27]. The Patient Global Symptom Control rating[20], and adverse events were ascertained at each treatment visit.

Statistical Analysis

Assuming a two-sided alpha of 0.05 and standard deviation (SD) of 7[28], using a 2:1 treatment allocation, 147 women provided 90% power to detect a between-group difference of 4 points in mean change from baseline in St. Mark's scores after 12 weeks of stimulation. After adjusting for 10% dropout, 165 (PTNS=110, Sham=55) was the target sample size for Part 1.

Baseline characteristics were compared between groups using Student's t tests for continuous variables and chi-square tests for categorical variables. The primary analysis used an intention-to-treat approach, and models included all eligible, randomized participants with outcome data at one or more time points. A general linear mixed model estimated the change from baseline in St. Mark's Score across all time points through 12 weeks of treatment. Treatment group, time as a linear and quadratic effect, the stratification factor of site, and interactions between treatment group and time were included as fixed effects. The correlation between repeated measures on the same participant was modeled using an auto-regressive covariance structure. The model-estimated change from baseline in

St. Mark's score after 12 treatments was compared between groups using a two-sided test at an alpha level of 0.05. In a sensitivity analysis, multiple imputation was used to estimate missing values.

A per-protocol analysis included participants who attended at least 10 of 12 stimulation sessions. Other secondary outcomes were analyzed using similar methods to the primary analysis for continuous variables, or analogous generalized linear mixed models for categorical outcomes. No alpha adjustments were made for evaluation of multiple outcomes. Analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Study Population

Between February 9, 2018 and September 24, 2019, 199 women entered the run-in, 166 of 170 eligible participants were randomized (111 PTNS vs. 55 sham) (Figure 1). Table 1 presents baseline sociodemographic and clinical characteristics. Overall, participants were 63.6 (±11.6) years old, predominantly White (80.7%), and overweight or obese (76.2%). The run-in resulted in modest improvement in symptom severity with mean change in St. Mark's Scores −0.54 (±2.75). Prior to randomization, participants reported 13.3 (±7.3) bowel movements and 6.6 (±5.5) leaks per week, of which half were associated with urgency.

Primary Outcome

The unadjusted mean St. Mark's Score for the PTNS group at baseline was 17.5 (±2.5) and after 12 weeks was 12.2 (±5.0), for an adjusted mean change of −5.3 points (95% confidence interval [CI], −6.2, −4.3) vs sham group unadjusted mean scores of 17.3 (±3.0) at baseline and 13.3 (±4.7) points after 12 weeks, for an adjusted mean change of −3.9 points (95% CI, −5.2, −2.7) (Table 2). There was no significant difference between groups in improvement of St. Mark's scores (adjusted difference −1.3, 95% CI,−2.8, 0.2). Responders to treatment were 64/104 (61.5%) assigned to PTNS and 26/54 (48.1%) of sham subjects (unadjusted OR 1.71, 95% CI 0.86, 3.39; p=0.12). Sensitivity and protocol analyses were consistent with the primary analysis. The observed divergence in total St. Mark's scores after 8 weeks (Figure 2) is largely due to a significantly lower proportion of PTNS subjects reporting daily or weekly of solid stool leakage and less use of protection with pads or plugs compared to sham (Table 3).

Secondary Outcomes

Prespecified secondary and exploratory outcomes are reported in Tables 2 and 3. Weekly frequency of diary-documented bowel events and fecal incontinence episode-free days did not differ between groups. Approximately half of participants reported ≥50% reduction in weekly FI episodes, and a third had a ≥ 75%reduction, without meaningful differences between groups. Furthermore, both groups reported high levels of symptom control 79% (PTNS) versus 74% (Sham) with no group difference in perceived improvement (Table 3). Significant group differences were noted in adaptive behaviors, with the PTNS group

reporting greater decreases from baseline in the hygiene and avoidance-related activities domains of the ABI (Table 2). Group differences in condition-specific QOL measures varied. Compared to sham, the PTNS group reported significantly greater improvement in three of four subscales of the FIQL for the Lifestyle, Depression/ Self-perception, and Embarrassment scores [Supplemental Digital Content Table 1]. Most other QOL measures did not indicate group differences.

Both groups demonstrated high adherence to the treatment schedule (99/111 (89.2%) PTNS, 51/55 (92.7%) sham). Validity of the sham was assessed at the close of Part 1: 61/103 (59.2%) of PTNS and 32/54 (59.3%) of the sham group reported not knowing their group assignment. Of those who guessed, 29/42 (69%) assigned to PTNS, and 10/22 (45.5%) in the sham group were correct. Interventionists recorded sensory, motor or both responses to PTNS in 97.5%, 31.8%, and 29.7% of sessions. New non-pharmacologic treatment for ABL was initiated by 5 PTNS and 3 sham participants with an additional 9 PTNS and 2 sham subjects starting new medication for ABL. The proportion of participants taking constipating medications was similar between groups at the end of Part 1.

Adverse events are summarized by classification [Supplemental Digital Content Table 2] and by system organ class [Supplemental Digital Content Table 3]. Paresthesia was reported in 11 (10%) of PTNS and 2 (4%) of the sham group. Bleeding (8%) and pain (2%) at the needle insertion site were exclusively reported in the PTNS group. Six participants experienced serious adverse events, 4 (4%) in the PTNS group and 2 (4%) in the sham group; none were treatment related.

Discussion

In this randomized controlled trial of women with refractory FI, PTNS and sham stimulation did not differ in their impact on symptom severity, incontinence events or most quality of life measures after 12 weekly sessions. Both groups experienced significant, clinically important reductions in patient-reported symptoms, weekly frequency of FI episodes compared to baseline, and compelling symptom control of 74 –78%, highlighting the importance of a sham arm when investigating therapeutic interventions for functional bowel disorders, in which placebo effects approximate 40%[29, 30] There were, however, secondary outcomes including the Fecal Incontinence Quality of Life and Adaptive Behaviors Index which favored PTNS over sham. Nonetheless, group differences were modest, and overall, the findings of this study do not support the broad use of this PTNS protocol as standard FI therapy.

This study was conducted to address conflicting evidence on the efficacy of PTNS for treatment of ABL and the need for confirmatory Level I evidence prior to clinical adoption of this therapy in the United States. Near the end of protocol development, Knowles and colleagues published the largest, most rigorous evaluation of PTNS for the treatment of FI, in 227 women and men recruited from colorectal surgery clinics in the United Kingdom. Similar to NOTABLe, the CONFIDeNT trial found no significant treatment response in active PTNS treatment compared to sham for the primary outcome of ≥50% reduction in weekly FI episodes, conditional and related pelvic symptom quality of life measures and

patient global impression of improvement.[9] The NOTABLe trial addresses some of the limitations of CONFIDeNT and distinguishes itself for its objective eligibility criteria of a study population with moderate to severe symptom burden in the absence of extremes of stool consistency; collection of bowel events with an electronic bowel diary to manage concerns of veracity of diary data; a run-in phase to address the potential therapeutic effect of journaling; selection of a comprehensive primary outcome which accounts for elements of frequency, severity, volume, bother, and desire for treatment, and use of a validated sham stimulation.

NOTABLe findings generally align with those of the CONFIDeNT trial; however, there are important differences in the population studied and design of the trial which lend confidence and generalizability to the combined conclusions. The populations had similar baseline frequency of incontinence episodes (6–7/week) with half associated with urgency and similar baseline fecal incontinence quality of life scores. However, the NOTABLe trial exclusively enrolled women, recruited from the community through advertising and from urogynecology clinics compared to colorectal specialty clinics. They were slightly older (by 6 years), more symptomatic based on St. Mark's score (17 vs. 15 points), and less likely to report prior ano/rectal surgery for FI than those enrolled in the CONFIDeNT trial. The difference in population, diary modality or inclusion of run-in in the current study may account for the differences in results between these studies. The UK study found significantly greater improvement in diary documented FI episodes/week compared to sham, but not in any of the FI quality of life domains. In contrast, the women in the current study had no group difference in reduction of incontinence episodes but did report greater improvements with PTNS compared to sham in lifestyle, depression, and embarrassment domains of the Rockwood FIQL questionnaire. Additionally, at the end of Part 1, the PTNS group reported less use of adaptive behaviors to manage their ABL symptoms which may reflect improved confidence in their ability to be continent despite unchanged symptom severity.

Despite deliberate, pre-randomization interventions intended to isolate the effects of education, lifestyle modifications and journaling in diaries, the sham stimulation group reported statistically significant reductions in St. Mark's Score of 3.9 points, within the MID range of 3–5 points leading to a non-significant difference between groups. The placebo effect noted in this trial is similar to that noted by this same research network in a 2×2 factorial designed trial comparing first line FI interventions: oral placebo to loperamide, and anal sphincter exercise training with biofeedback to an educational pamphlet.[28] Participants assigned to oral placebo and educational materials reported reductions in St. Mark's Scores of 3.4 at 12 weeks and 4.5 at 24 weeks. A systematic review of sham PTNS stimulation techniques in FI and constipation studies found variations in needle insertion and activation of nerve stimulators[31]. In the absence of a gold standard, this study employed a validated sham stimulation technique for PTNS studies of overactive bladder syndrome.[32] Despite the run-in and proven sham technique, the symptom reduction reported by the sham group was significant and consistent with the literature[28–31]. Though the underlying mechanism for sham effects is unknown, proposed theories include natural variation in symptoms, regression to the mean, and psychological and neurobiological effects[31, 33–36]. Future

analyses are planned to identify predictors of the sham response as well as potential genetic contributions to this phenomenon in this cohort of women.

The protocol choice of a generic electrical stimulation device in lieu of more costly proprietary devices for PTNS lends generalizability to study findings and accessibility of this therapy globally. The technique elicited the desired sensory and/or motor response in over 97% of sessions with outcomes comparable to other trials using marketed devices FDA-approved for urgency urinary incontinence (Cogentix/Uroplasty, Medtronic). While possible, it is unlikely that results of this trial would be different with use of an alternate pulse generators as FDA approvals of PTNS stimulators have been predicated on equivalence to the SANS unit. Consistent with other PTNS trials, adverse events were infrequent, mostly mild, and similar across treatment groups with no treatment-related serious adverse events.

Trial strengths include its rigorous study design with run-in and eligibility criteria that aided in enrollment of participants with moderate to severe symptoms less likely to spontaneously resolve with time or diary prompted dietary and behavioral modifications. The validated sham effectively maintained masking, likely contributing to the high adherence to treatment schedules in both groups.

Our findings are limited to females, many seeking care for pelvic floor disorders at urogynecology clinics, and to the protocol specified frequency and duration of PTNS sessions. Results should not be extrapolated to men who are equally affected by FI[1]. The absence of a ‘no treatment’ control arm, prevents us from quantifying the effect of the sham. Despite exclusion of women who regularly experienced watery diarrhea (Bristol stool 7), a substantial number of subjects reported symptoms of irritable bowel syndrome, with 75/166 (45.2%) reporting loose/mushy/watery stools, often/most of the time/always in the last 3 months. Though participants were not characterized with anorectal imaging or functional testing, a secondary analysis is planned to identify predictors of clinically meaningful response including stool frequency, consistency, and symptoms attributed to obstructive defecation. Lastly, the primary endpoint after 12 weekly, 30-minute treatment sessions was empirically adopted from OAB studies of PTNS. Continuation of assigned stimulation sessions in the maintenance phase (Part 2) will enable exploratory analyses of longer treatment exposure in both groups.

In conclusion, the study findings do not support the general use of PTNS in women with FI refractory to exercise and medication therapy. Although the improvement in St. Mark’s score after 12 weekly session of PTNS met the threshold of clinical importance, compared to sham stimulation, PTNS did not result in significantly greater improvement in symptom severity, incontinence events, or symptom specific quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS

WHAT IS KNOWN

- Fecal incontinence is common and debilitating with few non-invasive treatment options.
- Percutaneous tibial nerve stimulation (PTNS) is a potential low cost, minimally invasive neuromodulation therapy with conflicting evidence for efficacy.

WHAT IS NEW HERE

- Though improvement in St. Mark's score after PTNS exceeded the minimally important difference, PTNS did not differ from sham stimulation in reducing fecal incontinence severity, incontinence events, or quality of life.

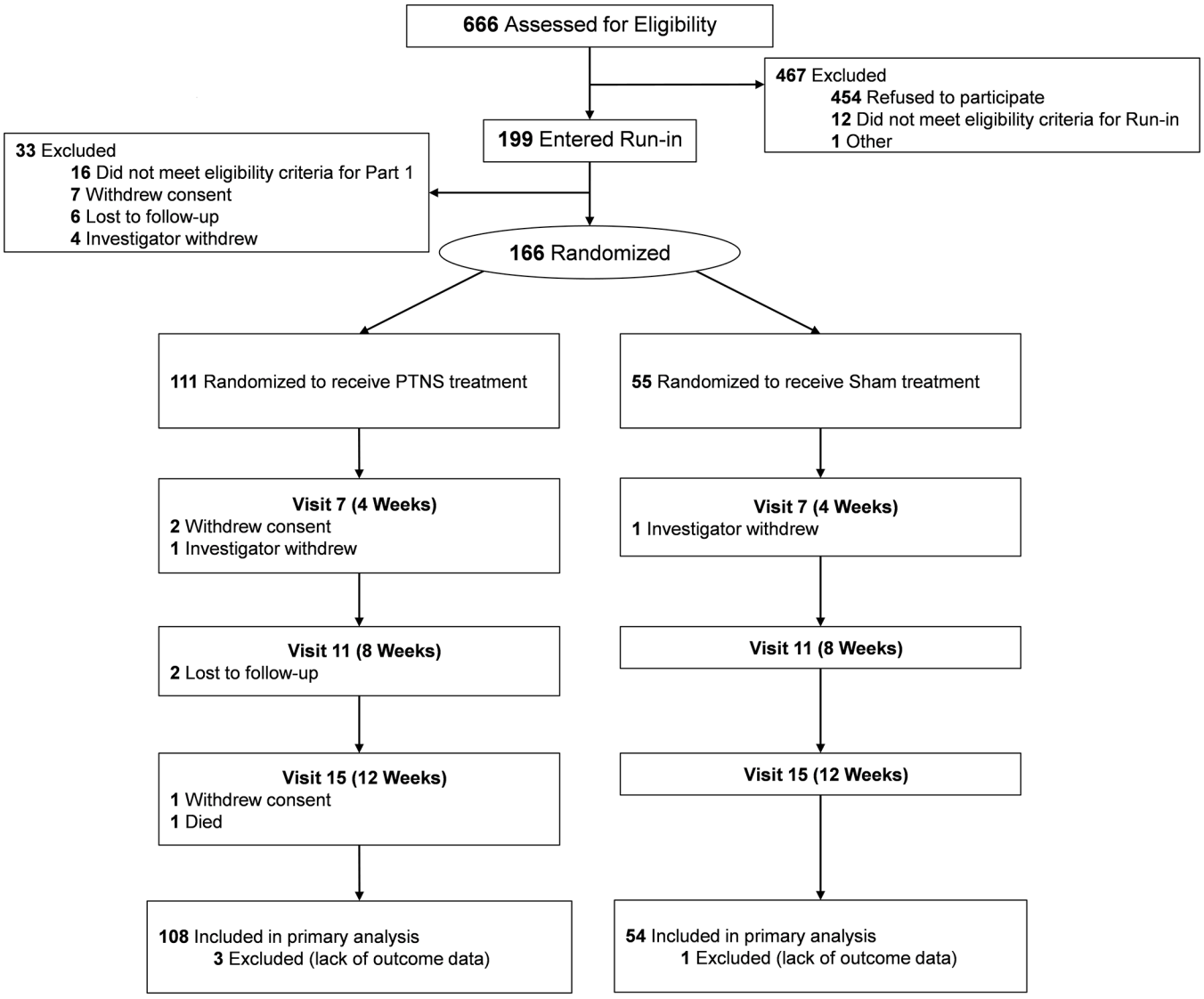

Figure 1.
NOTABLe Trial CONSORT Diagram

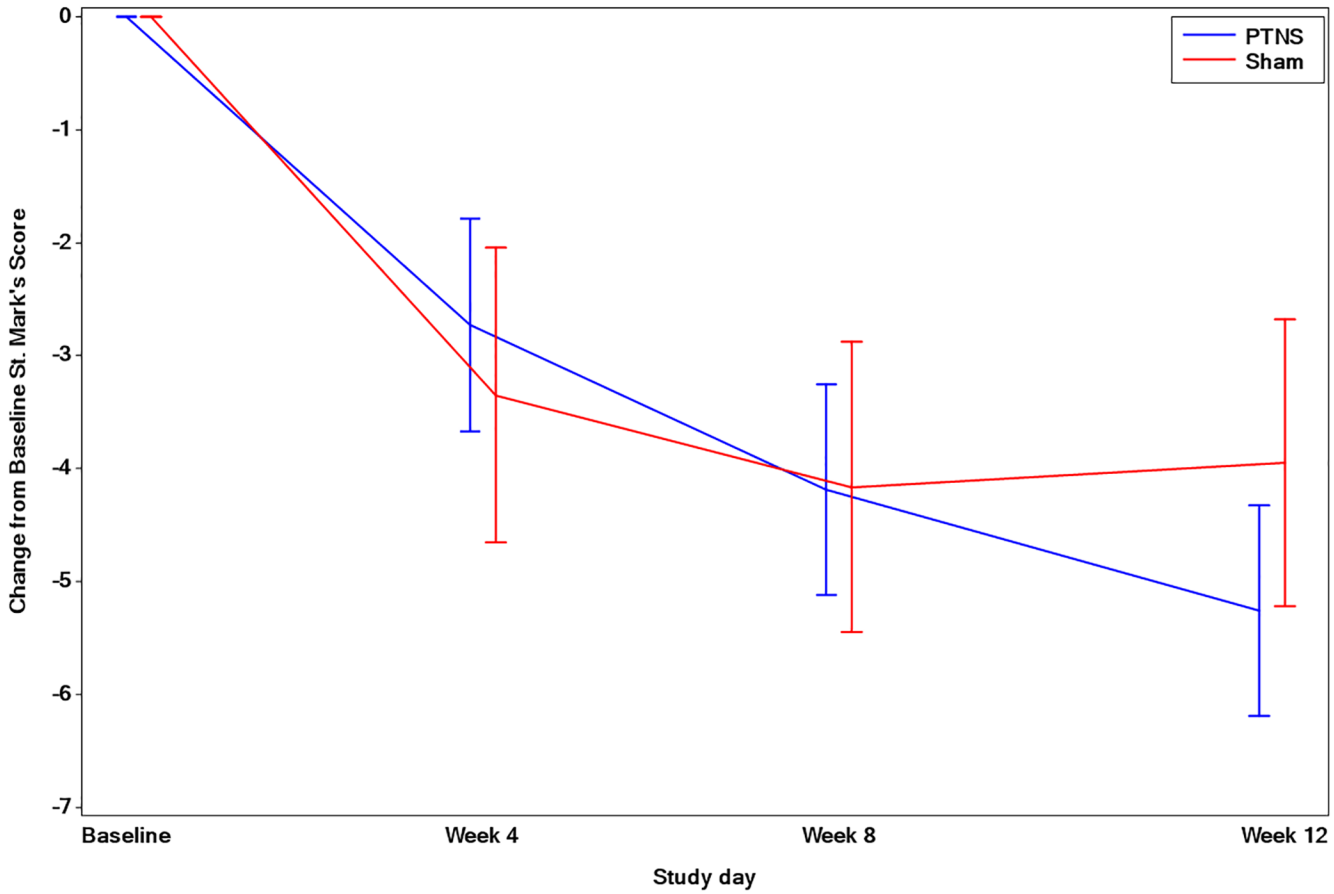

Figure 2.
NOTABLe Change from baseline St. Mark's Score

TABLE 1.

Baseline Characteristics of Eligible and Randomized Patients in Part 1.

Characteristic	Category	Total (N=166)	Treatment Group	
			PTNS (N=111)	Sham (N=55)
Age, mean (SD), y		63.6 (11.6)	63.5 (11.9)	63.8 (11.2)
Race, n/N (%)	American Indian/Alaska Native	2/166 (1.2)	1/111 (0.9)	1/55 (1.8)
	Asian	2/166 (1.2)	1/111 (0.9)	1/55 (1.8)
	Black or African American	19/166 (11.4)	10/111 (9.0)	9/55 (16.4)
	Native Hawaiian/Pacific Islander	2/166 (1.2)	1/111 (0.9)	1/55 (1.8)
	White	134/166 (80.7)	95/111 (85.6)	39/55 (70.9)
	Unknown/Not Reported	7/166 (4.2)	3/111 (2.7)	4/55 (7.3)
Ethnicity, n/N (%)	Hispanic/Latina	16/166 (9.6)	10/111 (9.0)	6/55 (10.9)
	Not Hispanic/Latina	148/166 (89.2)	99/111 (89.2)	49/55 (89.1)
	Unknown/Not Reported	2/166 (1.2)	2/111 (1.8)	0/ (0.0)
Primary language, n/N (%)	English	160/166 (96.4)	107/111 (96.4)	53/55 (96.4)
	Spanish	6/166 (3.6)	4/111 (3.6)	2/55 (3.6)
Education, n/N (%)	Some college or greater	115/166 (69.3)	78/111 (70.3)	37/55 (67.3)
	No college education	51/166 (30.7)	33/111 (29.7)	18/55 (32.7)
Insurance status, n/N (%)	Private/HMO	59/166 (35.5)	42/111 (37.8)	17/55 (30.9)
	Medicare/Medicaid	46/166 (27.7)	28/111 (25.2)	18/55 (32.7)
	Private and Medicare/Medicaid	42/166 (25.3)	28/111 (25.2)	14/55 (25.5)
	Other/None	19/166 (11.4)	13/111 (11.7)	6/55 (10.9)
Body Mass Index, mean (SD), kg/m^2		29.4 (6.6)	29.2 (6.9)	29.7 (6.0)
Body Mass Index, n/N (%)	<25 kg/m^2	39/164 (23.8)	28/110 (25.5)	11/54 (20.4)
	25 – 29.9 kg/m^2	55/164 (33.5)	39/110 (35.5)	16/54 (29.6)
	>= 30 kg/m^2	70/164 (42.7)	43/110 (39.1)	27/54 (50.0)
Anal sphincter squeeze, n/N (%)		146/164 (89.0)	99/110 (90.0)	47/54 (87.0)
Any vaginal deliveries, n/N (%)		146/166 (88.0)	98/111 (88.3)	48/55 (87.3)
Any cesarean deliveries, n/N (%)		19/166 (11.4)	16/111 (14.4)	3/55 (5.5)
Menopausal status, n/N (%)	Pre-menopausal	15/166 (9.0)	11/111 (9.9)	4/55 (7.3)
	Post-menopausal	141/166 (84.9)	92/111 (82.9)	49/55 (89.1)
	Not sure	10/166 (6.0)	8/111 (7.2)	2/55 (3.6)
Currently using estrogen, n/N (%)		46/166 (27.7)	28/111 (25.2)	18/55 (32.7)
Current smoker, n/N (%)		14/166 (8.4)	9/111 (8.1)	5/55 (9.1)
Prior fecal incontinence surgery, n/N (%)		8/166 (4.8)	6/111 (5.4)	2/55 (3.6)
Prior anal/rectal surgery, n/N (%)		28/166 (16.9)	21/111 (18.9)	7/55 (12.7)
Prior urinary incontinence surgery, n/N (%)		40/166 (24.1)	26/111 (23.4)	14/55 (25.5)
Prior prolapse surgery, n/N (%)		40/166 (24.1)	22/111 (19.8)	18/55 (32.7)
Hysterectomy, n/N (%)		75/166 (45.2)	48/111 (43.2)	27/55 (49.1)
Taking fiber supplements, n/N (%)		66/160 (41.3)	51/108 (47.2)	15/52 (28.8)
Dietary fiber intake, mean (SD), g		13.8 (4.2)	13.9 (4.1)	13.7 (4.3)
Bristol Stool Type, n/N (%)	Type 2 - Sausage-shaped but lumpy	13/166 (7.8)	10/111 (9.0)	3/55 (5.5)

Characteristic	Category	Total (N=166)	Treatment Group PTNS (N=111)	Sham (N=55)
	Type 3 - Like a sausage but with cracks on its surface	23/166 (13.9)	16/111 (14.4)	7/55 (12.7)
	Type 4 - Like a sausage or snake, smooth and soft	42/166 (25.3)	24/111 (21.6)	18/55 (32.7)
	Type 5 - Soft blobs with clear-cut edges	34/166 (20.5)	23/111 (20.7)	11/55 (20.0)
	Type 6 - Fluffy pieces with ragged edges, a mushy stool	54/166 (32.5)	38/111 (34.2)	16/55 (29.1)
Pain/discomfort in abdomen in last 3 months, n/N (%)				
	Less than once per week	102/166 (61.4)	61/111 (55.0)	41/55 (74.5)
	At least once per week	64/166 (38.6)	50/111 (45.0)	14/55 (25.5)
Pain/discomfort ≥6 months, n/N (%)		82/166 (49.4)	58/111 (52.3)	24/55 (43.6)
Diagnosed with Irritable Bowel Syndrome, n/N (%)		35/166 (21.1)	25/111 (22.5)	10/55 (18.2)
Frequency of loose/mushy/ watery stools in last 3 months, n/N (%)				
	Never or rare	57/166 (34.3)	32/111 (28.8)	25/55 (45.5)
	Sometimes	34/166 (20.5)	28/111 (25.2)	6/55 (10.9)
	Often/most of the time/always	75/166 (45.2)	51/111 (45.9)	24/55 (43.6)
Bowel movements per week, mean (SD), No.		13.3 (7.3)	13.6 (7.6)	12.7 (6.8)
Bowel movements with urgency per week, mean (SD), No.		6.8 (6.0)	7.3 (6.2)	5.9 (5.5)
Accident-free days per week, mean (SD), No.		3.4 (2.0)	3.3 (1.9)	3.6 (2.1)
Leaks per week, mean (SD), No.		6.6 (5.5)	6.8 (5.2)	6.3 (6.2)
Leaks with urgency per week, mean (SD), No.		3.4 (4.1)	3.6 (4.2)	2.9 (4.0)

Abbreviations:

PTNS, Percutaneous tibial nerve stimulation; SD, standard deviation.

Table 2.

Fecal incontinence, pelvic symptoms, and secondary functional outcomes from baseline through 12 weeks of stimulation sessions (ITT)[a]

Outcome Type	Baseline[b]		4 Weeks[b]		8 Weeks[b]		12 Weeks[b]	
	PTNS (N=111)	Sham (N=55)	PTNS (N=102)	Sham (N=50)	PTNS (N=105)	Sham (N=52)	PTNS (N=104)	Sham (N=54)
St. Mark's Score [c]								
Score, unadjusted mean (SD)	17.5 (2.5)	17.3 (3.0)	14.6 (4.2)	13.9 (5.0)	13.2 (4.9)	13.2 (4.8)	12.2 (5.0)	13.3 (4.7)
Difference from baseline, adjusted mean (95% CI)			−2.7 (−3.7, −1.8)	−3.3 (−4.7, −2.0)	−4.2 (−5.1, −3.3)	−4.2 (−5.4, −2.9)	−5.3 (−6.2, −4.3)	−3.9 (−5.2, −2.7)
Difference in difference, adjusted mean (95% CI)			0.62 (−0.94, 2.18)		−0.02 (−1.56, 1.51)		−1.31 (−2.84, 0.22)	
P-value			p=0.43		p=0.98		p=0.09	
Fecal Incontinence Episodes per Week								
Score, unadjusted mean (SD)	6.8 (5.2)	6.3 (6.2)			4.4 (4.5)	4.3 (5.3)	4.1 (5.3)	4.1 (5.1)
Difference from baseline, adjusted mean (95% CI)					−2.2 (−3.2, −1.2)	−1.5 (−2.8, −0.1)	−2.1 (−3.1, −1.2)	−1.9 (−3.2, −0.5)
Difference in difference, adjusted mean (95% CI)					−0.69 (−2.27, 0.90)		−0.26 (−1.85, 1.33)	
P-value					p=0.39		p=0.75	
Urgency Fecal Incontinence Episodes per Week								
Score, unadjusted mean (SD)	3.6 (4.2)	2.9 (4.0)			2.3 (2.7)	2.0 (3.2)	2.3 (3.5)	2.0 (3.5)
Difference from baseline, adjusted mean (95% CI)					−1.1 (−1.6, −0.6)	−0.3 (−1.0, 0.4)	−1.0 (−1.5, −0.5)	−0.6 (−1.3, 0.1)
Difference in difference, adjusted mean (95% CI)					−0.82 (−1.66, 0.01)		−0.40 (−1.24, 0.44)	
P-value					p=0.05		p=0.35	
Bowel Movements per Week								
Score, unadjusted mean (SD)	13.6 (7.6)	12.7 (6.8)			12.0 (5.7)	12.5 (8.8)	11.5 (5.4)	11.1 (6.2)
Difference from baseline, adjusted mean (95% CI)					−1.4 (−2.5, −0.3)	−0.1 (−1.6, 1.4)	−1.6 (−2.7, −0.5)	−1.2 (−2.7, 0.3)
Difference in difference, adjusted mean (95% CI)					−1.29 (−3.05, 0.47)		−0.43 (−2.20, 1.34)	
P-value					p=0.15		p=0.63	
Urgency Bowel Movements per Week								
Score, unadjusted mean (SD)	7.3 (6.2)	5.9 (5.5)			5.6 (5.2)	4.5 (5.2)	4.8 (4.6)	3.7 (4.8)
Difference from baseline, adjusted mean (95% CI)					−1.3 (−2.3, −0.4)	−0.9 (−2.2, 0.4)	−2.0 (−2.9, −1.0)	−1.7 (−3.1, −0.4)
Difference in difference, adjusted mean (95% CI)					−0.47 (−2.01, 1.07)		−0.21 (−1.76, 1.34)	

Outcome Type	Baseline[b]		4 Weeks[b]		8 Weeks[b]		12 Weeks[b]	
	PTNS (N=111)	Sham (N=55)	PTNS (N=102)	Sham (N=50)	PTNS (N=105)	Sham (N=52)	PTNS (N=104)	Sham (N=54)
P-value					p=0.55		p=0.79	
Fecal Incontinence Episode-Free Days per Week								
Score, unadjusted mean (SD)	3.3 (1.9)	3.6 (2.1)			4.4 (1.9)	4.5 (1.7)	4.7 (2.1)	4.5 (2.1)
Difference from baseline, adjusted mean (95% CI)					1.0 (0.5, 1.4)	0.8 (0.2, 1.3)	1.2 (0.8, 1.6)	0.8 (0.2, 1.4)
Difference in difference, adjusted mean (95% CI)					0.18 (−0.48, 0.85)		0.39 (−0.28, 1.06)	
P-value					p=0.59		p=0.26	
ABLe Overall Score [d]								
Score, unadjusted mean (SD)	2.9 (0.5)	2.7 (0.5)			2.6 (0.5)	2.5 (0.6)	2.4 (0.6)	2.3 (0.6)
Difference from baseline, adjusted mean (95% CI)					−0.3 (−0.4, −0.1)	−0.2 (−0.4, 0.0)	−0.5 (−0.6, −0.4)	−0.3 (−0.5, −0.2)
Difference in difference, adjusted mean (95% CI)					−0.05 (−0.25, 0.15)		−0.16 (−0.36, 0.04)	
P-value					p=0.63		p=0.12	
FISI Patient Score [e]								
Score, unadjusted mean (SD)	32.2 (8.3)	33.1 (10.7)			26.8 (10.5)	27.2 (11.1)	24.2 (9.9)	26.5 (11.6)
Difference from baseline, adjusted mean (95% CI)					−4.0 (−6.2, −1.7)	−5.0 (−8.0, −1.9)	−6.5 (−8.7, −4.2)	−5.9 (−8.9, −2.9)
Difference in difference, adjusted mean (95% CI)					0.99 (−2.62, 4.61)		−0.59 (−4.20, 3.02)	
P-value					p=0.59		p=0.75	
FISI Doctor Score [e]								
Score, unadjusted mean (SD)	34.5 (8.2)	35.5 (9.8)			29.0 (10.8)	29.2 (11.4)	26.5 (10.9)	28.6 (12.2)
Difference from baseline, adjusted mean (95% CI)					−3.9 (−6.3, −1.6)	−5.4 (−8.6, −2.2)	−6.3 (−8.7, −3.9)	−6.2 (−9.3, −3.1)
Difference in difference, adjusted mean (95% CI)					1.45 (−2.33, 5.23)		−0.10 (−3.87, 3.68)	
P-value					p=0.45		p=0.96	
PFDI Score [f]								
Score, unadjusted mean (SD)	111.7 (50.2)	115.6 (60.0)			94.4 (47.5)	88.8 (54.7)	83.9 (51.2)	78.8 (49.9)
Difference from baseline, adjusted mean (95% CI)					−15.1 (−24.0, −6.3)	−26.2 (−38.4, −13.9)	−25.9 (−34.8, −16.9)	−36.3 (−48.3, −24.3)
Difference in difference, adjusted mean (95% CI)					11.01 (−3.47, 25.49)		10.47 (−3.87, 24.81)	
P-value					p=0.14		p=0.15	
UDI Score [g]								

Outcome Type	Baseline[b]		4 Weeks[b]		8 Weeks[b]		12 Weeks[b]	
	PTNS (N=111)	Sham (N=55)	PTNS (N=102)	Sham (N=50)	PTNS (N=105)	Sham (N=52)	PTNS (N=104)	Sham (N=54)
Score, unadjusted mean (SD)	38.7 (26.9)	42.2 (29.6)			34.9 (27.2)	29.7 (26.5)	30.3 (28.0)	27.7 (24.1)
Difference from baseline, adjusted mean (95% CI)					−2.6 (−6.9, 1.7)	−11.5 (−17.4, −5.5)	−7.3 (−11.6, −2.9)	−14.3 (−20.2, −8.5)
Difference in difference, adjusted mean (95% CI)					8.89 (1.81, 15.97)		7.03 (0.02, 14.04)	
P-value					p=0.01		p=0.05	
POPDI Score [g]								
Score, unadjusted mean (SD)	24.4 (19.3)	25.2 (22.1)			19.3 (15.5)	20.1 (18.7)	16.8 (16.4)	15.1 (16.4)
Difference from baseline, adjusted mean (95% CI)					−4.0 (−7.4, −0.6)	−4.7 (−9.3, 0.0)	−6.5 (−9.9, −3.1)	−9.5 (−14.0, −4.9)
Difference in difference, adjusted mean (95% CI)					0.66 (−4.84, 6.17)		2.95 (−2.50, 8.41)	
P-value					p=0.81		p=0.29	
CRADI Score [g]								
Score, unadjusted mean (SD)	48.6 (17.4)	48.3 (19.1)			40.2 (17.1)	39.0 (19.9)	36.8 (18.6)	35.9 (20.2)
Difference from baseline, adjusted mean (95% CI)					−8.6 (−12.6, −4.5)	−10.1 (−15.7, −4.4)	−12.1 (−16.2, −8.0)	−12.6 (−18.1, −7.0)
Difference in difference, adjusted mean (95% CI)					1.50 (−5.17, 8.16)		0.50 (−6.11, 7.10)	
P-value					p=0.66		p=0.88	
PFIQ Score [h]								
Score, unadjusted mean (SD)	95.7 (59.9)	87.5 (58.5)			73.9 (54.6)	59.6 (45.2)	62.0 (51.9)	56.5 (46.9)
Difference from baseline, adjusted mean (95% CI)					−17.9 (−27.1, −8.7)	−27.4 (−40.0, −14.7)	−30.9 (−40.2, −21.7)	−30.1 (−42.5, −17.7)
Difference in difference, adjusted mean (95% CI)					9.49 (−5.50, 24.48)		−0.83 (−15.68, 14.02)	
P-value					p=0.21		p=0.91	
UIQ Score [i]								
Score, unadjusted mean (SD)	28.1 (27.1)	27.3 (27.5)			23.5 (24.1)	17.2 (20.5)	19.7 (23.6)	16.5 (21.4)
Difference from baseline, adjusted mean (95% CI)					−2.8 (−6.5, 0.9)	−9.4 (−14.6, −4.3)	−7.0 (−10.7, −3.2)	−10.2 (−15.2, −5.1)
Difference in difference, adjusted mean (95% CI)					6.65 (0.57, 12.73)		3.20 (−2.82, 9.21)	
P-value					p=0.03		p=0.30	
POPIQ Score [i]								
Score, unadjusted mean (SD)	13.7 (20.9)	10.5 (19.3)			9.5 (16.8)	5.3 (13.2)	7.5 (15.1)	5.1 (11.9)
Difference from baseline, adjusted mean (95% CI)					−3.7 (−7.1, −0.2)	−6.0 (−10.8, −1.3)	−5.9 (−9.4, −2.4)	−6.1 (−10.8, −1.4)

Outcome Type	Baseline[b]		4 Weeks[b]		8 Weeks[b]		12 Weeks[b]	
	PTNS (N=111)	Sham (N=55)	PTNS (N=102)	Sham (N=50)	PTNS (N=105)	Sham (N=52)	PTNS (N=104)	Sham (N=54)
Difference in difference, adjusted mean (95% CI)					2.39 (−3.25, 8.04)		0.18 (−5.41, 5.78)	
P-value					p=0.41		p=0.95	
CRAIQ Score [i]								
Score, unadjusted mean (SD)	53.9 (29.3)	49.7 (28.3)			40.9 (26.5)	37.0 (26.7)	34.8 (26.3)	34.9 (27.9)
Difference from baseline, adjusted mean (95% CI)					−11.4 (−16.5, −6.2)	−11.9 (−19.0, −4.9)	−18.0 (−23.2, −12.8)	−13.8 (−20.8, −6.9)
Difference in difference, adjusted mean (95% CI)					0.55 (−7.82, 8.93)		−4.20 (−12.52, 4.12)	
P-value					p=0.90		p=0.32	
ABI Hygiene Score [j]								
Score, unadjusted mean (SD)	53.9 (20.2)	54.7 (21.6)					44.5 (23.8)	51.4 (24.0)
Difference from baseline, adjusted mean (95% CI)							−10.0 (−14.1, −5.8)	−2.9 (−8.3, 2.6)
Difference in difference, adjusted mean (95% CI)							−7.08 (−13.59, −0.56)	
P-value							p=0.03	
ABI Avoidance Score [j]								
Score, unadjusted mean (SD)	41.6 (21.7)	38.8 (24.0)					29.7 (22.2)	32.2 (24.7)
Difference from baseline, adjusted mean (95% CI)							−12.4 (−16.4, −8.4)	−6.0 (−11.2, −0.7)
Difference in difference, adjusted mean (95% CI)							−6.39 (−12.64, −0.14)	
P-value							p=0.05	

Abbreviations:

ABLe, Accidental Bowel Leakage Symptom (ABLe) Questionnaire; FISI, Fecal Incontinence Severity Index; PFDI, Pelvic Floor Distress Inventory; UDI, Urogenital Distress Inventory; POPDI, Pelvic Organ Prolapse Distress Inventory; CRADI, Colorectal-Anal Distress Inventory; PFIQ, Pelvic Floor Impact Questionnaire; UIQ, Urinary Impact Questionnaire; POPIQ, Pelvic Organ Prolapse Impact Questionnaire; CRAIQ, Colorectal-Anal Impact questionnaire; ABI, Adaptive Behavior Index.

[a]Difference from baseline, difference in difference, and P-values are derived from longitudinal treatment models that accounted for multiple observations per participant and were adjusted for time since baseline, interaction between treatment and time and clinical site.

[b]Sample sizes present the number of participants with observed data at each time point.

[c]The St. Mark's score ranges from 0 to 24; the minimum clinically important difference (MCID) is 3 to 5 points, with higher scores indicating greater symptom severity.

[d]The ABLe overall score ranges from 0 to 4 with higher scores indicating greater condition severity.

[e]The FISI patient score ranges from 0 to 61 and the FISI doctor score ranges from 0 to 57 with higher scores indicating greater symptom severity.

[f] The PFDI total score ranges from 0 to 300 with higher scores indicating greater distress.

[g] The PFDI subscale scores range from 0 to 100 with higher scores indicating greater distress.

[h] The PFIQ total score ranges from 0 to 300 with higher scores indicating greater negative impact.

[i] The PFIQ subscale scores range from 0 to 100 with higher scores indicating greater negative impact.

[j] The ABI hygiene and avoidance scores range from 0 to 100 with higher scores indicating greater need for adaptive behaviors.

Table 3.

Additional Secondary Outcomes after 12 weeks of stimulation sessions (ITT)

	PTNS		Sham			
Outcome Type	**N**	**n (%)**	**N**	**n (%)**	**Odds Ratio, 95% CI**	**P-value**
Responders to Treatment	104	64 (61.5)	54	26 (48.1)	1.71 (0.86, 3.39)	0.12
50% Improvement in Fecal Incontinence Episodes/Week	97	51 (52.6)	48	19 (39.6)	1.70 (0.81, 3.56)	0.16
75% Improvement in Fecal Incontinence Episodes/Week	97	32 (33.0)	48	13 (27.1)	1.36 (0.59, 3.14)	0.46
Patient Global Impression of Improvement	103	47 (45.6)	54	21 (38.9)	1.31 (0.66, 2.59)	0.44
Patient Global Symptom Control	104	82 (78.8)	54	40 (74.1)	1.47 (0.65, 3.34)	0.35
St. Mark's (Vaizey) Questions [a]						
Incontinence for solid stool (weekly or daily)	104	21 (20.2)	54	19 (35.2)	0.47 (0.22, 0.97)	0.05
Incontinence for liquid stool (weekly or daily)	104	29 (27.9)	54	19 (35.2)	0.71 (0.35, 1.44)	0.37
Incontinence for gas (weekly or daily)	104	54 (51.9)	54	26 (48.1)	1.16 (0.60, 2.25)	0.74
Frequency of altered lifestyle (weekly or daily)	104	33 (31.7)	54	20 (37.0)	0.79 (0.40, 1.57)	0.59
Pad/plug use	104	66 (63.5)	54	43 (79.6)	0.44 (0.21, 0.96)	0.05
Taking constipating medicines	104	36 (34.6)	54	18 (33.3)	1.06 (0.53, 2.12)	>0.99
Inability to defer defecation for 15 minutes	104	63 (60.6)	54	36 (66.7)	0.77 (0.39, 1.53)	0.49

Abbreviations:

ITT, Intent-to-Treat; PTNS, Percutaneous tibial nerve stimulation; SD, standard deviation.

[a]Odds ratios and p-values for individual St. Mark's (Vaizey) questionnaire items are unadjusted.