





ORIGINAL CLINICAL ARTICLE

One-year outcomes of the ARTISAN-SNM study with the Axonics System for the treatment of urinary urgency incontinence

Kevin Benson¹  | Rebecca McCrery² | Chris Taylor³ | Osvaldo Padron⁴ | Bertil Blok⁵  | Stefan de Wachter⁶ | Andrea Pezzella⁷ | Jennifer Gruenenfelder⁸ | Mahreen Pakzad⁹ | Marie-Aimee Perrouin-Verbe¹⁰ | Philip Van Kerrebroeck¹¹ | Jeffrey Mangel¹² | Kenneth Peters¹³ | Michael Kennelly¹⁴ | Andrew Shapiro¹⁵ | Una Lee¹⁶  | Craig Comiter¹⁷  | Margaret Mueller¹⁸ | Howard Goldman¹⁹ | Felicia Lane²⁰

¹Sanford Hospital, Sioux Falls, South Dakota

²Adult and Pediatric Urology and Urogynecology, Omaha, Nebraska

³Taylor Surgical Arts, Harrison, Arkansas

⁴Florida Urology Partners, Tampa, Florida

⁵Department of Urology, Erasmus MC, Rotterdam, The Netherlands

⁶Department of Urology, University Hospital Antwerpen, Edegem, Belgium

⁷Southern Urogynecology, West Columbia, South Carolina

⁸Orange County Urology Associates, Laguna Hills, California

⁹Department of Urology, University College London Hospital, Marylebone, London, UK

¹⁰Department of Urology, CHU de Nantes Hotel Dieu, Nantes, France

¹¹Department of Urology, Maastricht University Medical Centre, Maastricht, The Netherlands

¹²MetroHealth, Cleveland, Ohio

¹³Beaumont Health, Royal Oak, Michigan

¹⁴Carolinas Healthcare System Charlotte, North Carolina

¹⁵Chesapeake Urology Research Associates, Owings Mills, Maryland

¹⁶Virginia Mason, Seattle, Washington

¹⁷Stanford University, Palo Alto, California

¹⁸Northwestern University, Chicago, Illinois

¹⁹Cleveland Clinic, Cleveland, Ohio

²⁰University of California, Irvine, California

Correspondence

Kevin Benson, Sanford Hospital, Sioux Falls, SD 57105.

Email: kevinbensonfpmrs@gmail.com

Abstract

Aims: Sacral neuromodulation (SNM) is a guideline-recommended treatment for voiding dysfunction including urgency, urge incontinence, and

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Axonics Modulation Technologies

nonobstructive retention as well as fecal incontinence. The Axonics® System is a miniaturized, rechargeable SNM system designed to provide therapy for at least 15 years, which is expected to significantly reduce revision surgeries as it will not require replacement as frequently as the non-rechargeable SNM system. The ARTISAN-SNM study is a pivotal study designed to treat patients with urinary urgency incontinence (UUI). Clinical results at 1-year are presented.

Methods: A total of 129 eligible UUI patients were treated. All participants were implanted with a quadripolar tined lead and neurostimulator in a single procedure. Efficacy data were collected using a 3-day bladder diary, a validated quality of life questionnaire (ICIQ-OABqol), and a participant satisfaction questionnaire. Therapy responders were defined as participants with $\geq 50\%$ reduction in UUI episodes compared to baseline. Data were analyzed on all 129 participants.

Results: At 1 year, 89% of the participants were therapy responders. The average UUI episodes per day reduced from 5.6 ± 0.3 at baseline to 1.4 ± 0.2 . Participants experienced an overall clinically meaningful improvement of 34 points on the ICIQ-OABqol questionnaire. All study participants (100%) were able to recharge their device at 1 year, and 96% of participants reported that the frequency and duration of recharging was acceptable. There were no serious device-related adverse events.

Conclusions: The Axonics System is safe and effective at 1 year, with 89% of participants experiencing clinically and statistically significant improvements in UUI symptoms.

KEYWORDS

clinical trial, implantable neurostimulator, overactive bladder, sacral neuromodulation, urinary urgency incontinence

1 | INTRODUCTION

The Axonics System® provides sacral neuromodulation (SNM) therapy for the treatment of overactive bladder, nonobstructive urinary retention, and fecal incontinence. With an approved functional life of at least 15 years, the Axonics System is the first rechargeable SNM system available for use in the United States (Figure 1). The Axonics System is designed to last approximately three times longer than the non-rechargeable SNM system, which needs surgical replacements at the end of battery life.¹ The prolonged battery life and reduced number of device replacements with the Axonics System is expected to offer significant advantages to patients, physicians, and the healthcare system by reducing surgical risks while providing significant cost savings.²

In addition, the Axonics System is approved for full-body magnetic resonance imaging (MRI) scans. Historically, patients needing MRI of the body either declined or were not offered SNM therapy and existing SNM patients needing MRI of the body had to have the device

surgically explanted or forgo this important diagnostic tool.³ In addition to the long-lived nature of this device, full-body MRI conditional safety is a significant benefit for this patient population.

The ARTISAN-SNM study is a single-arm, prospective, multi-center, pivotal study that was designed to evaluate the safety and efficacy of the Axonics System for the treatment of urinary urgency incontinence (UUI). Six-month results showed a favorable safety and efficacy profile for the Axonics System as well as clinically meaningful improvements in quality of life (QoL).⁴ This manuscript reports results at 1-year follow-up.

2 | METHODS

The ARTISAN-SNM study protocol was approved by Ethics Committees at all study sites, and all study participants gave informed consent before study enrollment. Detailed study methods have been previously published⁴ ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03327948) #NCT03327948).



FIGURE 1 The FDA-approved Axonics System includes a rechargeable, miniaturized implantable neurostimulator that is ~5cc in volume and has a 15-year approved life in United States, Europe, Canada, and Australia. In addition, the Axonics System is conditionally approved for full-body MRI scans at 1.5 and 3T

All eligible participants were implanted with the Axonics neurostimulator and quadripolar tined lead in a single procedure. Fluoroscopic guidance was used to implant the tined lead along the S3 (preferred) or S4 sacral nerve root following SNM best practices published by the International Continence Society (ICS).⁵ A positive response on a minimum of two electrodes at less than 4 mA was required to proceed with full implant, and none of the study participants undergoing the surgery failed this criterion. Patients were programmed to the optimal settings primarily based on intraoperative motor responses and postoperative sensory responses.

Postoperatively, participants were instructed to charge their device every 1 to 2 weeks after implant. This was accomplished using a wireless charging device that is placed on the skin over the implanted neurostimulator and held in place using a belt. The recharging process has been detailed previously,^{4,6} and details on ease of use and acceptability of the charging experience are reported in the Results section.

Efficacy data were collected using a consecutive 3-day voiding diary, health-related quality of life (QoL) questionnaire (ICIQ-OABqol), and a participant satisfaction questionnaire. Bowel symptoms, specifically targeting accidental bowel leakage, were also captured using the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS). All adverse events (AEs) were tracked, analyzed, and reviewed by a data safety monitoring board.

Participants were considered therapy responders if they had a $\geq 50\%$ reduction in UUI episodes on their voiding diary at follow-up compared to baseline. The primary efficacy outcome is the therapy responder rate for all implanted participants (as-treated group). Participants with missing data at follow-up visits were conservatively assumed to be therapy nonresponders. Analyses were also performed in the “Test Responders” cohort, defined as participants who were therapy responders at 1 month. These analyses are performed to

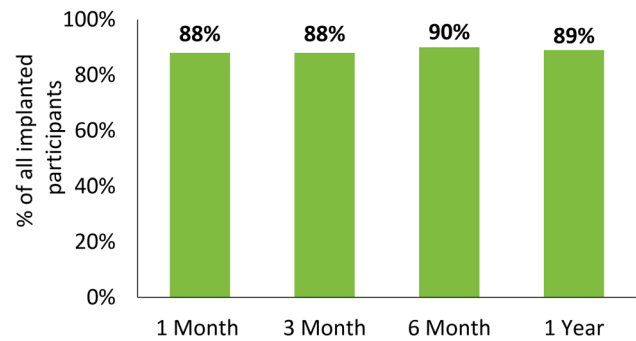


FIGURE 2 Therapy responder rates in all implanted participants at different follow-up visits post-implant. UUI therapy response is defined as $\geq 50\%$ reduction in UUI episodes at follow-up as compared to baseline. As-treated analysis is presented, where explanted or exited participants are considered as treatment failures. UUI, urinary urgency incontinence

allow comparison with the current clinical literature, where efficacy results are typically reported only for those participants that have a positive clinical response during an external trial period.

In addition to the therapy responder rate analyses, data analyses included the absolute change and percent change for the number of UUI episodes, the number of large UUI episodes, outcomes of the QoL questionnaire, and participant satisfaction questionnaire results. All efficacy results for urinary incontinence are assessed using urge incontinence episodes only. A conservative approach was taken to analyze missing or exited participants as therapy failures for measures on the diary, QoL, and satisfaction. Recharging experience is reported based on available data (ie, excludes missing or exited participants).

3 | RESULTS

3.1 | Study participants

A total of 129 participants met the IE criteria and were implanted with the Axonics System in a single procedure. There were no intraoperative test failures. The average age of participants was 59.3 years old (21–86 years) and 98% were female. At baseline, participants had 5.6 ± 0.3 (average \pm standard error) UUI episodes per day. Detailed demographics and baseline characteristics are shown in Table S1.

Over 96% of the participants (124 of 129) completed the 1-year visit. Five participants, including three Test Responders, exited before the 1-year visit (details in Safety section). An as-treated analysis was performed for symptom-specific measures, where participants

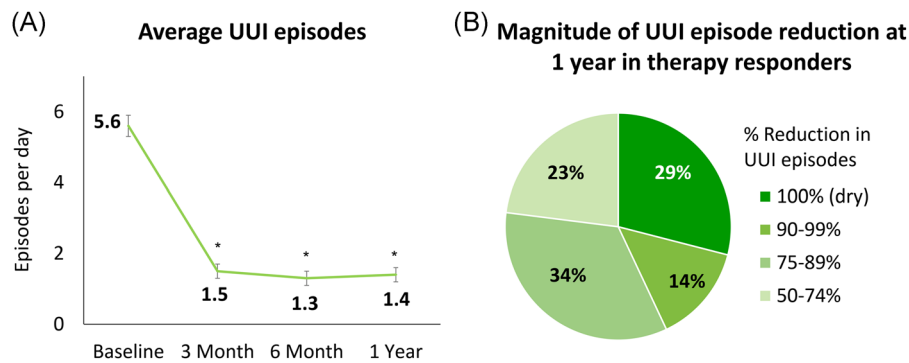


FIGURE 3 Symptom reduction in all implanted participants ($n = 129$) at 3 months, 6 months, and 1 year. A, Average number of UUI episodes in all implanted participants at baseline, 3 months, 6 months and 1 year. B, Magnitude of UUI episode reduction in therapy responders ($n = 115$) at 1-year follow-up. Error bars represent standard error. * $P < .0001$ compared to baseline. UUI, urinary urgency incontinence

unavailable at follow-up are considered treatment failures.

3.2 | Therapy responder rate and UUI symptom reduction

Eighty-nine percent of the study participants (115 of 129) were therapy responders at 1 year (ie, had $\geq 50\%$ reduction in UUI symptoms as compared to baseline; Figure 2A). Of the 129 participants, 113 (88%) were Test Responders at 1-month. Of the Test Responders, 94% (106 of 113) were therapy responders at the 1-year follow-up. A consistent responder rate was seen from 1-month to 1-year visits, showing sustained efficacy of the therapy.

In all implanted participants ($n = 129$), the average UUI episodes per day reduced from 5.6 ± 0.3 at baseline to 1.4 ± 0.2 at 1 year ($P < .0001$), which represents a 75% reduction in UUI episodes (Figure 3A). Seventy-seven percent of the therapy responders (88 of 115) had a greater than 75% reduction in UUI episodes, including

29% of responders that were completely dry (achieved complete urinary continence) (Figure 3B).

Eighty-one study participants had at least one large leak per day at baseline as reported on the 3-day bladder diary. In this group, the average large leaks per day reduced from 1.6 ± 0.2 at baseline to 0.2 ± 0.1 at 1 year ($P < .0001$), which represents an 87.5% reduction in large leak episodes. Seventy four percent of the participants with large leaks at baseline (60 of 81) had a 100% reduction in the large leak episodes, and 83% had $\geq 75\%$ reduction in large leak episodes.

3.3 | Quality of life and therapy satisfaction

At 1 year, study participants averaged a 34.4-point improvement on the health-related quality of life (HRQL) measure of the ICIQ-OABqol questionnaire ($P < .0001$), a clinically meaningful improvement as compared to baseline⁷ (Figure 4). Improvements in QoL were seen on

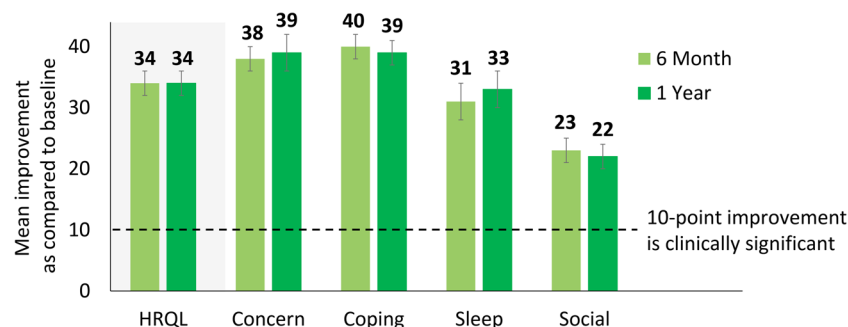


FIGURE 4 Quality of life scores in all implanted participants as assessed by ICIQ-OABqol in an as-treated analysis. Health-related QoL (HRQL) composite score and all subscale scores show clinically and statistically significant improvements compared to baseline ($P < .0001$ for all comparisons, $n = 129$). Error bars represent standard error. All scores exceeded the minimally important difference of 10 points, which is the minimally important difference typically considered clinically meaningful to patients⁷ for improvement in QoL

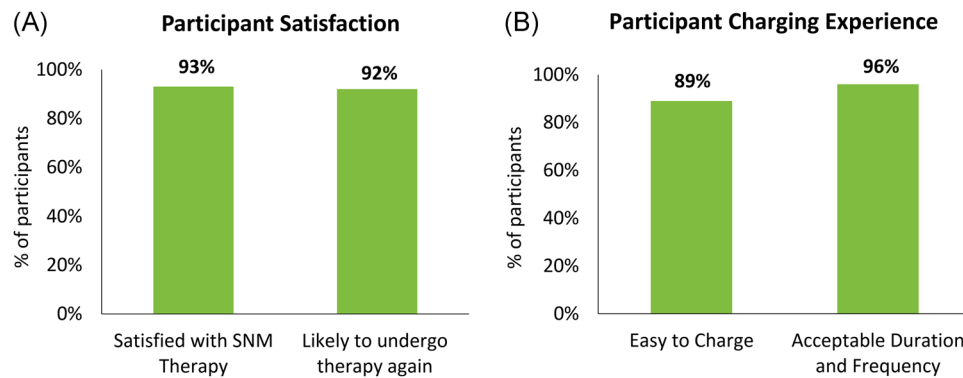


FIGURE 5 Participant satisfaction with therapy and recharging experience at 1 year. A, Participant satisfaction with SNM therapy and likeliness of undergoing therapy again for the same outcome. The as-treated analysis is performed in all implanted participants ($n = 129$), with missing participants conservatively considered as having negative responses. B, Ease of charging and acceptability of charging duration and frequency. Analyses performed in available participants at 1 year ($n = 124$). SNM, sacral neuromodulation

all domains of the ICIQ-OABqol subscales, with improvements of 39.3 points on Concern, 38.6 points on Coping, 32.6 points on Sleep, and 22.4 points on Social Interaction.

In addition, 93% of the 129 participants responded as being “satisfied” with their rechargeable SNM therapy, and 92% responded that they would undergo the therapy again (Figure 5A).

3.4 | Recharging experience

At 1 year, 100% of participants reported being able to recharge their system, and 89% of participants found it “easy” to recharge the system (Figure 5B).

At 1 year, 86% of participants (107 of 124) reported recharging their system for less than 1 hour, and 95% of participants reported going at least 7 days between recharging sessions. The duration and frequency of recharging was reported as “acceptable” by 96% of participants (Figure 5B).

3.5 | Additional outcome measures: urgency, urgency frequency, and fecal incontinence

Study participants also experienced reductions in overall urgency episodes (ie, urgent voids and/or leaks), urgency frequency, and fecal incontinence symptoms. At baseline, participants had 10.6 ± 0.3 urgency episodes per day which reduced to 7.4 ± 0.3 at 1 year ($P < .0001$).

Of the 129 participants, 103 had urinary frequency defined as ≥ 8 voids per day. These participants averaged

11.6 ± 0.3 voids per day at baseline, which reduced to 8.9 ± 0.2 voids per day at the 1-year follow-up ($P < .0001$).

Of the 129 participants, 42 (33%) had fecal incontinence at baseline, as determined by a score of 6 or greater on CCF-FIS.⁸ The average CCF-FIS score at baseline was 9.3 ± 0.5 and was reduced to 3.9 ± 0.6 at 1 year (Figure S1A; $P < .0001$). In addition, at 1 year 55 participants self-identified and reported their level of satisfaction with therapy for their fecal incontinence symptoms. Ninety-one percent of these participants (50 of 55 participants) reported being satisfied with the SNM therapy for their bowel symptoms (Figure S1B).

3.6 | Safety

A total of 15 device-related AEs were reported across 14 participants (10.8% of participants) at 1 year, with 10 AEs being reported before the 6-month follow-up. The most frequent AE was discomfort due to stimulation, which accounted for seven events in seven (5.4%) participants, all of which were resolved with reprogramming. One patient (0.8%) experienced some discomfort/heating near the charging area, which was resolved by retraining the patient on a proper charging technique.

Two events of pain at the neurostimulator site (1.6%) occurred, both of which resolved spontaneously. Two lead revisions were performed in two patients, one for a lead migration (0.8%) and another for high impedances (and suspected lead fracture, 0.8%). The lead revisions resulted in the successful return of efficacy in both patients.

A total of five participants exited before 1 year; three of whom exited before the 6-months visit. Reasons for

participant study exit were system explant in four participants (1 infection, 1 pain unrelated to the device, 2 insufficient efficacy), and death unrelated to study device or procedure in one participant.

4 | DISCUSSION

This study represents the 1-year safety and efficacy outcomes of the Axonics System for the treatment of UUI. The consistency of the results out to 1-year supports the durability of the therapy as well as an excellent safety profile. The as-treated 89% therapy response rate at 1 year is one of the highest reported in the literature and was calculated using the most conservative methodology. In addition, the magnitude of the therapy response, with 29% of participants being dry and 77% achieving $\geq 75\%$ improvement, far exceeds the traditional definition of success at 50% improvement. The ARTISAN-SNM therapy response rate was calculated in all implanted participants, including the initial therapy failures and participants that exited the study. This contrasts with the InSite study where the therapy response rate was evaluated in only participants available for evaluation at follow-up and excluded participants who were initial therapy failures and participants who exited the study.

As reported previously,⁴ we hypothesize that several factors may contribute to the high therapy responder rate. A recent study by Adelstein et al⁹ (2019) showed that high trial success rates (88%) can be achieved by optimal lead placement which includes the use of the curved stylet. The adoption of best practice techniques^{5,10,11} for optimal lead placement undoubtedly contributed to the success in this study as evidenced by the 88% responder rate at 1 month. The durability of the response from 1 month to 1 year may also be attributed in part to the additional features of the rechargeable system, including the use of constant current stimulation and the easy to use, intuitive patient remote control. Future comparative studies are needed to evaluate the specific contribution of these additional factors on short-term and long-term efficacy.

Although this study was not designed to evaluate the efficacy of the Axonics System in patients with fecal incontinence, 1/3 of the study cohort reported suffering from this condition. Based on our questionnaire data, participants had a reduction in the CCF-FIS from 9.3 at baseline down to 3.9 at 1-year. Recent data suggest that a reduction to a score < 9 correlates to an important improvement in patients' quality of life.⁸

The Axonics System is the first rechargeable SNM system with an approved device life of 15 years or longer. The long life of the Axonics System is made possible by

its rechargeable battery. Patient recharging experience with the Axonics System has been very encouraging. At 1 year, all study participants were able to recharge their system, and the vast majority (89%) reported it was easy to recharge the system and 96% reported recharging frequency and duration was acceptable. These results are consistent with the literature for rechargeable spinal cord and deep brain stimulation systems which have shown high satisfaction, including 85% to 90% of patients preferring or recommending rechargeable devices.¹²⁻¹⁴

At 1 year, the safety profile of the ARTISAN-SNM study remained excellent. There have been no unanticipated or serious device or procedure-related AEs. Most of the device-related AEs occurred within the first 6 months (63%), with only 37% of AEs occurring between 6 and 12 months. As previously reported, there was a $< 1\%$ infection rate which is one of the lowest reported in the SNM literature. The low infection rate may be attributable to the protocol requirements designed for infection prevention⁴ and smaller pocket size. A notable aspect of the safety results of this study is that there have been no surgical interventions for pain at the neurostimulator site. This contrasts with the Medtronic InSite study where 7% of participants reported pain at their neurostimulator site, of which 50% had to undergo surgical revision or explant. In the ARTISAN-SNM study, the overall surgical intervention rate remained low at six participants (4.6%), two of which were initial non-responders that were explanted due to continued lack of efficacy. The 1-year safety data for the Axonics System is reassuring and consistent with other reports of the safety of SNM.

Having a safe and effective treatment option for patients suffering from UUI and OAB is important given the recent JAMA article linking the risk of dementia and exposure to anticholinergic medications.¹⁵ The article adds to a growing body of evidence highlighting the importance of reducing exposure to anticholinergic drugs especially in middle-age and older adults, which correlates to the population of OAB/UUI sufferers. A long-lived, rechargeable SNM system provides a safe and effective alternative to using anticholinergics for the treatment of OAB/UUI.

The strengths of this study include the conservative data analysis methods, which provide an objective and robust measure of therapy response in all patients treated. In addition, the collection of recharging usability data provides insight into the patient charging experience, showing high participant satisfaction. Study limitations include that this was a nonrandomized study, with no comparator or placebo arm. However, given that SNM is a widely accepted treatment with well-known efficacy, the use of a placebo was considered unnecessary.

In addition, the majority of the study participants were female, potentially limiting the generalizability of the findings. However, given that UUI/OAB is more prevalent in female participants than males,^{16,17} this was expected. It should also be noted that another study with the same device (RELAX-OAB) had a higher percentage of males (25%) and showed that the therapy worked equally well for the male population.¹⁸

5 | CONCLUSION

The ARTISAN-SNM study demonstrates that the Axonics System provides sustained, long-term, safe and efficacious outcomes in patients with urgency urinary incontinence. At 1-year post-implant, clinically meaningful improvements in patient quality of life and high rates of satisfaction with the therapy and the recharging experience were achieved.

ORCID

Kevin Benson  <http://orcid.org/0000-0001-9512-7431>

Bertil Blok  <http://orcid.org/0000-0001-9354-7395>

Una Lee  <http://orcid.org/0000-0003-1128-5083>

Craig Comiter  <http://orcid.org/0000-0001-9921-601X>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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