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Original Article

Sacral Neuromodulation with the InterStim System for Intractable Lower Urinary Tract Dysfunctions (SOUNDS): Results of Clinical Effectiveness, Quality of Life, Patient-Reported Outcomes and Safety in a French Multicenter Observational Study

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Abstract

Background: Real-world data that support the use of sacral neuromodulation (SNM) for lower urinary tract dysfunctions are of continued interest.

Objective: To evaluate the effectiveness, quality of life (QoL), patient-reported outcomes (PROs), and safety of SNM with the InterStim system in real life during 1-yr postimplant.

Design, setting, and participants: This is a prospective, multicenter, observational study at 25 representative public and private French sites. Eligible patients received SNM therapy for overactive bladder (OAB) and non-obstructive urinary retention based on local standard of care. Overall, 320 patients were enrolled; 247 received permanent implant or replacement; 204 implanted patients completed second follow-up after mean of 10.0 ± 3.8 mo.

Outcome measurements and statistical analysis: Effectiveness outcomes were change in voids, leaks, and catheterizations/day. Other outcomes included validated QoL and disease severity scores as well as PROs and adverse event data. Outcomes at follow-ups were compared with baseline using the Wilcoxon signed-rank test.

Results and limitations: Voids in urinary frequency (UF) and leaks/day in urinary urge incontinence (UI) patients were significantly reduced after 10 mo in both *de novo* (mean baseline voids/day UF *de novo*: 12.7 vs 8.6 after 10 mo; $p < 0.001$; mean baseline leaks/day UI *de novo*: 4.3 vs 1.1 after 10 mo; $p < 0.001$) and replacement patients (mean baseline voids/day UF replacement: 11.5 vs 7.9 after 10 mo; $p < 0.001$; mean baseline leaks/day UI replacement: 5.4 vs 1.0 after 10 mo; $p < 0.001$). Disease bother, Urinary Symptom Profile score, and Ditrovie questionnaire score were also significantly improved. Revisions postimplant occurred in 20% of patients including in 9% due to permanent explantation during a mean exposure time of 24.3 mo.

Conclusions: Through a real-life study, SOUNDS (Sacral neuromodulation with InterStim therapy for intractable lower urinary tract dysfunctions) confirms the clinical effectiveness, safety, and positive effect of SNM on QoL and PROs for the treatment of OAB patients.

Patient summary: These analyses on French patients who received sacral neuromodulation (SNM) for retention or OAB during a 10-mo period showed that SNM improved OAB symptoms, quality of life, and reduced disease bother.

Trial registration: ClinicalTrials.gov: NCT02186041

Keywords: Double incontinence; Non-obstructive urinary retention; Overactive bladder; Sacral neuromodulation

1. Introduction

Overactive bladder (OAB) and non-obstructive urinary retention (NOUR) are highly prevalent conditions [1,2] which negatively impact quality of life (QoL) [3]. Affected patients are often reluctant to discuss their condition or seek medical care due to social stigma and embarrassment [2,4]. There is also a significant economic burden associated with OAB [5] which is comparable in magnitude to breast cancer and osteoporosis [6].

First-line therapy for OAB usually starts with lifestyle modifications and behavioral techniques which are augmented by medications (second-line therapy) in case of unsatisfactory results [7]. However, discontinuation rates of conservative management options are high and adequate symptom control is not always possible [8].

Sacral neuromodulation (SNM) with the InterStim system for the treatment of lower urinary tract dysfunctions has been CE marked and FDA approved since 1995 and 1997, respectively. It is recommended by several consensus guidelines as third-line therapy for OAB [7,9,10] and since its introduction more than 300,000 patients have been treated for all approved indications. Guideline recommendations have been based on well-designed, selective, and stringent clinical trials [7,9,10], but recent data about SNM outcomes in current clinical practice remain scarce.

SOUNDS (Sacral neuromodulation with InterStim therapy for intractable lower urinary tract dysfunctions) was designed as a prospective, multicenter observational study to collect real-world data on InterStim system use in France to satisfy the requirements of the French

Authority for Health. The study will collect long-term data up to 5 yr after device implant. Here we report results from the first two visits occurring within 12 mo after implantation.

2. Methods

2.1. Study design, participants, and outcomes

Adult patients were enrolled if their primary diagnosis was lower urinary tract dysfunction (whatever the medical history) including OAB, either wet [urinary urge incontinence (UI)] or dry [urgency frequency (UF)], and/or NOUR. In case of NOUR, obstruction was ruled out based on clinical judgment or further examination such as urodynamics. The presence of concomitant fecal incontinence (ie, double incontinence) was not an exclusion. Both patients that received a *de novo* system and patients that were scheduled for a system replacement (either neurostimulator or lead or both) were eligible for the study. Study patients were enrolled between August 2014 and March 2016. For this analysis, OAB patients were categorized based on voiding diaries with a minimum of two leaking episodes in 72 h (UI) and/or 8 or more voids/d (UF). As the study was observational following routine care, there was no requirement in France to have it approved by the institutional review boards. However, all patients signed informed consents prior to study participation.

Study sites were selected to ensure representativeness of the French health-care setting and were stratified according to the volume (high, medium, and low) and type of institution (public or private). All but one patient who received SNM therapy for the first time (*de novo*) underwent a timed lead test to evaluate therapeutic response. Decision to implant a permanent system was at the discretion of each study site with no formal requirement for test success. Sites usually used a mix of diary-based symptom improvement, patient satisfaction, and QoL benefits to decide on permanent implantation. Similarly, there were no requirements concerning implant

technique or antibiotic prophylaxis. Adjuvant medical treatments were allowed according to hospital standard of care. Patients were implanted with an InterStim system consisting of a neurostimulator and a quadripolar tined lead (neurostimulator models 3023/3058, lead models 3093/3889; Medtronic, Minneapolis, MN, USA). Follow-up visits were scheduled according to standard of care at each site with two follow-up visits during the first 12 mo (follow-up visit 1: 3.1 ± 2.7 mo; follow-up visit 2: 10.0 ± 3.8 mo).

The 3-d bladder diary data were used to evaluate change in voids/day, leaks/day for OAB patients, and number of catheterizations/day for NOUR patients. Patients were categorized as therapy responders if they had $\geq 50\%$ reduction in leaks/day (UI), $\geq 50\%$ reduction in voids/day, or a return to normal voiding frequency of < 8 voids/d (UF). For OAB a combined criterion was used as historically [11]. NOUR patients were categorized as therapy responders if they had $\geq 50\%$ reduction in catheterizations/day. QoL was assessed through the validated, disease-specific French Ditrovie questionnaire (range: 10–50; lower scores correspond to better QoL) [12] and the generic EQ-5D-5L [13]. The Urinary Symptom Profile (USP) was used to evaluate patient's symptoms in three domains with low scores indicating better urinary symptoms [14]. Patient-reported outcomes (PROs) were captured by evaluating the disease bother with a numeric rating scale [NRS; scale: 0 (no bother) to 10 (most severe bother)] and the Goal Attainment Scaling (GAS) [15] in which patients compared their therapy response against their own expectations [scores range from -3 (much less than expected) to $+2$ (much more than expected; patients with scores ≥ 0 were classified as responders)]. The symptoms of patients with double incontinence (urinary and fecal) were rated with the Wexner score (range 0–20, low scores indicate less severe fecal incontinence) [16].

In this paper we report on effectiveness, QoL, and PRO data for implanted patients from the first two routine care follow-ups within 1 yr after a mean of 3.1 and 10.0 mo postimplant,

respectively. Adverse events are reported for all patients (combined cohort of *de novo*, replacement, and not implanted patients) during test stimulation and after full system implant until database snapshot leading to an average device exposure time of 24.3 ± 7.3 mo for implanted patients.

2.2. Statistical analysis

All analyses on effectiveness, QoL, and PROs were performed using the intent-to-treat analysis with no missing data imputation. Data are presented as mean \pm standard deviation. Although no formal hypothesis testing was defined for this study, outcomes in effectiveness, QoL, and PROs at follow-up visits were compared with baseline at the significance level of 0.05. The change between baseline and follow-up measurements was analyzed by the Wilcoxon signed-rank test. To evaluate for representativeness of enrolling sites with respect to volume (low, medium, and high) and type of institution (private, public), we compared them with all eligible sites in the volume-type strata using a chi-square goodness-of-fit test. All analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA).

3. Results

In total, 320 patients were enrolled and 301 patients either received a *de novo* InterStim system (78%) or a replacement procedure of an existing system (22%; Fig. 1). Patients were predominantly female (84%; 268/320) with a mean age of 60.5 ± 15.1 yr. In replacement patients with reasons reported, 39% (25/64) received a new neurostimulator, 14% (9/64) received a new lead, and 47% (30/64) received a replacement of both components. The 25 sites that enrolled patients were representative regarding both patient volume and institution type ($p = 0.748$). A listing of tested/implanted patients per institution volume and type is summarized in the

Supplementary Table 1. Baseline demographics and patient characteristics are presented in Table 1.

Mean number of voids/day in UF patients was significantly reduced in both the *de novo* and replacement groups. For *de novo* patients, mean number of baseline voids was reduced from 12.7 ± 4.0 to 9.1 ± 3.1 at 3 mo and to 8.6 ± 2.9 at 10 mo, respectively (both $p < 0.001$). For replacement patients mean baseline voids were 11.5 ± 4.3 which decreased to 9.0 ± 2.2 ($p < 0.05$) and 7.9 ± 1.8 ($p < 0.001$) at 3 and 10 mo, respectively. Mean number of baseline leaks/day in UI *de novo* patients was reduced from 4.3 ± 3.3 to 1.4 ± 2.4 at 3 mo and to 1.1 ± 1.6 at 10 mo (both $p < 0.001$). Mean number of baseline leaks/day in UI replacement patients was reduced from 5.4 ± 4.9 to 2.0 ± 2.5 at 3 mo and to 1.0 ± 1.9 at 10 mo (both $p < 0.001$; Fig. 2).

Therapy responder rates in UI patients were 78% and 84% in the *de novo* group at the 3- and 10-mo visits, respectively. In the replacement group responder rates were 71% and 88% at 3- and 10-mo visits, respectively. Complete continence was achieved in 36% and 46% of patients in the *de novo* and 25% and 53% in the replacement group at 3 and 10 mo, respectively (Fig. 3). In UF patients responder rates were 45% and 41% in the *de novo* group and 44% and 62% in the replacement group at 3 and 10 mo, respectively. Concerning OAB patients (UI + UF or UI only or UF only), 62% and 66% of *de novo* and 67% and 77% of replacement patients were categorized as therapy responders at 3 and 10 mo, respectively.

The USP showed a significant improvement in all domains and follow-ups except for USP3 in replacement patients at the 3-mo visit (Table 2). NRS-rated disease bother was significantly improved for *de novo* and replacement OAB patients at both follow-ups (Table 2). Likewise, disease-specific QoL measured with the Ditrovie questionnaire was significantly improved in both OAB groups at both follow-ups. Generic QoL assessed by the EQ-5D-5L was

significantly improved at all follow-ups except in the *de novo* group at the 10-mo visit (Table 2). EQ-5D-5L-VAS was significantly improved as well except for the replacement group at the 10-mo visit. According to the GAS, 55–67% of OAB patients in the *de novo* and replacement groups were categorized as responders (Table 2).

The mean number of catheterizations for NOUR *de novo* patients decreased significantly from a mean of 3.5 ± 2.4 per d at baseline to 0.5 ± 1.1 at the 3-mo visit ($p < 0.05$) with no significant changes between baseline and 10-mo visit (3.0 ± 4.7). At the 3-mo visit, four of seven *de novo* patients no longer needed to self-catheterize and six of seven *de novo* patients showed at least 50% improvement in the number of catheterizations. No significant changes were seen over the course of the follow-up for replacement patients. NRS-rated disease bother was only significantly improved for NOUR *de novo* patients at the 3-mo visit. According to the GAS, 50–67% of NOUR patients in the *de novo* and replacement groups were categorized as responders (Table 3).

For patients with double incontinence, we pooled *de novo* and replacement patients in order to look at a larger sample size (combined cohort: $N = 40$). The Wexner score of this combined cohort was significantly reduced ($p < 0.05$) at both the 3-mo visit (-4.4 ± 6.3) and the 10-mo visit (-3.7 ± 7.1).

There were no unanticipated adverse device effects. Adverse device effects occurred in 33% (98/301) of all patients during a mean exposure time of 24.3 mo (for implanted patients) and were most frequently addressed by reprogramming. A total of 71 reprogramming procedures were performed in 18% (53/301) of patients. The most frequent device or procedure-related events included implant site pain (5%; 16/301) and implant site infections (4%; 13/301). According to the Clavien-Dindo classification 59% of ADEs were categorized as grade I, 9% as

grade II, and 19% and 13% as grade IIIa and grade IIIb, respectively. Furthermore, 8% (23/301) of patients experienced 28 serious adverse device effects. Most frequent actions taken (per patient) included explantation of the lead (7%; 20/301) or neurostimulator (4%; 13/301) as well as reprogramming (3%; 10/301) or antibiotic treatment (4%; 13/301).

Reports of a decrease in device effect were not categorized as adverse device effects for this analysis as a decrease in device effect does not necessarily mean a deterioration of symptoms below baseline and symptom fluctuation is to some level expected. Yet, there were nine patients (3%; 9/301) with a serious decrease in device effect which was addressed by explantation of the lead (2%; 5/301) or the neurostimulator (2%; 5/301) or reprogramming (1%; 4/301).

Overall, 59 surgical revisions (definition includes replacement, repositioning or explant of one or more device components) occurred in 20% (49/247) of implanted patients after the full system implant, including permanent device explantation in 9% (21/247). The majority of revisions (40/59) and about half of the explantations (12/21) were performed within the first 12 mo postimplant.

4. Discussion

This prospective, multicenter, observational study is among the largest studies to date reporting real-world data on SNM treatment in patients with lower urinary tract dysfunction and a continuation of earlier work with similar objectives [17].

Voiding diary data from SOUNDS confirmed the clinical benefit of SNM that has been previously demonstrated in both randomized controlled trials and observational studies [11,18–20]. The overall reduction in leaks in UI *de novo* and voids in UF *de novo* patients at 10 mo was comparable to the 12-mo InSite data [11]. It is interesting to note that the baseline number of leaks and voids/day in SOUNDS was similar for *de novo* compared with replacement patients.

One could assume that replacement patients should have a lower number of leaks and voids at baseline as they were already treated effectively with SNM. However, it is common practice in France to wait for the battery replacement until there is a loss of effective stimulation (eg, due to complete battery depletion) which would mean that symptoms before replacement may return up to a pretreatment level.

Responder rates for UI patients in SOUNDS were high and comparable with published data [11,18,19] with 78% and 84% in the *de novo* group and 71% and 88% among replacement patients at 3 and 10 mo, respectively. In contrast to the high responder rates in UI patients, response rate in UF patients was 45% and 41% in the *de novo* group and 44% and 62% in the replacement group at 3 and 10 mo, respectively, and thus a bit lower than previously reported [11]. To put responder rates in SOUNDS into perspective we have to consider that patients were implanted at the discretion of each participating site without any formal criteria for test success. In clinical practice the decision to permanently implant a patient with an SNM system is often dependent on a mix of diary-based symptom improvement, patient satisfaction, and QoL benefits, whereas therapy response is usually defined based on diary improvements alone. If we look at the subgroup of *de novo* patients that would have received a permanent system based on diary data alone (ie, using the same criteria that are used during analysis to categorize a patient as a responder) responder rates at 3 and 10 mo would increase [21].

SOUNDS also evaluated the impact of SNM on QoL and patients' perceived bother. Significant QoL improvements were seen in the French disease-specific Ditrovie questionnaire which is in-line with published data on disease-specific QoL measures [11,19]. In case of the generic EQ-5D-5L, which has been utilized on specific request of the French Authority for Health, improvements were statistically significant at most visits. However, if we assume a minimally important clinical difference between 0.037 and 0.069 [22], the clinical benefit as

identified through the EQ-5D-5L is borderline. Mixed results are also reported in the literature concerning generic QoL questionnaires that have been claimed not to be applicable to certain disease areas because they are missing a domain which directly captures the impact of particular diseases [23,24]. Specifically, in the EQ-5D-5L none of the domains relate directly to incontinence/retention, although the impact of incontinence/retention on QoL may be expected to be picked up indirectly through changes in usual activities or anxiety/depression. Patients' perceived bother was significantly improved at all follow-up visits in OAB patients which is in agreement with the improvement in symptom interference measured with the ICIQ-OABqol that has been reported previously [11].

SOUNDS also enrolled patients with NOUR and double incontinence. A statistically significant reduction in mean number of catheterizations and an improvement in NRS score was observed in NOUR *de novo* patients at the 3-mo visit but not at the 10-mo visit or in replacements patients (at either 3- or 10-mo visit) although a general trend toward symptom improvement was seen. In general, patient numbers that were implanted with SNM for NOUR ($N = 18$) and double incontinence ($N = 40$) were small (for NOUR patients: only $n = 7$ and $n = 5$ in the *de novo* group and $n = 4$ and $n = 1$ in the replacement group had available diary data at 3 and 10 mo, respectively) and results should be interpreted cautiously.

When looking at safety data it is obvious that the percentage of patients affected from implant site infection (4%) is lower than during the early evolution of the therapy [25–27]. This is most likely due to refinements in the implant technique such as minimally invasive tined lead placement, change of neurostimulator position from abdomen to buttock [28], smaller neuromodulator size, and improved infection prevention protocols. At the same time, implant site infection rates in SOUNDS are comparable to recent results from InSite [29]. The rate of adverse device effects and surgical revisions is also comparable to InSite: in SOUNDS 33% (98/301) of

all patients were affected by an adverse device effect (within approximately 24 mo) and 40 revisions were performed within the first 12 mo postimplant, whereas in InSite 16% (56/340) had an adverse device effect during test stimulation, 30% (82/272) after full system implant, and 38 surgical revisions were performed within 12 mo [29]. If we look at serious adverse device effects, it is evident that the rate in SOUNDS was much higher compared with InSite. The discrepancy may be explained by differences in hospital procedures between France (SOUNDS study sites) and the United States (InSite study sites). In France it is quite common that patients are staying overnight after a surgical procedure which would mean that an associated event would be coded as serious as it led to an in-patient hospitalization. This is not the case in the United States where surgical interventions are usually performed in an ambulatory setting.

The biggest limitation of SOUNDS is also its biggest asset: the heterogeneous patient population due to the enrollment according to routine practice in the French InterStim system implanting sites. This allows the generalizability of the SOUNDS results to the French setting; however, we have to keep in mind that there were no protocol requirements regarding the choice of antibiotics, lead and stylet as well as procedural techniques (type of anesthesia, etc.) and thus results might differ in other geographies due to different workflows and procedures. Inclusion was not stratified for indication and only a low number of NOUR patients were enrolled which makes interpretation of those data challenging. Furthermore, although dropouts were below 10% and thus within expected ranges, getting completed voiding diary information remains a challenge compared with the data that can be acquired during the follow-up visits. Finally, there are ongoing attempts to further standardize and improve the SNM implant procedure [30] with potential positive impact on therapy efficacy, battery longevity, and adverse event rate which were most likely not fully captured within SOUNDS due to timing of the patient enrollment phase.

5. Conclusions

This large, observational study confirmed that SNM confers significant symptom and QoL improvements in OAB patients routinely treated in the French health-care setting that are similar in magnitude to what has been previously published. Adverse device effects are usually transient and can be treated effectively by reprogramming or other measures. Most surgical revisions were performed within the first 12 mo postimplant which hints to the fact that further improvements in implant and lead placement techniques might be both desirable and achievable.

Author contributions: Emmanuel Chartier-Kastler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chartier-Kastler, Le Normand, Ruffion.

Acquisition of data: Le Normand, Dargent, Braguet, Saussine, Tanneau, Graziana, Ragni, Rabut, Rousseau, Biardeau, Gamé, Pierrevelcin, Brassart, Fourmarier, Stoica, Berrogain, Yaghi, Pecoux, Capon, Ferchaud, Peyrat, Karsenty, Cornu.

Analysis and interpretation of data: Chartier-Kastler, Le Normand, Ruffion, Cornu, Melotti, Keller, Abouihia.

Drafting of the manuscript: Chartier-Kastler, Cornu, Keller.

Critical revision of the manuscript for important intellectual content: Chartier-Kastler, Le Normand, Ruffion, Cornu, Dargent, Braguet, Saussine, Tanneau, Graziana, Ragni, Rabut, Rousseau, Biardeau, Gamé, Pierrevelcin, Brassart, Fourmarier, Stoica, Berrogain, Yaghi, Pecoux, Capon, Ferchaud, Peyrat, Karsenty, Melotti, Keller, Abouihia.

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REFERENCES

- [1] Irwin D, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC Study. *Eur Urol* 2006;50:1306–15.
- [2] Milsom I, Abrams P, Cardozo L, Roberts R, Thüroff J, Wein A. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2002;87:760–6.
- [3] Kinsey D, Pretorius S, Glover L, Alexander T. The psychological impact of overactive bladder: a systematic review. *J Health Psychol* 2014;21:69–81.
- [4] Irwin D, Milsom I, Kopp Z, Abrams P, Cardozo L. Impact of overactive bladder symptoms on employment, social interactions and emotional well-being in six European countries. *BJU Int* 2006;97:96–100.
- [5] Reeves P, Irwin D, Kelleher C, et al. The current and future burden and cost of overactive bladder in five European countries. *Eur Urol* 2006;50:1050–7.
- [6] Hu T, Wagner T. Health-related consequences of overactive bladder: an economic perspective. *BJU Int* 2005;96:43–5.

- [7] Lightner D, Gomelsky A, Souter L, Vasavada S. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. *J Urol* 2019;202:558–63
- [8] Yu Y, Nichol M, Yu A, Ahn J. Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the California Medicaid Program. *Value Health* 2005;8:495–505.
- [9] Burkhard FC, Bosch JLHR, Cruz F, et al. Urinary Incontinence: EAU Guidelines 2018. European Association of Urology Presented at the EAU Annual Congress Copenhagen 20 (2018). <http://uroweb.org/guideline/urinary-incontinence/>.
- [10] Abrams P, Cardozo L, Wagg A, Wein A. Incontinence. ed. 6. Bristol, UK: International Continence Society; 2017.
- [11] Noblett K, Siegel S, Mangel J, et al. Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. *Neurourol Urodyn* 2014;35:246–51.
- [12] Amarenco G, Marquis P, Leriche B, Richard F, Zerbib M, Jacquetin B. Une échelle spécifique d'évaluation de la perturbation de la qualité de vie au cours des troubles mictionnels: l'échelle Ditrovie. *Ann Readapt Med Phys* 1997;40:21–6.
- [13] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
- [14] Haab F, Richard F, Amarenco G, et al. Comprehensive evaluation of bladder and urethral dysfunction symptoms: development and psychometric validation of the Urinary Symptom Profile (USP) Questionnaire. *Urology* 2008;71:646–56.
- [15] Kiresuk T, Smith A, Cardillo J. Goal Attainment Scaling. London, UK: Psychology Press; 2014.

- [16] Jorge M, Wexner S. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993;36:77–97.
- [17] Chartier-Kastler E, Ballanger P, Belas M, et al. Sacral neuromodulation with InterStim™ system: results from the French national register. *Prog Urol* 2011;21:209–17.
- [18] Schmidt RA, Jonas U, Oleson KA, et al. Sacral nerve stimulation for treatment of refractory urinary urge incontinence. Sacral Nerve Stimulation Study Group. *J Urol* 1999;162:352–7.
- [19] Amundsen C, Richter H, Menefee S, et al. OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women. *JAMA* 2016;316:1366–74.
- [20] Spinelli M, Bertapelle P, Cappellano F, et al. Chronic sacral neuromodulation in patients with lower urinary tract symptoms: results from a national register. *J Urol* 2001;166:541–5.
- [21] Chartier-Kastler E, Ruffion A, Le Normand, et al. Sacral neuromodulation with the InterStim™ system for intractable urinary voiding dysfunction (SOUNDS): responder rates in a real-world French patient collective: submitted to EAU conference (to appear in *European Urology Supplements*).
- [22] McClure N, Sayah F, Xie F, Luo N, Johnson J. Instrument-defined estimates of the minimally important difference for EQ-5D-5L Index scores. *Value Health* 2017;20:644–50.
- [23] Haywood K, Garratt A, Lall R, Smith J, Lamb S. EuroQol EQ-5D and condition-specific measures of health outcome in women with urinary incontinence: reliability, validity and responsiveness. *Qual Life Res* 2008;17:475–83.
- [24] Davis S, Wailoo A. A review of the psychometric performance of the EQ-5D in people with urinary incontinence. *Health Qual Life Outcomes*. 2013;11:20.
- [25] Hassouna MM, Siegel SW, Lycklama AA, et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. *J Urol* 2000;163:1849–

- [26] van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *J Urol* 2007;178:2029–34.
- [27] Siddiqui N, Wu J, Amundsen C. Efficacy and adverse events of sacral nerve stimulation for overactive bladder: a systematic review. *Neurourol Urodyn* 2010;29:S18–S23.
- [28] Scheepens W, Weil E, van Koevinge G, et al. Buttock placement of the implantable pulse generator: a new implantation technique for sacral neuromodulation – a multicenter study. *Eur Urol* 2001;40:434–8.
- [29] Noblett K, Benson K, Kreder K. Detailed analysis of adverse events and surgical interventions in a large prospective trial of sacral neuromodulation therapy for overactive bladder patients. *Neurourol Urodyn*. 2016;36:1136–39.
- [30] Matzel K, Chartier-Kastler E, Knowles C, et al. Sacral neuromodulation: standardized electrode placement technique. *Neuromodulation* 2017;20:816–24.

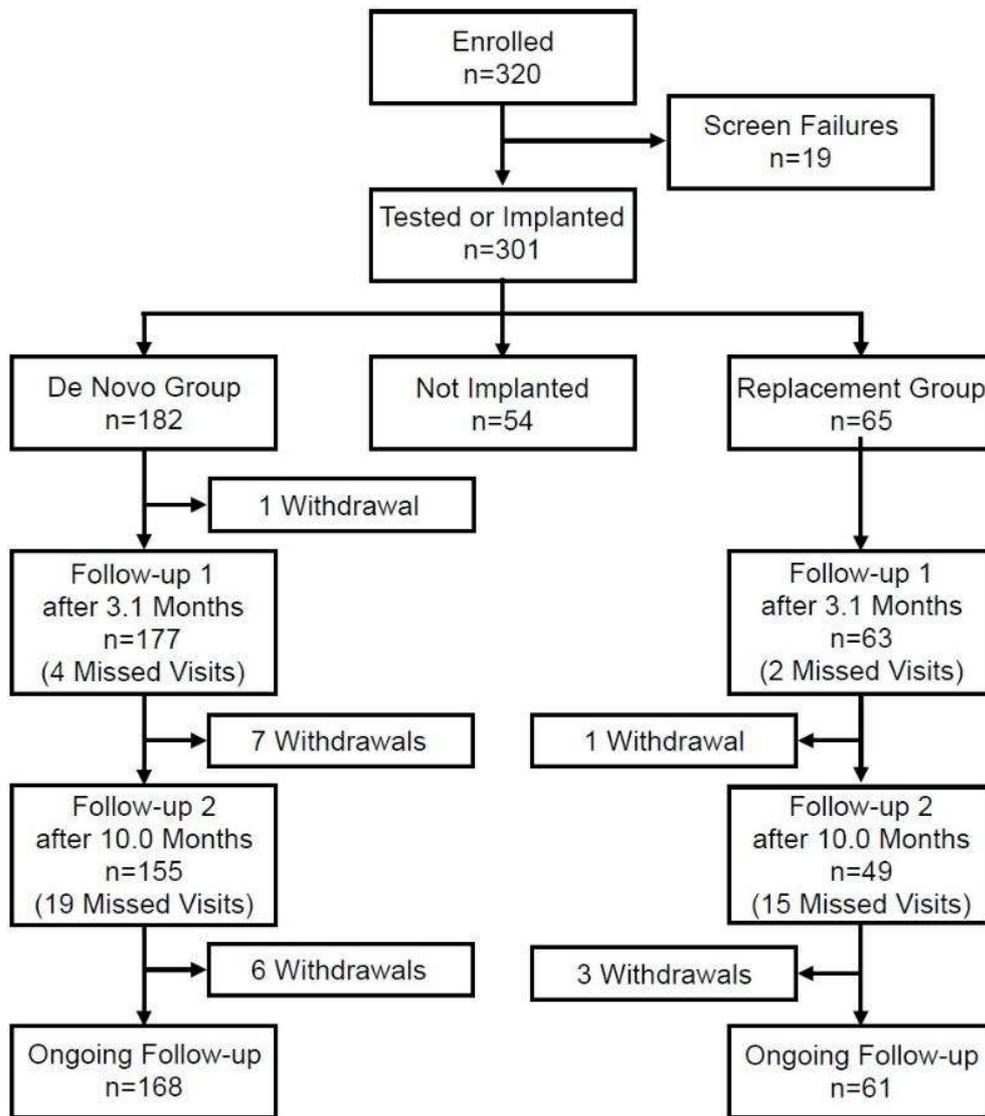


Fig. 1 – Patient flow diagram. Patients in the not implanted group were *de novo* patients with a negative test except for one patient from the replacement group which was negatively tested and likewise not implanted. Patients that missed their visit at follow-up 1 were still able to contribute data at follow-up 2. Screen failures: Three patients were lost to

follow-up after they were first approached, nine refused the treatment after signing the data release form, and seven were screen failures for other reasons.

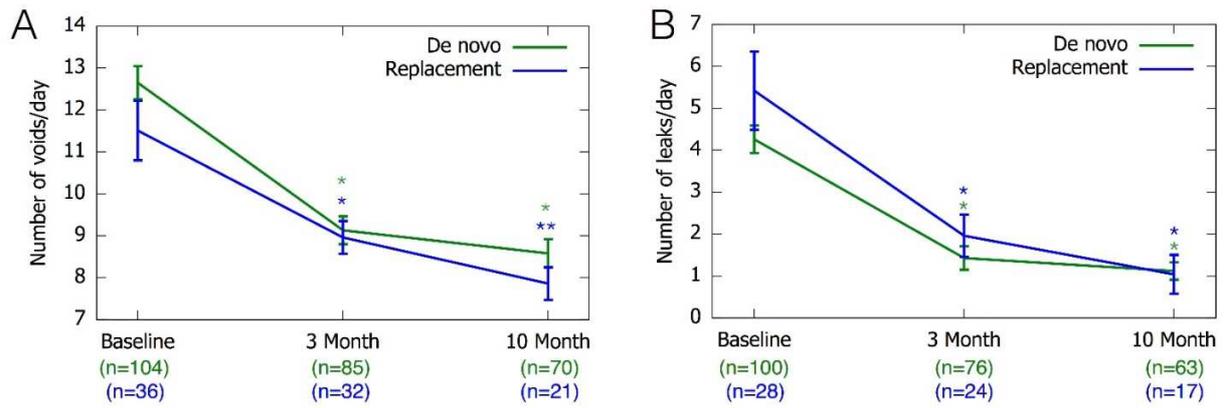


Fig. 2 – (A) Change in mean number of voids/day in urgency frequency patients. (B) Change in mean number of leaks/day in urinary urge incontinence patients. In both panels, error bars represent standard error of the mean.

*** $p < 0.001$; ** $p < 0.05$.**

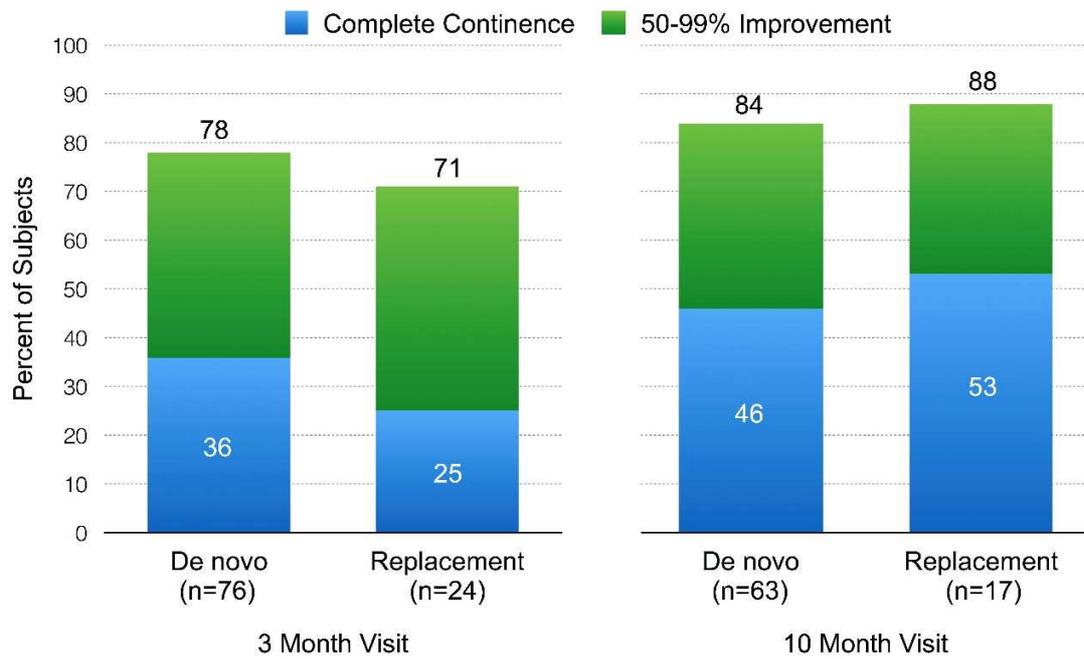


Fig. 3 – Therapeutic success in urinary urge incontinence patients. Analysis included patients with diary data at baseline as well as at 3- and 10-mo visit.

Table 1 – Baseline demographics and medical history^a

Demographics	Total (N = 320)
OAB patients	291 (91)
Female	248/291 (85)
NOUR patients	29 (9)
Female	20/29 (69)
Double incontinence patients	45 (14)
<i>De novo</i> patients	235 (78) ^b
Replacement patients	66 (22) ^b
Age at enrollment, yr	60.5 ± 15.1
Body mass index at enrollment	27.4 ± 5.5 ^b
Years since diagnosis	8.7 ± 7.4 ^b
Prior treatment before enrollment (OAB/NOUR)	
Medications	289 (90)
Anti-incontinence surgery	98 (31)
Other surgery	89 (28)
Percutaneous tibial nerve stimulation	60 (19)
Botox (intradetrusor)	12 (4)
Other	100 (31)
OAB qualification per diary (implanted patients) ^c	
Both UI + UF	98 (43)
UI	38 (17)
UF	46 (20)
Medications for pelvic and urinary disorders tried before enrollment	
1	107 (37)
2	94 (33)
3	58 (20)
4–7	29 (10)

NOUR = non-obstructive urinary retention; OAB = overactive bladder; SD = standard deviation;

UI = urinary urge incontinence; UF = urgency frequency.

^aData are presented as *n* (%) or mean ± SD.

^bBased on tested/implanted patients.

^cThe CRFs had an option to select OAB as the patient's indication. However, based on the criteria that were used for the analysis, it is possible that a minority of patients were classified as having OAB by the site but were not in scope of the analysis on OAB patients. In some patients, number of voids and leaks was missing at baseline but they were categorized as having OAB by the site.

Table 2 – Patient-reported outcomes (PROs), quality of life data (QoL), and Urinary Symptom Profile (USP) domains for *de novo* and replacement patients^a

PROs, QoL, and USP	Baseline	3 mo	<i>p</i> value	10 mo	<i>p</i> value
<i>De novo</i> patients					
NRS OAB	158 (7.9 ± 1.6)	146 (3.2 ± 2.3)	<0.001	122 (3.9 ± 2.6)	<0.001
GAS OAB	NA	148 (63)	NA	130 (55)	NA
Ditrovie OAB	153 (34.4 ± 7.5)	139 (20.6 ± 8.4)	<0.001	119 (22.0 ± 9.1)	<0.001
EQ-5D-5L OAB/NOUR	168 (0.62 ± 0.30)	148 (0.69 ± 0.26)	<0.05	128 (0.67 ± 0.32)	n.s.
EQ-5D-5L VAS OAB/NOUR	167 (59.6 ± 21.0)	147 (72.2 ± 18.9)	<0.001	129 (70.3 ± 21.1)	<0.001
Urinary Symptom Profile OAB/NOUR	159 (3.3 ± 3.3)	141 (1.3 ± 2.2)	<0.001	120 (1.5 ± 2.4)	<0.001

USP1	166 (12.4 ± 3.9)	140 (7.3 ± 4.3)	<0.001	126 (8.0 ± 4.0)	<0.001
USP2	169 (2.0 ± 2.2)	146 (1.0 ± 1.4)	<0.001	127 (1.0 ± 1.6)	<0.001
USP3					
Replacement patients					
NRS OAB	54 (7.1 ± 2.6)	49 (3.7 ± 2.8)	<0.001	38 (4.1 ± 2.9)	<0.001
GAS OAB	NA	51 (67)	NA	41 (66)	NA
Ditrovie OAB	54 (32.0 ± 10.1)	51 (21.2 ± 9.2)	<0.001	37 (22.0 ± 8.8)	<0.001
EQ-5D-5L OAB/NOUR	57 (0.61 ± 0.31)	56 (0.68 ± 0.33)	<0.05	39 (0.70 ± 0.28)	<0.05
EQ-5D-5L VAS OAB/NOUR	56 (64.9 ± 22.3)	56 (71.5 ± 22.6)	<0.05	39 (68.1 ± 21.9)	n.s.
Urinary Symptom Profile					
OAB/NOUR	55 (3.3 ± 3.4)	48 (2.1 ± 2.6)	<0.001	37 (2.2 ± 2.9)	<0.05
USP1	58 (11.7 ± 5.1)	56 (8.1 ± 4.5)	<0.001	39 (8.7 ± 5.0)	<0.001

USP2	56 (1.7 ± 2.3)	55 (1.3 ± 1.8)	n.s.	39 (0.9 ± 1.1)	<0.05
USP3					

GAS = Goal Attainment Scaling; NA = not applicable; NOUR = non-obstructive urinary retention; NRS = numeric rating scale; n.s. = not significant; OAB = overactive bladder; SD = standard deviation; USP = Urinary Symptom Profile; VAS = visual analog scale.

^aData are presented as *n* (mean ± SD) or *n* (%).

Table 3 – Patient-reported outcomes (PROs) for non-obstructive urinary retention (NOUR) *de novo* and replacement patients^a

PROs	Baseline	3 mo	<i>p</i> value	10 mo	<i>p</i> value
<i>De novo</i> patients					
NRS NOUR	13 (7.6 ± 1.5)	10 (3.4 ± 3.5)	<0.05	6 (4.0 ± 3.4)	n.s.
GAS NOUR	NA	9 (67)		6 (50)	
Replacement patients					
NRS NOUR	4 (6.0 ± 1.8)	5 (3.6 ± 3.2)	n.s.	4 (5.0 ± 4.4)	n.s.
GAS NOUR	NA	5 (60)		4 (50)	

GAS = Goal Attainment Scaling; NA = not applicable; NRS = numeric rating scale; n.s. = not significant.

^aData are presented as *n* (mean ± SD) or *n* (%).