A prospective, multicenter, international study to explore the effect of three different amplitude settings in female subjects with urinary urge incontinence receiving interstim therapy

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Abstract
Aims: The aim of this study is to evaluate the effect of sub-sensory amplitude settings of sacral neuromodulation therapy on overactive bladder symptoms in subjects with urinary urge incontinence.

Methods: Subjects who qualified for a neurostimulator device implant were randomized to one of three amplitude settings (50% of sensory threshold [ST], 80% of ST, and ST). Subjects completed urinary voiding diaries (3-day), International consultation on incontinence modular questionnaire—overactive bladder symptoms quality of life questionnaire, and patient global impression of improvement (PGI-I) to assess change in voiding symptoms and quality of life (QoL) from baseline through 12 weeks.

Results: Forty-eight subjects had a successful test stimulation, 46 were implanted with a neurostimulator device and 43 completed the 12-week follow-up visit. The change from baseline to 12 weeks is −3.0 urinary incontinence (UI) episodes/day (95% confidence interval [CI]: −4.4 to −1.7) for the 50% of sensory threshold group, −2.9 UI episodes/day (95% CI: −4.7 to −1.2) for 80% of sensory threshold group, and −3.6 UI episodes/day (95% CI: −5.2 to −1.9) for the sensory threshold group. In each randomized group, improvements were observed in health-related QoL, its subscales, and symptom interference. Subjects across all three randomization groups reported on the PGI-I that their bladder condition was better at 12 weeks compared to before they were treated with InterStim therapy.

Conclusion: These findings provide insights into possible advancements in the postimplantation phase of therapy with potential for improved patient comfort and increased device longevity.
1 | INTRODUCTION

Sacral neuromodulation (SNM) is a minimally-invasive treatment option for patients with overactive bladder (OAB) refractory to conservative and oral pharmacologic therapy. Eligibility for SNM is determined through either a percutaneous nerve evaluation and placement of a temporary lead, or staged implantation of the quadripolar tined lead to the S3 or S4 sacral nerve root. The trial lead is then connected to an external nerve stimulator. Each approach has its own merits and disadvantages. A successful trial is typically defined as a reduction or normalization in urinary urgency-frequency or incontinence by 50% or greater from untreated conditions.

Since its inception, there have been multiple evolutions in device and procedural techniques that have led to current practice standards for SNM. The percutaneous nerve evaluation for assessing eligibility enabled patients to have an office-based procedure free of any systemic anesthesia. For those undergoing staged implantation, the shift to eliciting motor response only rather than both sensory and motor responses to assess lead placement led to reduction in operative times and improved patient satisfaction without compromising outcomes. In the implantation of the quadripolar tined lead, the use of a curved stylet compared to the traditional straight stylet has resulted in better clinical success rates in the long-term. These examples are some of the many iterations in SNM over the years. ClinicalTrials.gov identifier: InterStim Amplitude Study, NCT03335761.

However, the majority of these improvements have occurred in the initial patient evaluation or intraoperative phase of therapy. Postoperatively, device programming is an equally important component in maintaining success of the therapy. Optimal settings are currently dependent on the evoked sensory response on lead stimulation, with the perineal, genital and anal regions thought to be ideal areas for stimulation. Regular re-programming is not uncommon, and is most frequently performed due to an undesirable change in stimulation, a loss in the evoked sensory response or a lack of efficacy with current settings. The generally accepted view regarding programming is to set stimulation levels at the sensory threshold, in other words, at a level that the patient can feel the stimulation. In some instances, where stimulation is felt to be undesirable or bothersome, sub-sensory stimulation, a level below which can be perceived, may otherwise be satisfactory or even preferred.

Currently, there is a paucity of evidence regarding sub-sensory amplitude effects on OAB symptoms. The aim of this study is to evaluate the effect of sub-sensory amplitude settings on OAB symptoms as measured by urinary voiding diaries at 6 and 12 weeks of SNM therapy in subjects with urinary urge incontinence (UUI).

2 | MATERIALS AND METHODS

2.1 | Study overview

Authors met ICMJE Uniform Requirements. The study was approved by appropriate institutional review boards and ethics committees. To be selected, principal investigators and sub-investigators were required to be qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures. Principal investigators were required to have implanted at least six patients with an InterStim system for OAB in the past 12 months. Eligible subjects signed a study-specific informed consent form before initiation into the study. Enrolled subjects were required to meet all inclusion and no exclusion criteria (Table 1). Inclusion criteria included subjects who had a primary diagnosis of UUI as demonstrated by at least 3 UUI episodes on a 3-day baseline voiding diary.

Following verification of eligibility criteria, subjects underwent therapy evaluation (basic or advanced) with the Verify External Neurostimulator (Model 3531) and either the InterStim Tined Lead (Model 3889) or the temporary Test Stimulation Lead (Model 3057); Medtronic, Inc.). In this post market study, implanting physicians were required to follow instructions in the InterStim™ implant manuals. Subjects who had successful therapy evaluation (≥50% improvement in urinary incontinence (UI) or urinary frequency (UF) voiding symptoms or return to normal voiding of less than eight voids per day for UF subjects) proceeded to a neurostimulator device implant (InterStim II Model 3058) and randomization procedure. Sensory threshold was defined as the lowest amplitude where the subject first perceived sensation of the stimulation in the perineum, perianal, vaginal, or any location deemed appropriate by the investigator while in a seated position.
Subject's sensory threshold amplitude was determined by following this protocol: start at 0.05 volts (V) and increase voltage using fine resolution in 0.05 V increments until the subject reports sensation. At Neurostimulator implant visit, the subjects were randomized to one of three amplitude settings: 50% of sensory threshold, 80% of sensory threshold, or sensory threshold. Randomization was assigned in a 1:1:1 ratio with permuted block sizes of 3 and 6 and was stratified by site. If a subject did not meet all eligibility criteria, the subject was exited and did not proceed to the neurostimulator device implant and randomization procedures.

Subjects completed enrollment/baseline visits, lead implant, therapy evaluation, neurostimulator device implant, randomization, 1, 6, and 12-week follow-up visits. At the neurostimulator device implant visit following determination of sensory threshold before discharge (seated position), the amplitude was programmed based on the assigned randomization of sensory threshold, 80% of sensory threshold, or 50% of sensory threshold. Fifty percent and 80 percent of sensory threshold was calculated as sensory threshold × 0.5 or ×0.8, respectively. At each follow-up visit, sensory threshold was reassessed, and the amplitude was reprogrammed based on the assigned randomization.

Symptoms related to OAB were evaluated using a 3-day paper voiding diary. The diaries were completed at baseline, therapy evaluation, and at the 6 and 12-week follow-up visits.

Quality of life (QoL) was assessed using the validated International consultation on incontinence modular questionnaire—overactive bladder symptoms quality of life (ICIQ-OABqol) at baseline and 12 weeks. The ICIQ-OABqol provides a detailed and robust measure to assess the impact of OAB symptoms on QoL. The subject-completed questionnaire included 26 questions, which include 4-week recall for symptom assessment, and also consists of four subscales, and a single item on urinary symptom interference. The four subscales of concern (seven items), coping (eight items), sleep (five items), and social (five items) are measured on a scale from 0 to 100 using a range percentile transformation on the summed value from individual listed items. The health-related QoL (HRQL) score is a calculated score with a range from 0 to 100 using a range percentile transformation on the summed value from the subscales. Responses to the “Interference” question on the OABqol measured how much urinary symptoms interfere with everyday activities.

Patient impression of improvement was evaluated using the patient global impression of improvement (PGI-I) at 6 and 12-week follow-up visits. This questionnaire is a single question asking the patient to rate their urinary condition now (at time of follow-up) compared with before beginning treatment on a scale from 1 (very much better) to 7 (very much worse).

Motor and sensory threshold amplitudes were collected at the time of neurostimulator implant, and sensory threshold was collected at each follow-up visit in the active programmed electrode configuration. This was a single-blinded study. Subjects remained blinded to their assigned randomization for the duration of the study.
2.2 Statistical considerations

This study required approximately 42 implanted and randomized subjects with 12-week follow-up data to have sufficient precision for characterizing the study’s primary objective in each randomization group. Assuming 10% attrition after full system implant, and an 80% therapy evaluation success rate, approximately 60 subjects were estimated to be enrolled to ensure that 42 subjects completed the study. However, the number enrolled was exceeded to ensure that a minimum of 42 subjects completed the study.

Based on a confidence interval (CI) constructed with a t-statistic, a two-sided type-I error rate of 0.05, a mean reduction (±standard deviation) of 1.8 ± 2.7 UI episodes per day, and a sample size of 14 subjects per group, the precision was estimated to be 1.56 in each group. Precision was defined as one-half of the CI. This precision was less than the assumed treatment effect of 1.8 UI episodes per day, so it was expected that the lower 95% CI would be greater than 0 for each randomization group.

Study objectives were evaluated to determine efficacy and QoL under three different amplitude settings. Efficacy was characterized by change from baseline through 12 weeks in UI episodes; QoL was characterized with change from baseline through 12 weeks for the ICIQ-OABqol and with PGI-I at 6 and 12 weeks. Continuous variables were reported as means and 95% CIs. Categorical variables were reported as frequencies and percentages. Post hoc testing was conducted using paired t tests to compare change from baseline for UI episodes. No missing data imputations were performed. p Values were unadjusted for multiple testing.

![FIGURE 1](Pathway for enrolled subjects)
Since testing was conducted with three groups and two different endpoints, unadjusted \( p \) values were compared to a Bonferroni-adjusted alpha of \( 0.05/6 = 0.008 \). A post hoc test was also conducted to assess poolability by site with a linear regression model that was adjusted by randomization group and site. SAS (SAS Institute Inc.) version 9.4 was used for all analyses.

### 3 | RESULTS

#### 3.1 | Subject demographics and disposition

Sixty-five (66) subjects met inclusion and exclusion criteria and received test stimulation in 15 sites in 5 countries. There were 42 advanced evaluations and 24 basic evaluations, and all leads were implanted in the S3 foramen. Surgeon experience is evidenced by the low motor thresholds obtained with 88% of all tested configurations having a threshold less than 2 mA. Additionally, all principal investigators in the study had at least 5 years of implant experience before study initiation. Forty-eight subjects had a successful test stimulation (≥50% improvement in UI or UF voiding symptoms or return to normal voiding of less than 8 voids per day for UF subjects), 46 were implanted with a neurostimulator device and 43 completed the 12-week follow-up visit (Figure 1). Ninety-three percent of subjects implanted with a neurostimulator completed their final visit. Demographics are listed in Table 2. Mean age for randomized subjects was 60 ± 15.7 years (\( n = 48 \)). At baseline, randomized subjects averaged 4.8 UI episodes per day (±3.5 SD, \( n = 48 \)). The first subject enrollment occurred in February 2018, and the last subject’s last visit was in November 2019.

#### 3.2 | Urinary incontinence outcomes

For the primary analyses, UI episodes/day from baseline to 6 and 12 weeks are summarized in Figure 2. The change from baseline to 12 weeks is \(-3.0 \) UI episodes/day (95% CI: \(-4.4 \) to \(-1.7 \)) for the 50% of sensory threshold group (\( n = 17 \)), 80% sensory threshold group (\( n = 13 \)), sensory threshold group (\( n = 13 \)) Mean number UI episodes/day from baseline through 12 weeks for each randomized group. The error bars represent the standard error.

| TABLE 2 | Demographics for randomized subject set (48 subjects) |
| --- | --- |
| **Demographics** | 50% of sensory, \( N = 19 \) | 80% of sensory, \( N = 14 \) | Sensory, \( N = 15 \) | Total, \( N = 48 \) |
| Age (years) | 64.1 ± 16.0 | 57.9 ± 16.1 | 56.7 ± 14.9 | 60.0 ± 15.7 |
| BMI | 30.0 ± 5.7 | 36.3 ± 11.2 | 33.1 ± 6.4 | 32.8 ± 8.1 |
| Female | 100% | 100% | 100% | 100% |
| Years since OAB diagnosis | 10.8 ± 13.2 | 4.3 ± 2.7 | 5.9 ± 6.3 | 7.4 ± 9.5 |
| UI episodes per day | 4.3 ± 2.8 | 5.0 ± 3.2 | 5.1 ± 4.6 | 4.8 ± 3.5 |
| Degree of urgency | 2.1 ± 0.7 | 2.3 ± 0.8 | 1.9 ± 0.5 | 2.1 ± 0.7 |

**Note:** Table shows mean ± SD (N) %. Urgency was measured on a scale ranging from 0 (no urgency) to 4 (severe urgency).

**Abbreviations:** BMI, body mass index; OAB, overactive bladder; UI, urinary incontinence.
3.3 | Quality of life

Change from baseline to 12 weeks for the primary analysis of HRQL, and its subscales (concern, coping, sleep, social), and Interference are summarized in Figure 3A. A positive change in overall HRQL and its subscales indicates improvement in QoL; a negative change in Interference indicates improvement in QOL. HRQL change from baseline to 12 weeks was 38.1 ± 24.4 at 50% of sensory threshold, 40.5 ± 16.7 at 80% of sensory threshold, 37.1 ± 23.4 at sensory threshold. In each randomized group, there was a significant improvement in overall HRQL and all its domains from post hoc analyses.

Subjects across all three randomization groups reported that their bladder condition was better at 12 weeks compared to before they were treated with InterStim therapy (PGI-I questionnaire 82.4%, 92.3%, and 92.3% for the 50%, 80%, and sensory threshold groups, respectively). A summary of PGI-I at 6 and 12 Weeks is provided in Figure 3B.

3.4 | Motor and sensory thresholds

Motor response at time of tined lead placement was obtained for 98% of the randomized subjects (n = 48). The mean motor response was 0.6 mA ± 0.4 (n = 47). Mean sensory thresholds and programmed amplitudes are provided by groups in Table 3 and mean sensory thresholds in the seated position at baseline and each follow-up visit for the full subject cohort is provided in Figure 4. At the 12 week follow up visit, 65.1% of randomized subjects demonstrated a sensory threshold amplitude within ± 0.5 V of their sensory threshold at neurostimulator implant.

4 | DISCUSSION

This study demonstrated that patients with sub-sensory amplitude settings at 50% and 80% of sensory threshold demonstrated a reduction in UI episodes of −3.0 (95% CI: −4.4 to −1.7) and −2.9 (95% CI: −4.7 to −1.2) UI episodes/day, respectively. Patients with amplitude settings at the sensory threshold also had a reduction at −3.6 (95% CI: −5.2 to −1.9) UI episodes/day. Our findings are similar to the results published by Amundsen et al.10 in the randomized ROSETTA trial with a reduction of over −3.5 UI episodes/day at 12 weeks follow-up and comparable to the results of Insite trial published by Siegel et al.11 with a reduction of 2.3 UI episodes/day at the 3 months follow-up. There was also reported improvement in all domains of the ICIQ-OABqol questionnaire amongst all randomized groups. It should be noted that no statistical comparative testing was performed between randomized groups, as the study was not designed to assess between-group statistical testing. These findings are important as the conventional approach has been in favor of setting amplitudes that evoke sensory, and potentially concurrent motor, response to achieve ideal results.12

The efficacy of sub-sensory amplitude settings has potential impacts to both patients and providers. The
most common device related concern reported post SNM implantation is an undesirable change in stimulation.\textsuperscript{6,13,14} In the SNM cohort of the ROSETTA trial, 58% of patients required reprogramming at 24 months, with 17% requiring three or more reprogramming visits.\textsuperscript{5} Sub-sensory settings could thus alleviate some of the patient and provider burden for more frequent reprogramming. In a prospective study assessing patient preferences for above and below threshold waveforms with spinal cord stimulation devices, the investigators found that there was a trend towards below threshold preference by patients during vigorous activity and sleep.\textsuperscript{15} Thus, stimulation at sensory threshold may serve as either a reassurance or a distraction depending on the situational context. Sub-sensory settings may enable patients to tailor SNM therapy to their day-to-day activities without compromising efficacy.

Sub-sensory amplitude settings may also benefit the longevity of the neurostimulator. Bin-Mahfoodh et al.\textsuperscript{16} showed that the longevity of neurostimulators for deep brain stimulation was influenced by the total electrical energy delivered. Sub-sensory amplitude settings may be a strategy to increase device longevity for patients with SNM therapy. Less frequent neurostimulator revisions due to battery depletion would also be advantageous for both payers and patients.

There are, however, limitations to conclusions that can be drawn for the study and the data presented. It is unclear what the optimal sub-sensory amplitude setting would be given the lack of between group comparisons which was not designed for this study. In the ROSETTA trial, 30% of patients reported a greater than 75% reduction in UUI episodes at 6 months while decreasing to only 21% having the same response at

### Table 3

| Visit     | Device Implant | Sensory Threshold Mean ± SD (N) | Programmed Amplitude Mean ± SD (N) |
|-----------|----------------|--------------------------------|-----------------------------------|
| 1 Week    | Sensory threshold 1.1 ± 0.8 (18) | 0.8 ± 0.3 (13) |
|           | Programmed amplitude 0.6 ± 0.4 (18) | 0.8 ± 0.3 (13) |
| 6 Weeks   | Sensory threshold 1.3 ± 0.9 (13) | 1.1 ± 0.6 (12) |
|           | Programmed amplitude N/A | N/A |
| 12 Weeks  | Sensory threshold N/A | N/A |
|           | Programmed amplitude N/A | N/A |

![Figure 4](https://example.com/figure4.png)

**FIGURE 4** Sensory response for complete case set (n = 43)
Mean of the lowest threshold of sensory response in seated position (n = 43) Baseline represents the neurostimulator implant on this figure. The error bars represent the standard error.
24 months. This finding of decreasing efficacy or late failure in some patients was also reported by Groen et al. at 60 months follow-up. While results in SNM for OAB studies are not gender specific, because this study enrolled only female participants, the results may not necessarily be generalizable to male patients. Future studies may be directed towards determining whether sub-sensory stimulation may result in less therapy fade over time due to reduction in neural accommodation, habituation, or other neural mechanism.

5 | CONCLUSION

Sub-sensory amplitude settings of 50% and 80% of sensory threshold demonstrated a similar reduction in urgency incontinence episodes. There was also an improvement in patient reported QoL outcomes across all settings. These findings provide insights into possible advancements in the postimplantation phase of therapy with potential for improved patient comfort and increased device longevity.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Medtronic. Restrictions apply to the availability of these data, which were used under license for this study.

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