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Treatment of Urinary Urgency Incontinence Using a Rechargeable SNM System: 6-Month Results of the ARTISAN-SNM Study

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Purpose: Sacral neuromodulation is a guideline recommended treatment of urinary dysfunction and fecal incontinence in patients in whom conservative treatments have failed. Historically sacral neuromodulation has been delivered using a nonrechargeable device with an average life span of 4.4 years. Surgery is required to replace the implanted neurostimulator due to battery depletion. Implantation of a long-lived implanted neurostimulator can eliminate the need for replacement surgeries, potentially reducing patient surgical risks and health care costs. The Axonics r-SNM System™ is a miniaturized, rechargeable sacral neuromodulation system designed to deliver therapy for at least 15 years. The ARTISAN-SNM (Axonics® Sacral Neuromodulation System for Urinary Urgency Incontinence Treatment) study is a pivotal study using rechargeable sacral neuromodulation therapy to treat urinary urgency incontinence. Six-month results are presented.

Materials and Methods: A total of 129 eligible patients with urinary urgency incontinence were treated. All participants were implanted with a tined lead and the rechargeable sacral neuromodulation system in a nonstaged procedure. Efficacy data were collected using a 3-day bladder diary, the validated ICIQ-OABqol (International Consultation on Incontinence Questionnaire Overactive Bladder quality of life) questionnaire and a participant satisfaction questionnaire. Therapy responders were identified as participants with a 50% or greater reduction in urinary urgency incontinence episodes compared to baseline. We

Abbreviations and Acronyms

AE = adverse event
ARTISAN-SNM = Axonics® Sacral Neuromodulation System for Urinary Urgency Incontinence Treatment
CCF-FIS = Cleveland Clinic Florida Fecal Incontinence Score
ICIQ-OABqol = International Consultation on Incontinence Questionnaire Overactive Bladder QoL
IE = inclusion and exclusion
INS = implanted neurostimulator
OAB = overactive bladder
QoL = quality of life
r-SNM = rechargeable SNM
SNM = sacral neuromodulation
UUI = urinary urgency incontinence

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performed an as-treated analysis in all implanted participants.

Results: At 6 months 90% of participants were therapy responders. The mean ± SE number of urinary urgency incontinence episodes per day was reduced from 5.6 ± 0.3 at baseline to 1.3 ± 0.2. Participants experienced a clinically meaningful 34-point improvement on the ICIQ-OABqol questionnaire. There were no serious device related adverse events.

Conclusions: The Axonics r-SNM System is safe and effective with 90% of participants experiencing clinically and statistically significant improvements in urinary urgency incontinence symptoms.

Key Words: urinary bladder, overactive; urinary incontinence, urge; implantable neurostimulators; quality of life; patient reported outcome measures

Sacral neuromodulation was approved in the United States to treat UUI in 1997 with subsequent approvals for urinary frequency, nonobstructive urinary retention and fecal incontinence in 1999 and 2011, respectively.[1] It is a guideline recommended treatment of refractory urinary dysfunction and bowel incontinence which has been shown to have durable and long-term efficacy and safety.[2–6]

Historically SNM has been delivered using a nonrechargeable device requiring replacement of the INS an average of every 4.4 years.[7] This has resulted in significant health care costs and risks of multiple surgeries,[8] given the chronic nature of OAB.

To our knowledge the Axonics r-SNM System™ is the only r-SNM system with regulatory approval in Europe, Canada and Australia to treat urinary and bowel dysfunction. In Europe the system is conditionally approved for full body 1.5 and 3 Tesla magnetic resonance imaging. The system includes a long-lived INS designed to function a minimum of 15 years in the body, a claim which has been approved in Europe, Canada and Australia. At 5 cc in volume it is a third the size of the currently marketed nonrechargeable INS (fig. 1).

The ARTISAN-SNM study is a single arm, prospective, multicenter, pivotal study performed under investigational device exemption from the United States FDA (Food and Drug Administration) with the purpose of gaining United States marketing approval of the Axonics r-SNM System. The primary aim of the study was to evaluate the safety and efficacy of the system to treat UUI symptoms.

Figure 1. System includes rechargeable, miniaturized INS about 5 cc in volume with 15-year approved life in Europe, Canada and Australia.

This report provides 6-month study results in all implanted participants in the ARTISAN-SNM study.

MATERIALS AND METHODS

The ARTISAN-SNM (NCT03327948, ClinicalTrials.com) study protocol was approved by all study sites (centralized IRB No. 20172588 at 5 centers). All participants provided informed consent prior to study participation. Participants were eligible for treatment with the Axonics r-SNM System if they met all inclusion criteria (supplementary Appendix, https://www.jurology.com).

Participants were implanted with the tined lead and the INS in a single nonstaged procedure without requiring prior testing with an external trial system. According to study IE criteria participants were only implanted if positive intraoperative motor responses were observed on at least 2 electrodes at less than 4 mA. Fluoroscopic guidance was used to implant the tined lead along the S3 (preferred) or the S4 sacral nerve root according to published SNM best practices.[9]

Patients recharged the system at home using the system charging device, which is placed on the skin over the implanted stimulator and held in place with a belt. Participants were instructed to recharge the device every 1 to 2 weeks. The recharging process has been detailed previously.[10,11]

All study participants will be followed for 2 years. This report includes data up to the 6-month postimplantation time point. Efficacy data were collected using a 3-day bladder diary, the symptom related ICIQ-OABqol survey and a participant satisfaction questionnaire. Bowel symptoms were also captured using the CCF-FIS. All AEs were tracked and analyzed to assess safety. A Data Safety Monitoring Board of 3 expert clinicians who did not participate as study investigators reviewed and adjudicated all AEs.

Participants were considered therapy responders if they had a 50% or greater reduction in UUI episodes per day according to the bladder diary at followup compared to baseline. The primary effectiveness end point of the study is the therapy responder rate of all implanted participants, referred to as the as-treated group. Participants who were therapy responders at 1 month are referred to as the test responders. Analyses in test responders were performed to enable comparison with the current clinical literature, in which efficacy results have typically been reported only in participants with a positive therapy

response during an external trial period while those in whom the external trial failed were excluded from analysis.

In addition to therapy responder rate analyses, the data analysis included absolute and percent changes in the number of UUI episodes, the number of large UUI episodes, outcomes of the QoL questionnaire and participant satisfaction questionnaire results. For most questionnaires participants with missing data at followup were included in analysis using baseline data. This conservative approach considered missing or exited participants as having experienced therapy failure according to diary, QoL and satisfaction measures. Recharging experience is reported based on available data (ie excluding data on missing or exited participants). QoL questionnaire guidelines were followed to calculate subscale and summary scores, including accounting for missing data entries.

Sample size calculations were performed using the 65% literature based, as-treated responder rate[3] (true proportion), a null proportion of 50%, a 1-sided type 1 error rate of 0.021 and 90% power, which resulted in a sample size of 116 participants. Descriptive statistics were calculated. Statistical significance testing was performed with the 1-sided binomial test for categorical variables and the 2-sided paired t-test or the Wilcoxon signed rank test for continuous variables. SAS®, version 9.3 was used for all analyses.

RESULTS

Study Participants

In this study 129 participants met study IE criteria and were implanted with the Axonics r-SNM System in a nonstaged procedure. All participants met intraoperative criteria for motor response thresholds. Of the 129 participants 126 completed the 6-month visit and 3 exited the study prior to 6 months. Average study participant age was 59.3 years (range 21 to 86) and 98% of participants were female. At baseline participants had a mean ± SE of 5.6 ± 0.3 UUI episodes per day. The table lists additional baseline characteristics.

Baseline demographics and clinical characteristics

No. implanted participants	129
Mean ± SD age/median (range)	59.3 ± 13.0/61.0 (21.0-86.0)
No. gender (%):	
Female	127 (98)
Male	2 (2)
No. race (%):	
White	114 (88)
Black or African American	9 (7)
Other or declined to answer	4 (3)
Asian	2 (2)
Mean ± SD yrs UUI clinical diagnosis/median (range)	6.6 ± 7.0/4.6 (0.5-53.6)
No. concomitant medication for condition (%)	40 (31)
No. current nocturia (%)	89 (69)
No. secondary diagnosis (%)*	
Urinary frequency	65 (50)
Stress incontinence	50 (39)
Fecal incontinence†	42 (33)
None	38 (30)
Retention	2 (2)
No. previous surgical treatment (%):*	
Botulinum toxin	17 (13)
Tibial nerve stimulation	17 (13)
SNM external trial	9 (7)

* Not mutually exclusive.
† CCF-FIS score 6 or greater.

Therapy Responders and Urinary Urgency Incontinence Episode Reduction

At 6 months 116 of the 129 implanted participants (90%) were therapy responders based on a 50% or greater reduction in UUI episodes compared to baseline (fig. 2). Since this report presents as-treated analysis, explanted or exited cases were considered treatment failures. Across all participants the average daily number of UUI episodes was reduced from 5.6 ± 0.3 at baseline to 1.3 ± 0.2 at 6 months ($p < 0.0001$), representing a 79% reduction in UUI episodes (fig. 3, *A*). The magnitude of the UUI episode reduction at 6 months was 75% or greater in 80% of therapy responders, including 34% of dry responders (ie 100% reduction) (fig. 3, *B*). The responder rate and the overall UUI episode reduction were similar when analyzing all UUI episodes regardless of urgency. Of the 129 implanted participants 113 (88%) were test responders (ie they had 50% or greater improvement in UUI symptoms at 1 month). Of the 113 test responders 107 (95%) were therapy responders at the 6-month followup (fig. 2).

Quality of Life and Participant Satisfaction

At 6 months the average health related QoL improvement in study participants was 34.2 points on the ICIQ-OABqol questionnaire. All scores exceeded a 10-point MID (minimally important difference), representing a statistically and clinically significant QoL improvement[3,12] relative to baseline (fig. 4). All QoL aspects improved in participants. This was reflected by improvement in each QoL subscale, including 38.6 points on Concern, 38.6 on Coping, 31.4 on Sleep and 22.6 on Social Interaction.

Additionally, participants reported a high satisfaction rate with r-SNM therapy. Of the 129 participants 93% responded at 6 months that they were satisfied with the therapy and 92% responded that they would undergo it again.

Recharging Experience

At 6 months 99% of participants reported being able to recharge the r-SNM system. The recharging interval ranged from less than 1 hour (90%) to at least 7 days (97%). Recharging duration and frequency were acceptable in 98% of participants while 95% found it easy to recharge the system.

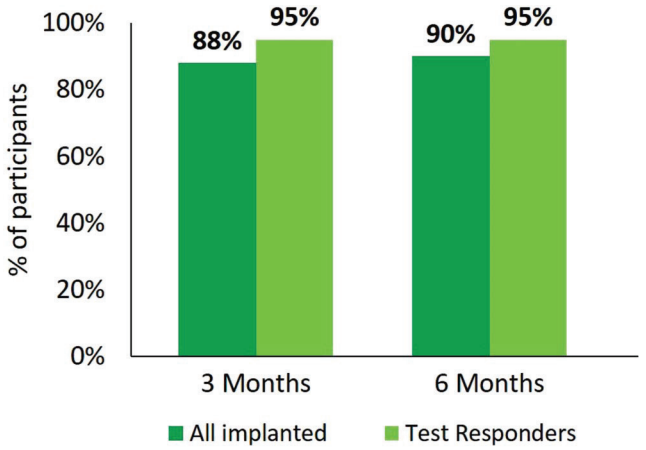

Figure 2. Therapy responder rate in all implanted participants (dark green bars) and test responder participants (light green bars). Test responders were defined as those who responded to SNM therapy at 1 month. UUI therapy response was defined as 50% or greater UUI episode reduction at followup vs baseline.

Additional Urinary and Fecal Symptoms

Study participants also experienced reductions in overall urgency episodes (ie urgent voids and UUI episodes), urgency frequency and fecal incontinence symptoms. At baseline participants had a mean of 10.6 ± 0.3 urgency episodes per day, which was reduced to 6.9 ± 0.3 at 6 months ($p < 0.0001$). Of the 129 participants 103 had urgency frequency, defined as 8 or more voids per day. These participants had an average of 11.6 ± 0.3 voids per day at baseline, which decreased to 8.7 ± 0.2 at 6 months ($p < 0.0001$).

Additionally, 42 of 129 participants (32%) had fecal incontinence at baseline as determined by a score of 6 or greater on the CCF-FIS.[13] At 6 months the average CCF-FIS score in the 41 participants available at followup was 4.6 ± 0.3 compared to 9.3 ± 0.3 at baseline. In 30 of these 41 participants (73%) the score was less than 6 at 6 months.

Safety

At 6 months a total of 10 device related AEs were reported by 10 participants (8%). The most frequent AE was discomfort due to stimulation, which accounted for 6 events in 6 participants, of which all resolved with reprogramming. Other device related AEs were 2 pain events (less than 2% of cases) at the neurostimulator site, which resolved spontaneously, and 1 lead migration (less than 1%), which was successfully revised. Three participants exited the study before 6 months, including 2 who underwent explantation due to postoperative wound infection in 1 and pain unrelated to the study device in 1. One participant died of complications resulting from perforation of multiple diverticula in the colon, which occurred about 145 days after the implant procedure. The death was not related to the study device or procedure.

DISCUSSION

SNM is a guideline recommended therapy indicated in patients with refractory OAB, nonobstructive urinary retention and fecal incontinence. The ARTISAN-SNM study is a prospective, multicenter, United States pivotal study designed to test the safety and efficacy of the first rechargeable SNM system in patients with refractory UUI. The study results demonstrate that the Axonics r-SNM System is safe and highly effective.

The 90% therapy response rate achieved in the entire cohort of 129 implanted as-treated participants is one of the highest rates reported in the literature. We hypothesize that this high response rate was due to a combination of factors. 1) The study investigators followed the most recent guidelines for the best implant techniques.[9,14,15] This includes use of the curved stylet to optimize placement of the tined lead, potentially improving therapeutic outcomes. 2) The Axonics r-SNM System uses constant current stimulation, which is designed to automatically compensate for changing tissue impedance to provide more consistent activation at the target nerve. This has been shown to provide superior efficacy and patient preference than voltage controlled stimulation.[16,17] It is possible that this may contribute to more stable

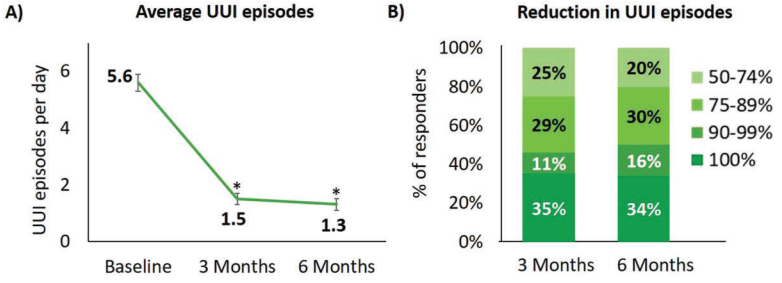

Figure 3. Symptom reduction in all 129 implanted participants at 3 and 6 months. *A*, average number of UUI episodes. Error bars indicate SE. Asterisk indicates $p < 0.0001$ compared to baseline. *B*, reduction in UUI episode magnitude in therapy responders.

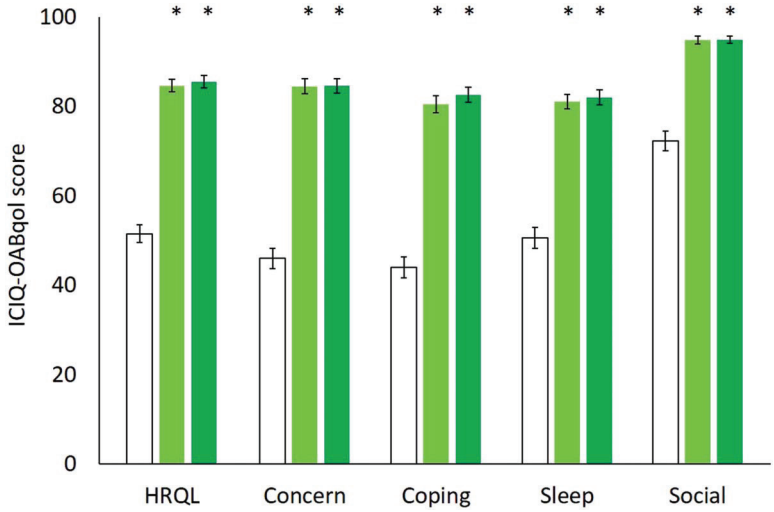

Figure 4. As-treated analysis of QoL scores in all 129 implanted participants. Health related QoL (*HRQL*) composite score and all subscale scores showed clinically and statistically significant improvement vs baseline (all $p < 0.0001$). White bars indicate baseline. Light green bars indicate 3 months. Dark green bars indicate 6 months. Error bars indicate SE.

therapeutic outcomes and less need for patients to adjust stimulation or have the device reprogrammed. 3) The simple user-friendly design of the remote control allows patients to manage stimulation settings without the risk of accidentally turning stimulation off.

While the study had strict inclusion and exclusion criteria, the population was representative of the broader UUI population with a wide age range of 21 to 86 years old and a body mass index range of 18 to 58 kg/m^2. This indicates that the study was selected from a representative patient population, which would make these data generalizable among OAB populations. The results suggest that in appropriately selected patients and using the recommended implant technique this therapy can achieve a 90% or higher response rate.

The Axonics System has been approved for 15 years of functional life based on rigorous test methods set by the regulatory bodies in Europe, Canada and Australia. The claim was supported by providing data on INS battery testing performed under accelerated aging test conditions. The batteries were tested to more than 1,000 charge cycles and they retained more than 90% capacity during the equivalent of more than 20 years of performance.

An important advantage of a long-lived rechargeable INS over a nonrechargeable INS is the cost savings. A cost consequence model demonstrated that adopting a long-lived rechargeable INS could save the United States health care system up to 12 billion dollars during 15 years.[8] Additionally, 98% of participants in the ARTISAN-SNM study were satisfied with the recharging experience. This result is consistent with rechargeable spinal cord and deep brain neurostimulators, for which several studies have reported high patient satisfaction with rechargeable neuromodulation systems.[18–20] These results provide a compelling rationale for widespread adoption of the r-SNM system.

In the ARTISAN-SNM study there were no unanticipated device or procedure related adverse events and no serious device or procedure related AEs. The overall device related AE rate was low at 8%. There were no explants or revisions for implant site pain, which was anticipated due to the small size of the Axonics INS. There was only 1 implant site infection (less than 1% of cases), which was reported 3 weeks after the procedure and resolved with device explantation. The low infection rate may have been due to the study protocol requirements for infection prevention, which included perioperative antibiotics and an antibiotic (chlorhexidine) wash mandated for all study participants the night before and the day of surgery. Postoperative antibiotics were given at physician discretion. Additionally, the lower infection rate may have been due to the fact that participants did not undergo an external trial period in which it is necessary to externalize a lead extension which may be associated with increased infection risk.

In most SNM studies analyses have been performed only in test responders (ie the group of patients with a successful external trial who were subsequently implanted with the INS).[3,6] In the ARTISAN-SNM study participants received the chronic implant (the tined lead and the INS) at a single nonstaged procedure. Our analysis was performed in the as-treated population and it included

nonresponders, who are typically excluded from analysis. Thus, the ARTISAN-SNM data represent a robust analysis of the as-treated population.

The study has several strengths. A large cohort of participants was implanted with the system. Only 3 participants (less than 2%) exited the study and no participant was lost to followup at 6 months. Data were analyzed in the as-treated population and still demonstrated a high success rate. Also, the combination of academic centers and private practice physicians in the study reflects real world experience with the therapy.

Limitations are that this study was not randomized and it did not have a placebo group. However, given the nature of this therapy, it is difficult to develop an ethical and plausible placebo study design. Most participants were female, potentially limiting the generalizability of the findings. However, females have a higher prevalence of UUI/OAB and most intervention studies on UUI/OAB treatment have had a much higher percent of female than male participants.[21,22] Also, because SNM therapy has been shown to work equally well in men in other studies, including the RELAX-OAB (Treatment of Refractory Overactive Bladder with the Axonics Sacral Neuromodulation System) study,[23] there is no reason to expect any difference in outcome using the Axonics r-SNM System.

CONCLUSIONS

The ARTISAN-SNM study is an ongoing, prospective, multicenter study evaluating the safety and efficacy of what is to our knowledge the first rechargeable sacral neuromodulation system for participants with refractory symptoms of UUI. We report 6-month results demonstrating that 90% of study participants had clinically and statistically significant improvements in UUI symptoms accompanied by significant improvements in QoL. The safety profile of the r-SNM system is highly favorable, as was participant satisfaction and ease, duration and frequency of recharging.

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EDITORIAL COMMENTS

This study has inherent design limitations and significantly better results than previous studies of SNM. There is no placebo or other comparison treatment arm (medical therapy or pelvic floor therapy), which would have made the study findings more powerful and relevant. There is a well-known placebo effect in patients with voiding dysfunction, especially early on. This study could have controlled that issue with a delayed group which was implanted but in which the device was not initially turned on to serve as a comparison group.

The response rate in this study is significantly higher than in other SNM studies, such as the MDT-103 trial.[1] This may be due to a combination of experienced implanters, careful patient selection, response definition and evaluation, and perhaps device related factors. Even in experienced hands the response rate using other SNM systems has been at best in the 60% to 70% range (reference 5 in article). Whether the response rate will stay at the 90% level at 2 or 5 years in this group of patients and whether the response rate will be reproducible in the hands of general urologists or urogynecologists remains an open question.

To our knowledge the cost of this rechargeable system is currently unknown. However, if this system is competitively priced, maintains a 60% to 70% response rate for more than 7 years and lasts the claimed life of 15 years, it represents a significant advance over current systems. Hopefully these conditions are met and will result in cost savings to the United States health care system.

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The usefulness of SNM has been established to treat refractory UUI and/or fecal incontinence. This SNM system has been developed as a rechargeable system which can be used for 15 years compared with the nonrechargeable device with an average life span of 4.4 years. A similar 12-month study has already been reported (reference 23 in study).

The rechargeable system may be better than the nonrechargeable one and it may be cost-effective because patients do not need to replace the battery. However, patients must recharge every 1 to 2 weeks. Although recharging takes only 1 hour, this may be a burden for patients.

This series is a short-term efficacy study for 6 months. Thus, it is not surprising that efficacy was comparable to that of the nonchargeable device. The major concern for readers may be whether the device and the battery will still be durable for more than 15 years in real-life practice.

Two-stage surgery is recommended for SNM but a 1-stage procedure was performed in this study. The authors state that the 1-stage surgery is cost-effective. This is not true if the surgery is not successful because the whole system must be removed after short-term failure. The authors stated that 90% of cases were successful but this study was performed by experts in strictly selected cases. It was reported that 30% of cases were not successful on test stimulation. Therefore, I recommend a 2-stage operation as the usual procedure.

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REPLY BY AUTHORS

We appreciate the comments and agree that the long-lived system has the potential to provide significant health care costs savings.

As 1 comment highlights, the therapy responder rate reported in the ARTISAN-SNM study is significantly higher than what has been reported in comparable multicenter studies in the literature. The high responder rate could be attributable to adherence to guideline recommended implant techniques as well as the features of the Axonics System (small size, constant current stimulation and intuitive patient tools). We believe that these results using the rechargeable system should be reproducible by our peers if they adopt the most recent best practices (reference 9 in article).

We agree with the comment that a 2-stage approach is the recommended approach for commercial treatment of patients. In the study the nonstaged, single procedure approach was used to minimize patient surgical risk because a high responder rate was anticipated, and device cost and reimbursement were not concerns in the clinical study. The commercial system includes an external trial system which is currently being used in patients treated in Europe.

Lastly, the study shows that patients found charging to be easy and acceptable at 6 months. Longer term data from another study using this rechargeable SNM system showed that patients continued to charge at 2 years and 93% of patients were satisfied with therapy.[1] Additional evidence of the long-term acceptability of recharging has been shown in patients with chronic pain with a rechargeable spinal cord stimulator.[2] Those rechargeable systems have existed for more than 10 years and have become the standard of care.

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