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RESEARCH ARTICLE

Spinal cord stimulation for chronic refractory pain: Long-term effectiveness and safety data from a multicentre registry

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on behalf of the French SCS Study Group

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Abstract

Background: Spinal cord stimulation (SCS) is an established therapy for refractory neuropathic pain. To ascertain the balance between treatment benefits and risks, the French National Authority for Health requested a post-market registry for real-world evaluation of the long-term effectiveness and safety of the therapy.

Methods: A total of 402 patients undergoing implantation with a Medtronic SCS device as either a primo-implant ($n = 264$) or replacement implant ($n = 138$) were enrolled across 28 representative sites in France. Outcome measures at 2 years included pain intensity, satisfaction with treatment, improvement of pain relief and daily life activity, willingness to undergo the treatment again and use of pain treatments. A patient was considered a responder if, compared to baseline, predominant pain reduction was $\geq 50\%$.

Results: At the 2-year follow-up visit, predominant pain intensity for primo-implant patients had decreased from baseline ($p < 0.001$), with responder rates of 55%, 36% and 67% for the lower limbs, back and upper limbs, respectively. Most patients acknowledged an improvement in pain relief (89%) and daily life activity (82%) were satisfied with treatment (91%) and willing to undergo the treatment again (93%). A significant decrease ($p < 0.01$) in the proportion of patients receiving pain treatment was observed for all drug and non-drug treatments. Reported adverse events were in line with the literature. Pain intensity at 2 years was comparable for patients in the replacement group, supporting the long-term stability and effectiveness of SCS.

Conclusion: Real-world evaluation of the use of spinal cord stimulation under the recommendations of the French Health Authority shows that two years after the first implantation of an SCS device close to 60% of the patients retain a significant pain reduction and 74% show improvement in pain scores [of at least 30%] with significant decreases in drug and non-drug pain treatments.

Significance: This observational, prospective study in a real-life setting followed a large cohort of patients suffering from chronic pain and implanted with SCS devices in France. The study assessed the long-term effectiveness and safety of SCS therapy in a representative sample of implanting sites in France.

1 | INTRODUCTION

Neuropathic pain may affect between 7% and 10% of the general population (Bouhassira, Lanteri-Minet, Attal, Laurent, & Touboul, 2008; Colloca et al., 2017; Van Hecke, Austin, Khan, Smith, & Torrance, 2014), significantly affecting quality of life and increasing the burden on healthcare resources (Attal, Lanteri-Minet, Laurent, Fermanian, & Bouhassira, 2011). The complexity of chronic neuropathic pain along with the lack of efficacy of many current pharmacological treatments contributes to poor outcomes in this patient population (Finnerup et al., 2015).

Spinal cord stimulation (SCS), introduced by Shealy, Mortimer, and Reswick (1967), is an effective option for patients with refractory neuropathic pain and is the recommended treatment for refractory neuropathic pain related to failed back surgery syndrome (Crucchi et al., 2016; Dworkin et al., 2013). It also has been shown to be cost-effective (Blond et al., 2004). The technique involves the placement of an electrical lead in the epidural space and the use of electrical pulses to stimulate the dorsal columns of the spinal cord, inducing analgesic paraesthesia. Spinal cord stimulation has also been used successfully to relieve different types of neuropathic pain (Taylor, Desai, Rigoard, & Taylor, 2014).

In France, SCS therapy for neuropathic pain was approved for reimbursement in 2002 and, as of 2014, was indicated after the failure of alternative therapeutic treatments for chronic neuropathic pain or type I or II complex regional pain syndrome (Haute Autorité de Santé, 2014). Chronic ischaemic pain resulting from Buerger's disease was also indicated for treatment with SCS.

The French Authority for Health (HAS—see Supporting Information Introduction S1) requested a post-market observational study to assess the long-term effectiveness and safety of SCS therapy in a real-life setting in the country. While many studies have reported the efficacy of SCS (Grider et al., 2016; Kriek, Groeneweg, Stronks, de Ridder, & Huygen, 2017; Kumar et al., 2007; North, Kidd, Farrokhi, & Piantadosi, 2005; North, Kidd, Petrucci, & Dorsi, 2005), few have focused on the long-term efficacy and safety of this technique and few multicentre prospective registries exist (Gatzinsky, Baardsen, & Buschman, 2017; Rosenberg et al., 2016; Schultz et al., 2016).

In this prospective, observational study, we provide long-term effectiveness and safety data from a representative cohort of sites in France using Medtronic devices. Patients were either implanted for the first time with an SCS device (primo-implant group) or were implanted with a new SCS device as a replacement of a previous device because of end of life of Implantable NeuroStimulator (INS) or for other reasons (e.g., change of electrode with change of INS)—replacement group. The proportion of patients with predominant pain relief of at least 50% at the 1- and 2-year follow-up visits was

assessed, along with patient satisfaction, the use of concomitant pain medications and the safety of the device.

Data from patients in the primo-implant group were used to assess the effectiveness of the treatment compared to the pre-operative situation, whereas data from patients in the replacement group were used to collect long-term safety and stability information. The data generated from this study will be used by the National Committee for Medical Devices and Technologies Assessment (CNEDiMTS—Supporting Information Introduction S1) to renew the reimbursement of the SCS devices used in the study.

2 | METHODS

2.1 | Study design

This post-market observational study was a national (France) study, with a prospective, multicentre, representative, non-randomized and non-controlled design, conducted at 28 sites performing SCS therapy (ClinicalTrials.gov identifier NCT01778426).

The study was conducted in accordance with the Declaration of Helsinki and French laws and regulations and was overseen by an independent Scientific Committee. No ethics committee or institutional review board approval was required for this non-interventional post-market study. Approval was obtained from the relevant national authorities, that is, the National Commission for Data Protection and Liberties (CNIL), the Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) and the French National Council of the Medical Order (CNOM); a brief explanation on their functions can be found in the supplementary material (Supporting Information Introduction S1).

2.2 | Study sites and patients

Study sites were randomly selected from the 92 sites in France performing implantation of SCS neurostimulators and specialized in pain treatment, based on their status (private vs. public) and level of activity (high, medium or low). The probability proportional to size (PPS) sampling technique was used to randomly select sites in each stratum to be included in the study (Cochran, 1977). A total of 59 sites were contacted; 42 agreed to participate, of which 35 were initiated (7 did not return their signed clinical agreement) and 28 included at least one patient in the study. In general, the 28 sites were found to be comparable to the 92 SCS implanter sites in France (Supporting Information Figure S1).

Patients were recruited between 13 January 2012 and 19 December 2013, and the last follow-up visit was performed on 11 January 2016.

At each site during the 2-year inclusion period, study participation was offered to patients suitable for SCS therapy per HAS requirements. Eligible participants had undergone implantation of the Medtronic SCS device within 3 months prior to enrolment or were hospitalized for such an implantation: Patients receiving their first implant (primo-implant group) or a replacement implant (replacement group) were included. Where available, data regarding pre-operative treatments and pain (lower/upper limbs, back) for the 3 days preceding implantation (or re-implantation) were recorded. Patients were excluded if long-term follow-up was not possible, or if they were receiving another type of stimulation (e.g., occipital, cortical, subcutaneous). All patients signed a patient data release form before study participation.

As this was an observational study, local institutional practices were preserved. This implies that no recommendations or changes were made to the selection of patients, trialling or the implantation technique of each site. In France, the HAS requires preimplantation trialling in all candidates to SCS; however, few controls are in place to enforce this prerequisite. On the other hand, HAS does not make recommendations for lead selection. Furthermore, no visit schedule was imposed; however, it was recommended that visits occurred at least once per year.

2.3 | SCS devices

Primary implantation or replacement of SCS devices included the following models: ITREL3™, ITREL™4, RESTOREADVANCED™, RESTOREULTRA™, RESTORESENSOR™ and PRIMEADVANCED™ (Medtronic) with either surgical or percutaneous leads.

2.4 | Outcome measures

Pain intensity was assessed at baseline and during follow-up for the selected pain area (lower limbs, back and upper limbs) using an 11-point (0–10) Numeric Pain Rating Scale (NPRS), ranging from 0 (no pain) to 10 (maximum pain possible). The NPRS score was collected at the time of the visit as an average of the NPRS scores on the 3 days prior to the visit (no diary was used, assessment was based on patient recollection of pain intensity).

Where multiple pain locations were reported at baseline, the one with the highest pain intensity (i.e., the location assumed to be targeted by SCS therapy) was defined as the predominant pain area, in agreement with the HAS. Importantly, predominant pain was only defined for the primo-implant group, as at baseline their NPRS scores were collected without active SCS treatment (not necessarily the case for patients in the replacement group).

Pain relief treatments, including analgesics level 1–3 (i.e., non-opioids, weak opioids and strong opioids, respectively;

WHO drug classification), non-steroidal anti-inflammatories, antiepileptics, antidepressants, physiotherapy, psychotherapy, acupuncture, relaxation and transcutaneous electrical nerve stimulation (TENS) were evaluated at baseline and at each follow-up visit. Satisfaction was assessed by patient responses regarding pain relief and daily life activity (improvement vs. no improvement), treatment (rather satisfied vs. rather not satisfied) and willingness to undergo treatment again (yes vs. no).

Safety was assessed by analysis of complications, defined as adverse events (AEs) related to the device or procedure (including definitive explant or repositioning), and device deficiencies (i.e., deficiencies that did not cause any symptom that would be reported as an AE, including those related to the malfunction, misuse or use errors and inadequate labelling of the device). Serious adverse events (SAE) were defined as AEs that: (a) led to death, (b) led to a serious deterioration in the health of the patient (i.e., that either resulted in [1] a life-threatening illness or injury, or [2] a permanent impairment of a body structure or a body function, or [3] inpatient or prolonged hospitalization, or [4] medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function), or (c) led to foetal distress, foetal death or a congenital abnormality or birth defect. To note, planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, was not considered an SAE.

2.5 | Outcomes

The primary outcome was the percentage of patients (responder rate) with pain relief (reduction in pain intensity) of $\geq 50\%$ at 2-year follow-up (compared to baseline) in the predominant pain area at baseline, measured by NPRS (primo-implant group only).

The percentage change of pain relief was computed at 1- and 2-year follow-up as relative change as indicated by the following formula: percentage change of pain relief = $100 * (\text{NPRS at baseline} - \text{NPRS at follow-up}) / \text{NPRS at baseline}$.

Key secondary outcomes included the percentage of patients in the primo-implant group with pain relief of $\geq 50\%$ after (a) 1 year of follow-up in the predominant pain area, and (b) 1 and 2 years of follow-up in the non-predominant pain area. Other secondary outcomes included use of pain medication, patient satisfaction, assessment of complications related to the device or procedure (including implantable neurostimulator [INS] replacement) and revision and explant rates.

In the replacement group, the reduction in pain intensity compared to baseline was not considered as the main outcome since information about the activation of the device prior to its replacement was not available. Instead post-implantation

(1 and 2 years) pain scores were compared between themselves and to post-implantation pain scores of primo-implant patients and patient satisfaction was recorded and reported as a major outcome measure.

2.6 | Statistical analyses

Assuming a dropout rate of 20%, a total of 270 patients in the primo-implant group were required to estimate the primary outcome with a precision of at least 6.5%. As it was expected that approximately one-third of patients receiving SCS therapy would be re-implantations, a total of 400 patients were planned to be enrolled.

The full analysis set (FAS; all enrolled patients from the primo-implant and replacement groups) was primarily the analysis set for demographic characteristics and safety. The intention-to-treat completer set (ITT completer; all primo-implant patients with a baseline and a follow-up visit at 2 years \pm 6 months with NPRS completed for the predominant pain) was the primary analysis set for all planned efficacy analyses. An ITT set (all patients in the primo-implant group) was also defined for secondary objective analysis. Imputation rules were applied for sensitivity analysis of the primary objective of the study (Supporting Information Methods S1).

For qualitative variables analysed at different follow-up stages, the analysis provided the number of available and missing data as well as the percentage in each category and the 95% confidence interval (CI). For quantitative variables, the number of available and missing data was provided, along with mean, standard deviation (*SD*), median and range values. For pain relief treatments, the proportion of patients treated with each type of treatment at baseline was compared with the proportion after 1 and 2 years of follow-up using a McNemar's test and the proportion of patients having stopped and started medication between baseline and last follow-up visit was compared using Fisher's exact test. For analgesics level 3, the mean dose taken at baseline was compared with the mean dose taken after 1 and 2 years of follow-up using a Wilcoxon signed-rank test. Statistical tests were performed with a significance level of 5%. Analyses were performed using SAS version 9.3 and R 3.3.3 software.

3 | RESULTS

A total of 414 patients were assessed for eligibility, 12 patients were excluded: eight who did not fulfil the study criteria, three who were enrolled prior to site initiation and one who was enrolled outside of the enrolment period (Figure 1). Therefore, 402 patients were enrolled in the study and included in the FAS (264 patients in the primo-implant group and 138 patients in the replacement group). Overall, 345

patients (83%) completed the 1-year follow-up and 321 patients (77%) completed the 2-year follow-up. Of the 402 enrolled patients, 354 (88%) were marked as having completed the study (223 patients in the primo-implant group and 131 patients in the replacement group). As no visit schedule was imposed, completed patients might not have a 2-year follow-up visit completed (see imputation rules: Supporting Information Methods S1 and Results S1 for the timing of follow-up visits). Overall, the study had a 12% dropout rate.

Of the 264 primo-implanted patients included in the ITT set, 198 had baseline and follow-up pain intensity data at 2 years \pm 6 months and were included in the ITT completer set (Figure 1).

Of interest, 266 patients were reported as “not included in the study,” primarily due to a lack of time or omission of proposing the study to the patient (208 patients [78%] across 11 sites [39%]). This “non-inclusion registry” indicated that there was no bias in patient enrolment.

3.1 | Demographic characteristics

Over half of the study patients were male in both the primo-implant (56%) and replacement (57%) groups, with a mean age of 49.6 and 56.5 years, respectively (Table 1). The median time since the onset of pain was 3.5 years in the primo-implant group and 10 years in the replacement group. Predominant pain (primo-implant group only) was located mainly in the lower limbs (77%), with a mean \pm *SD* intensity of 7.9 ± 1.4 , as measured by the NPRS. Almost all patients (98%) were treated for chronic neuropathic pain. Among these, 78% suffered from pains associated with chronic radiculopathy. The main drug pain relief treatments for both the primo-implant and replacement groups included antiepileptics (67% and 46%), analgesics level 2 (60% and 51%) and analgesics level 1 (57% and 59%).

The use of percutaneous ($n = 133$; 51%) and surgical leads ($n = 130$; 49%) was similar in the primo-implant group, whereas the majority of patients in the replacement group were implanted with a surgical lead ($n = 89$; 65%), Supporting Information Table S1.

3.2 | Pain reduction and responder rates

3.2.1 | Predominant pain reduction and responder rates in the primo-implant group

For patients with predominant pain defined and having completed visits at 1 or 2 years, the mean \pm *SD* intensity of pain decreased from 7.9 ± 1.5 at baseline ($n = 262$) to 3.7 ± 2.3 at 1 year ($n = 225$) and 3.7 ± 2.5 at 2 years ($n = 198$, ITT completer; Figure 2). This corresponds to an overall mean \pm *SD* reduction in patient pain intensity of $51.1\% \pm 31.5$ and $52.2\% \pm 31.8$ at 1 and 2 years, respectively. The differences in

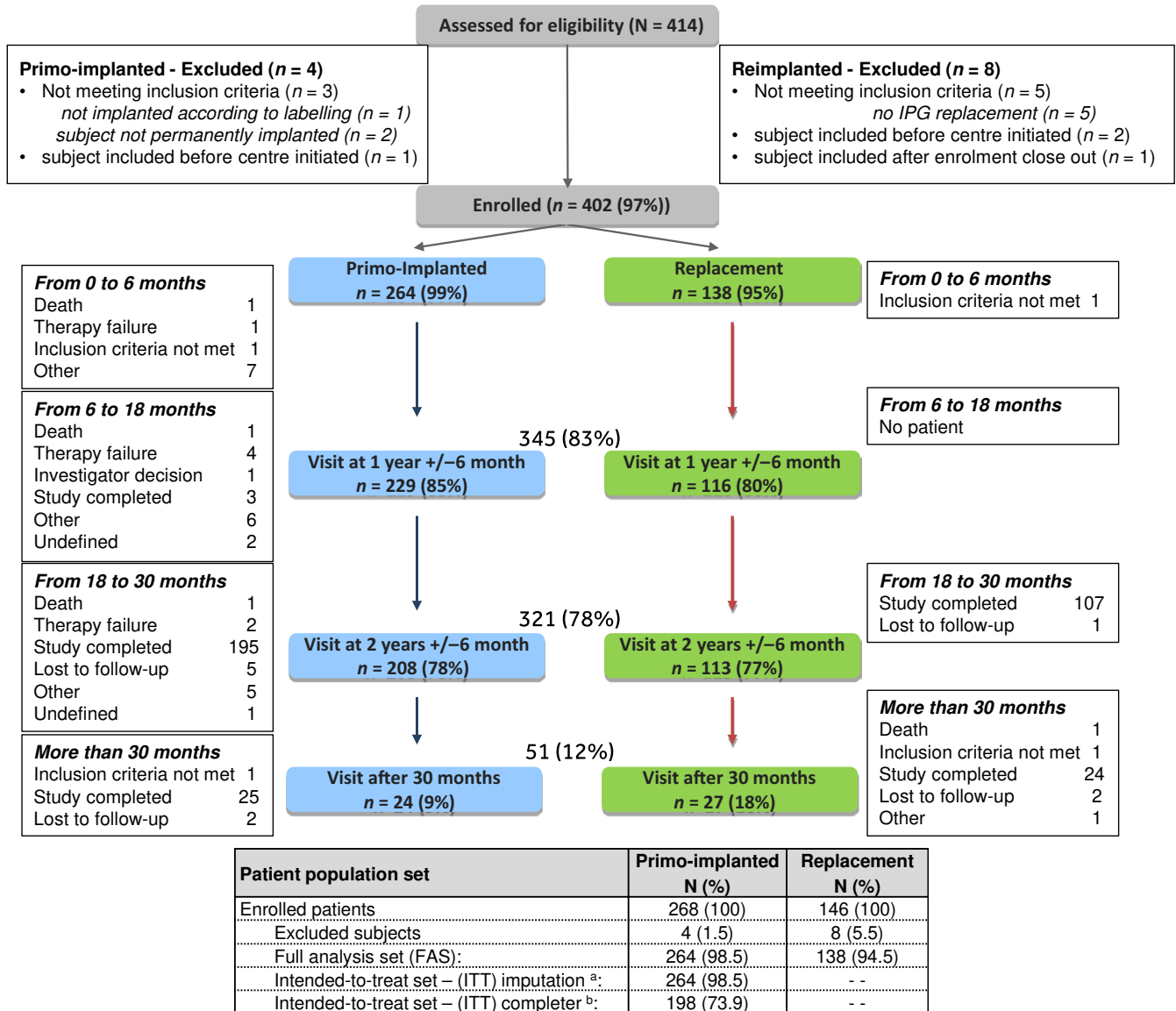


FIGURE 1 Study flow chart. ^aAll primo-implanted patients—imputation rules were applied to responder rate at 2 years. ^bPrimo-implanted patients with a baseline and follow-up visit at 2 years±6 months with NPRS completed for the predominant pain. Percentages computed on 414 patients (i.e., primo-implant: 268 and replacement: 146). INS: implantable neurostimulator; NPRS: Numeric Pain Rating Scale

pain intensity were statistically significant between baseline and the 1- and 2-year visits (both $p < 0.0001$ [paired t test]).

When considering pain intensity by pain location, in patients with predominant pain located in lower limbs ($n = 203$; 77%), pain reductions of $51.5\% \pm 30.5$ ($n = 177$) and $52.5\% \pm 32.3$ ($n = 156$) were observed at 1 and 2 years, respectively. The back was the predominant pain area for 33 patients (13%), with pain reductions of $42.2\% \pm 37.3$ ($n = 28$) observed at 1 year and $46.6\% \pm 28.9$ ($n = 23$) at 2 years. For 24 patients (9%), predominant pain was located in the upper limbs. Reduction in pain intensity for these patients at 1 and 2 years was $60.4\% \pm 31.3$ ($n = 18$) and $56.6\% \pm 32.4$ ($n = 18$), respectively. The differences in pain intensity were statistically significant between baseline and the 1- and 2-year visits (both $p < 0.0001$ [paired t test]) for the three pain areas.

When considering pain intensity from all follow-up visits available and by pooling them in 6-month intervals, pain reduction was found to occur within the initial 6 months after study inclusion and appeared stable over time (Figure 3).

For the primary outcome, at 2 years the overall responder rate ($\geq 50\%$ predominant pain decrease at 2 years) was 59% in the ITT completer analysis ($n = 198$) and 60%, 39% and 78% for the lower limbs ($n = 156$), back ($n = 23$) and upper limbs ($n = 18$) predominant pain areas, respectively (Table 2). Despite the responder rate in back pain being less than 50%, at 2 years, 74% of patients had an average pain reduction of at least 30% from baseline. For the lower limbs and upper limbs, 75% and 83% of patients had an average pain reduction of at least 30% from baseline. Responder rates at 1 year were in the same range.

TABLE 1 Demographic and baseline characteristics

By implant type	Primo-implant (N = 264)	Replacement (N = 138)
Gender		
Male	147 (56)	78 (57)
Age at inclusion		
Mean (years) ± SD	49.6 ± 9.6	56.5 ± 11.4
Working status ^a		
Active	130 (49)	30 (22)
Invalid	61 (23)	51 (37)
Retired	27 (10)	44 (32)
Unemployed	15 (6)	3 (2)
Other	18 (7)	3 (2)
Time since onset of pain		
Years: [min;median;max]	[0.2;3.5;35]	[2;10;40]
Implant indication		
Chronic neuropathic intractable pain after failure of alternative therapeutic means	258 (98)	137 (99)
Peripheral ischaemic pain (arteriopathy stage III–IV)	5 (2)	1 (1)
Other	4 (2)	—
Combination of pain location ^a		
Lower limbs/back	172 (65)	95 (69)
Lower limbs	56 (21)	27 (20)
Upper limbs	21 (8)	4 (3)
Lower and upper limbs/back	7 (3)	7 (5)
Predominant pain location		
Lower limbs	203 (77)	NA
Back	33 (13)	
Upper limbs	24 (9)	
Other	2 (1)	
Not defined	2 (1)	
Pain treatments		
Analgesics level 3 (morphinics)	120 (46)	49 (36)
Analgesics level 2	159 (60)	71 (51)
Analgesics level 1	150 (57)	81 (59)
NSAIDs	83 (31)	51 (37)
Antiepileptic	176 (67)	64 (46)
Antidepressant	145 (55)	58 (42)
Physiotherapy	140 (53)	56 (41)
Psychotherapy	56 (21)	16 (12)
Acupuncture	20 (8)	9 (7)
Relaxation	38 (14)	16 (12)

(Continues)

TABLE 1 (Continued)

By implant type	Primo-implant (N = 264)	Replacement (N = 138)
TENS	196 (74)	31 (22)
Method of lead implantation		
Percutaneous lead	133 (51)	48 (35)
Surgical lead	130 (49)	89 (65)
Implant indication		
Chronic neuropathic intractable pain	255 (97)	137 (99)
Peripheral ischaemic pain	5 (2)	1 (1)
Chronic neuropathic pain/other	3 (1)	—
Other	1 (0)	—

All N (%) unless otherwise indicated.

^aCategories that represent at least 3% of all patients are displayed.

When considering all 264 patients in the primo-implant group and imputing missing data (Supporting Information Methods S1), the overall responder rate was 53%, with responder rates of 55%, 36% and 67% for patients with predominant pain in the lower limbs ($n = 203$), back ($n = 33$) and upper limbs ($n = 24$), respectively.

Ad hoc analysis was performed to evaluate the time to becoming a non-responder. Patients were classed as non-responders from the first visit at which pain relief was <50% and where pain relief was <50% for all subsequent visits. The Kaplan–Meier curve of this analysis decreased smoothly with time and no major break was observed (Figure 4). At 24 months, the probability of being responder with a cut-off of 50% pain relief in the primo-implanted group was 59.4% (55%–63%, 95% CI) with 92 reaching that time point. Figure 4 shows the number of patients at risk, cumulative number of events and cumulative number of censoring at each time point.

The probability of being definitively explanted at 1 and 2 years was 4% and 8%, respectively. Sixteen primo-implant patients were definitively explanted during the study.

3.2.2 | Non-predominant pain reduction in the primo-implant group

Non-predominant pain was reported in 182 patients (69%) in the primo-implant group and could be located in more than one area; lower limbs ($n = 33$), back ($n = 151$) and upper limbs ($n = 7$). At 2 years, mean ± SD pain intensity was reduced by 50.9% ± 31.7 ($n = 23$), 27.7% ± 84.2 ($n = 118$) and 60.0% ± 80.0 ($n = 4$) for patients with non-predominant pain in the lower limbs, back and upper limbs, respectively. Similar reductions were observed at 1 year. Two-year responder rates for lower limbs, back and upper limbs were

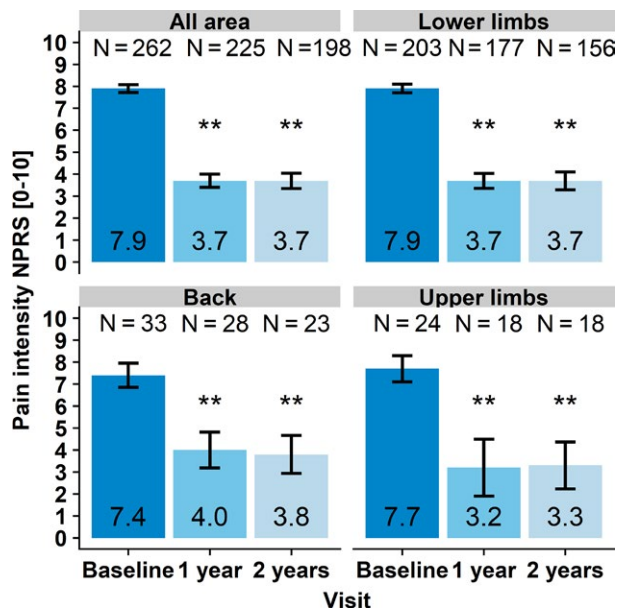


FIGURE 2 Predominant pain intensity at baseline, 1 and 2 years—ITT. Number of patients with available data and measured using the Numeric Pain Rating Scale (NPRS) for primo-implanted patients (no imputation). Two patients had their predominant pain in another area and for two patients the predominant pain area could not be defined. Overall, 264, 229 and 208 patients had a visit at baseline, and at 1 and 2 years, respectively (predominant pain intensity vs. baseline $**p < 0.0001$). *N* corresponds to the number of patients with available data. Error bars correspond to 95% confidence intervals. ITT: intention-to-treat

56%, 44% and 75%, respectively. For lower limbs and back pain, the pain reduction from baseline was significant at 1 year and 2 years (Supporting Information Figure S2) with both $p < 0.0001$ (paired *t* test).

3.2.3 | Pain stability in the replacement group

The 138 patients enrolled in the study following replacement of a neurostimulator had been treated with SCS for a median [1st; 3rd quartile] time of 7.2 years [4.0; 10.2]. Since patients may still have been under some stimulation from their existing device at baseline, pain reduction could not be accurately determined in these patients and so only pain intensity at 1 and 2 years was considered. It was also not possible to define the predominant pain area for these patients.

For the majority of patients, pain was located in both their lower limbs and back ($n = 95$; 69%; Table 1). Mean \pm SD pain intensity in the lower limbs was 3.8 ± 2.4 ($n = 106$) and 3.5 ± 2.2 ($n = 104$) at 1 and 2 years, respectively (Supporting Information Figure S3). For patients with pain located in their back, mean pain intensity was 4.2 ± 2.3 ($n = 84$) at 1 year and 4.0 ± 2.6 ($n = 82$) at 2 years. Fifteen patients had pain in the upper limbs, with mean \pm SD pain intensity of 3.6 ± 3.1

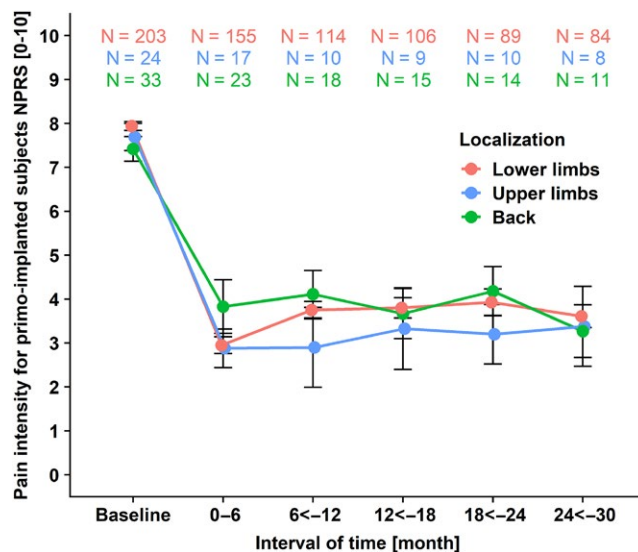


FIGURE 3 Evolution of predominant pain intensity over time—ITT. Predominant pain intensity was collected at all follow-up visits and presented by 6-month intervals. Two patients had their predominant pain in another area and for two patients the predominant pain area could not be defined and are not included in the graph. *N* corresponds to the number of patients with available data. Error bars correspond to standard error of the mean. ITT: intention-to-treat; NPRS: Numeric Pain Rating Scale

($n = 13$) and 4.4 ± 3.9 ($n = 12$) at 1 and 2 years, respectively. At follow-up visits, pain intensity in the lower limbs and back was in the same range as values observed for predominant pain in the primo-implant group. Values for pain intensity in the upper limbs were slightly higher in the replacement group.

3.3 | Patient satisfaction

At 1 and 2 years after primary implant, patients reported a similarly high level of satisfaction for all criteria assessed: Patient declared improvement in pain relief due to stimulation (87% and 89%, respectively), daily life activity improvement (79% and 82%), treatment satisfaction (88% and 91%) and willingness to undergo the treatment again (91% and 93%; Figure 5a).

Patient satisfaction was also high in the replacement group, ranging from 86% to 98% for each item assessed, with similar levels of satisfaction at 1 and 2 years (Figure 5b).

3.4 | Concomitant pain relief treatments

In the primo-implant group, there was a statistically substantial reduction in the percentage of patients taking drug and non-drug pain relief treatment between baseline and the 1-year and 2-year visits with both ($p < 0.01$ [McNemar's test] regardless of the treatment; Supporting Information

Responder rate ^a n/total (%) [95% CI]	1 year		2 years	
	ITT completer N = 179	ITT N = 229	ITT completer N = 198	ITT ^b N = 264
All areas	108/178 (60.7) [53.1–67.9]	134/225 (59.6) [52.8–66.0]	117/198 (59.1) [51.9–66.0]	141/264 (53.4) [47.2–59.5]
Lower limbs	89/139 (64) [55.5–72.0]	109/177 (61.6) [54.0–68.8]	93/156 (59.6) [51.5–67.4]	111/203 (54.7) [47.6–61.7]
Back	8/22 (36.4) [17.2–59.3]	12/28 (42.9) [24.5–62.8]	9/23 (39.1) [19.7–61.5]	12/33 (36.4) [20.4–54.9]
Upper limbs	11/16 (68.8) [41.3–89.0]	12/18 (66.7) [41.0–86.7]	14/18 (77.8) [52.4–93.6]	16/24 (66.7) [44.7–84.4]

TABLE 2 Responder rate at 1 and 2 years

CI: confidence interval; ITT: intention-to-treat.

^a≥50% decrease in pain reduction. ^bImputation was performed on the responder rate at 2 years. Results for “other” pain areas are not displayed.

Figure S4, Table S2a,b). The proportion of patients that were using specific medication at baseline and stopped it as well as those not having used it but starting it is given in Figure 6. For all types of medication, differences were significant in the sense of a larger proportion of patients having stopped medication.

Apart from analgesics level 3, smaller, but significant decreases from baseline to 2 years were also observed in the replacement group with ($p < 0.05$ [McNemar's test] regardless of the treatment; Supporting Information Figure S4). Interestingly, the significant differences between groups observed at baseline on antiepileptic and antidepressant drugs, TENS, physiotherapy and psychotherapy ($p \leq 0.05$ [chi-square or Fisher's exact tests]) were not reported at the 1- and 2-year follow-up visits.

When considering the dose of analgesics level 3 in primo-implant patients with information at baseline and 1 year, a statistically significant reduction in the equivalent mean±SD morphine dose was observed from baseline ($n = 35$; baseline: 143.4 mg ± 103.8; 1 year: 107.1 mg ± 95.3; $p = 0.0144$ [Wilcoxon signed-rank test]). However, there was no significant difference in the equivalent morphine dose between baseline and 2 years ($n = 29$; baseline: 138.8 mg ± 86.5; 2 years: 111.5 mg ± 103.1; $p = 0.0683$).

3.5 | Device safety and deficiencies

Overall, a total of 242 AEs were reported in 164 patients (41%); 181 AEs in 123 patients (47%) in the primo-implant group and 61 AEs in 41 patients (30%) in the replacement group (Table 3). Adverse events occurred mainly in the first 6 months after enrolment.

All complications were minor, with only one neurological deficit reported. The most frequent complications, reported in 78 patients (19%), were hardware related and

included lead migration (24 patients [6%]) and lead/extension fracture/torqued contacts/connector issues (25 patients [6%]). A total of 26 patients (6%) experienced events relating to the end of life of the INS. Considering local complications, the most frequently reported events were pain at the INS or incision site (26 patients [6%]) and infection (10 patients [2%]) within 30 days of primary implant or replacement and seven patients [2%] more than 30 days after implant).

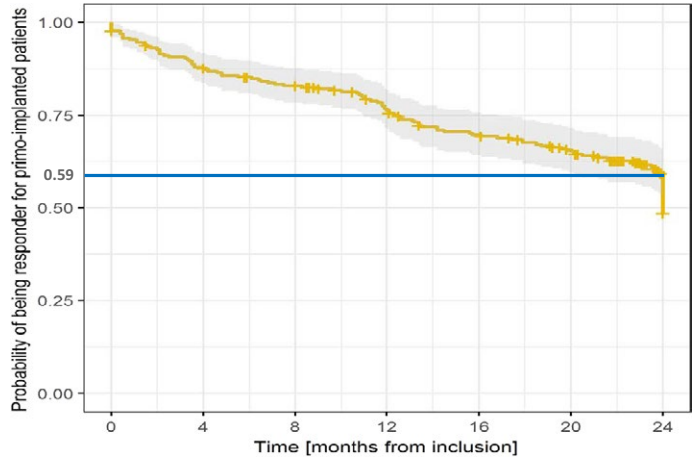
Revision surgery (any AE that required a surgical procedure without definitive explant of the neurostimulator or any part of the device implanted) was performed in 98 patients (24%).

A total of 107 events in 89 patients (22%) were considered serious (Supporting Information Table S3). Four patients died during the study, but there was no evidence that the cause of death was related to SCS therapy. A total of 23 events (21%) were considered related to the implant procedure and 49 events (46%) were considered related to the SCS device.

The most frequent serious complications, reported in 52 patients (13%), were hardware related and included lead/extension fracture/torqued contacts/connector issues (20 patients [5%]) and lead migration (11 patients [3%]). A total of 18 patients (4%) experienced events relating to the end of life of the INS. Considering local complications, the most frequently reported events were pain at the INS or incision site (seven patients [2%]) and infection (six patients [1%]) within 30 days of primary implant or replacement and three patients [1%] more than 30 days after implant).

Revision surgery associated with an SAE was performed in 64 patients (16%; 16% in the primo-implant group and 15% in the replacement group), while definitive device explants were performed in 16 patients (4%). For 84 patients (21%), SAEs were associated with a hospitalization.

FIGURE 4 Kaplan–Meier analysis of the responder rate in the primo-implantation group. Probability of being a responder (y-axis) in relation to FU (x-axis). The numbers at risk are given for each time point. At last scheduled FU, the probability of being a responder was 59.4% at which point 92 patients are still at risk



Time from inclusion [Month]	0	4	8	12	16	20	24
Number at Risk	260	226	211	187	166	147	92
Cumulative number of events	6	32	44	60	76	86	115
Cumulative number of censoring	1	3	6	14	18	27	145

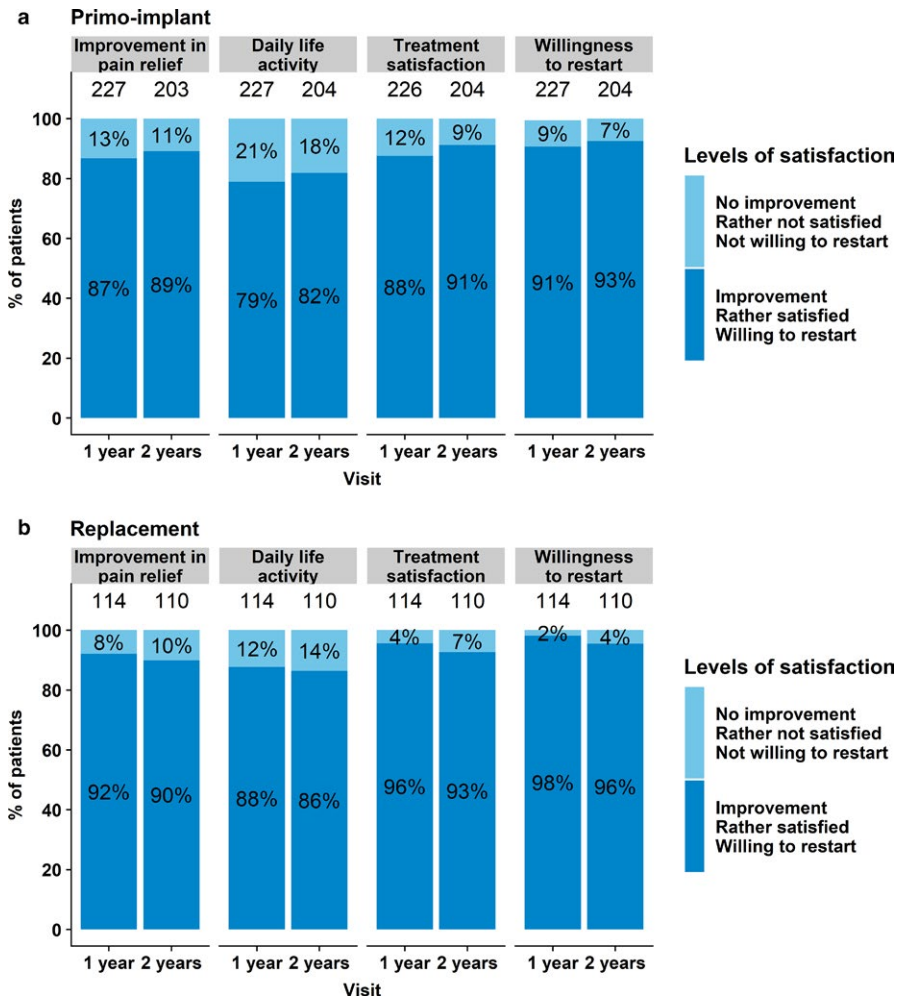


FIGURE 5 Patient satisfaction at 1 and 2 years—FAS. Number of patients with available data, % of patients by categories of satisfaction. In total, 229 and 208 primo-implant patients (a) had a visit at 1 and 2 years, respectively. In the replacement group (b), 116 and 113 patients had a visit at 1 and 2 years. FAS, full analysis set

Evolution of pain medication between baseline and last follow-up

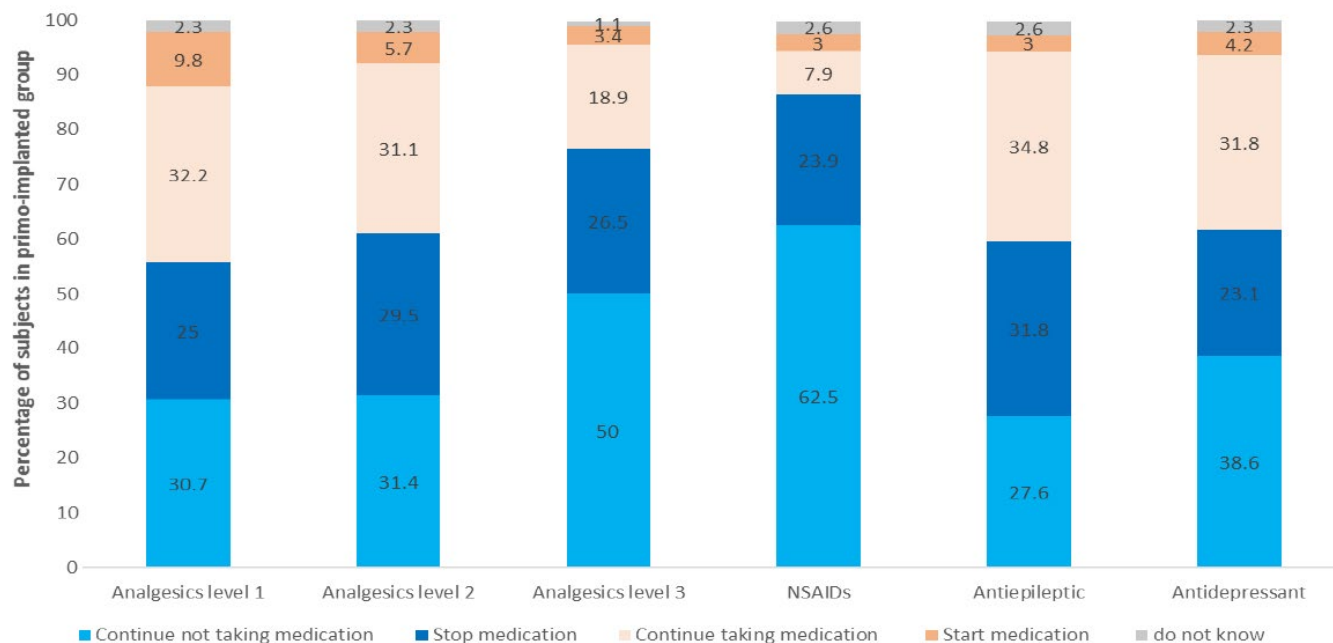


FIGURE 6 Concomitant use of pain medications in the primo-implant group. Proportion of patients having never taken, started, continued or stopped different pain medication types. Exact numbers are given in Supporting Information Table S2a,b

All of the 16 patients in whom the device was explanted were in the primo-implant group (6% of said group). Of the 16, eight were explanted at their request for inefficacy of the SCS, four because of infection, one was explanted soon after the implantation due to a neurological deficit (reversible). A further three patients were explanted after their pain had completely disappeared during the treatment and observation period (i.e., these patients were not explanted because of failure of the device).

Device deficiencies were reported in 31 patients (8%) during the study (Supporting Information Table S4).

4 | DISCUSSION

This observational study aimed to assess the effectiveness of SCS therapy and collect long-term safety information in patients with chronic refractory lower limb, back or upper limb pain from a representative sample of implanting sites in France. Patient demographics were very similar to those reported in the literature in terms of age and pain location (Gatzinsky et al., 2017; Kumar et al., 2008; Rosenberg et al., 2016). The median pain duration of 3.5 years at study entry for patients in the primo-implant group was shorter than the 10 years reported in the multicentre, observational EMP3OWER™ study (Rosenberg et al., 2016), but comparable with the “time since last surgery” reported in the PROCESS trial (Kumar et al., 2008).

In this study, in more than half the patients (59%) highly clinically relevant pain reduction (i.e., $\geq 50\%$) was reported for primo-implant patients. Furthermore, there was a high proportion of patients who reached what is considered to be a minimally clinically important difference in pain scores, that is, 30% pain relief (Farrar, Young, LaMoreaux, Werth, & Poole, 2001) in, respectively, 75%, 74% and 83% of patients with predominant pain in the lower limbs, back and upper limbs, respectively. Probability of being a responder (50% pain reduction) at 24 months of FU was close to 60% as seen on the KM curve.

These rates are similar to those reported in other registries (Gatzinsky et al., 2017; Rosenberg et al., 2016), although the follow-up in this study was longer (2 years vs. 1 year). Multi-focal pain was also treated, and pain reduction of $\geq 50\%$ was reported for primo-implant patients with non-predominant pain in lower limbs, back and upper limbs, with responder rates of 56%, 44% and 75% at 2 years, respectively. In line with the reported reduction in pain, a significant decrease in the use of all concomitant drug and non-drug treatments was observed at the 1-year visit and maintained after the 2-year follow-up. This is one of the first studies to show such a sustainable change in treatment use, especially the decrease of opioid treatment. In a study of sites across the Benelux region and Scandinavia, only a reduction in the proportion of patients taking antidepressants (31% to 19%) and antiepileptics (42% to 24%) was observed (Gatzinsky et al., 2017) at 1 year. However, this

TABLE 3 Device safety—FAS

Patients (N [%]) by group	Primo-implant (N = 264)	Replacement (N = 138)	Total (N = 402)
Patients with ≥ 1 adverse event (N [%])	123 (47)	41 (30)	164 (41)
Patients with ≥ 1 adverse event (level 1 and level 2 ^a) (N [%])			
Hardware related	52 (20)	26 (19)	78 (19)
INS issue or recharging equipment issue	3 (1)	3 (2)	6 (1)
INS Migration	1 (0)	1 (1)	2 (0)
INS end of life	15 (6)	11 (8)	26 (6)
Lead migration	20 (8)	4 (3)	24 (6)
Lead/extension fracture/torqued contacts	16 (6)	9 (7)	25 (6)
Programming/stimulation therapy	31 (12)	11 (8)	42 (10)
Loss of paraesthesia coverage (territory too small)	3 (1)	3 (2)	6 (1)
Loss of therapy effect	12 (5)	2 (1)	14 (3)
Persistent pain despite stimulation	13 (5)	0 (0)	13 (3)
Unpleasant sensation (shock like—unpleasant—territory too large)	4 (2)	7 (5)	11 (3)
Surgery/anaesthesia	24 (9)	3 (2)	27 (7)
Dural puncture	2 (1)	1 (1)	3 (1)
Inappropriate lead/INS positioning at implant	22 (8)	2 (1)	24 (6)
Local complications	43 (16)	8 (6)	51 (13)
Allergy	1 (0)	1 (1)	2 (0)
Focal reaction	1 (0)	0 (0)	1 (0)
Infection >30 days after final implant (or replacement during study)	5 (2)	2 (1)	7 (2)
Infection ≤ 30 days of final implant (or replacement during study)	9 (3)	1 (1)	10 (2)
Neurostimulator pocket: IPG seroma—Haematoma	5 (2)	0 (0)	5 (1)
Pain at IPG/incision site	22 (8)	4 (3)	26 (6)
Wound breakdown	2 (1)	0 (0)	2 (0)
Other (non-device related)	10 (4)	3 (2)	13 (3)
Death	3 (1)	1 (1)	4 (1)
New/increased pain due to new disc hernia	2 (1)	0 (0)	2 (0)
Other (non-device related)	6 (2)	2 (1)	8 (2)
Other (device related)	0 (0)	1 (1)	1 (0)
Other (device related)	0 (0)	1 (1)	1 (0)

INS: implantable neurostimulator.

^aLevel 1 and Level 2 categories used by the independent Scientific Committee.

may be due to the practice in France where focus is given to reducing drug and non-drug treatments (Attal et al., 2011). In addition, most patients reported satisfaction with treatment (91%) and with the improvement in pain relief (89%) and daily life activity (82%), with 93% of patients willing to undergo the treatment again. While patient satisfaction with treatment was reported at a similar level in the PROCESS trial (93%), satisfaction with pain relief at 2 years was higher in the patients included in this study (89% vs. 66%; Kumar et al., 2008). Very few patients chose to have their devices explanted during the study period with less than 6% explanations on request of the patient and not due to device complications.

The incidence of complications (41%) was similar to that reported in the literature (30-40%) and, in accordance with other studies, was primarily lead related and highest during the first 6 months (Eldabe, Buchser, & Duarte, 2016; Gatzinsky et al., 2017; Kumar et al., 2008). All complications were minor, with no deaths related to the implant or therapy and only one neurological deficit reported. In the primo-implant group, 28% of patients required revision surgery, similar to the study by Kumar et al. (2008) where revision surgery was reported in 31% of patients after a 2-year follow-up, with most revisions occurring in the first 12 months (79%). Device replacement is an expected event (end of life of the INS) and is not usually considered as a complication. Complications due to infection are a common reason for removal of SCS devices and can be expected given that the procedure involves part of the material being externalized for a few days during trial screening. In this study, trial screening was performed as per HAS guidelines. The relatively high infection rate observed in this study (5%) was within the 4%–10% range observed across studies in a recent review (Eldabe et al., 2016) despite the use of a conservative approach, whereby all suspected/possible infections where antibiotics were prescribed were included, even when infection was not confirmed.

Overall, the positive long-term efficacy and safety results obtained for patients receiving primary implants were similar for patients receiving replacements, demonstrating the stability of the treatment over time. Despite the costly replacement of an SCS device, the stability in pain intensity observed in the replacement group at 2 years is encouraging, suggesting that such treatment can continue to provide relief to patients.

4.1 | Study strengths and limitations

One of the limitations of this study relates to the fact that in the replacement group, data pertaining to the activity of the therapy at the time of INS replacement were not collected which limits baseline results interpretation/comparison as the group might include patients still under neurostimulation as well as patients with complete battery depletion.

Trialling data and programming parameters were also not collected. Trialling is used prior to implantation of a permanent device to screen out patients that are clearly not responders. This therefore induces an important selection bias in favour of the therapy. Trialling is mandatory in many European countries including France. HAS requires trialling to be performed but this is not enforced in daily practice. One assumes that most patients will receive trialling per the requirement, nevertheless in some situations the physicians may choose not to do so—for either objective reasons (such as high risk of surgical complications) or non-objective ones (such as local practice and habit). Given the observational nature of the study design, no trialling success criterion was included and selection of sites based on trialling practice was not performed. This renders the primo-implantation study group somewhat heterogeneous thus constituting a study limitation. However, it is also a strength in that the results reflect current standard of practice. Trialling is in general used in prospective randomized and non-randomized studies with similar overall results (Gatzinsky et al., 2017; Kumar et al., 2007; Rosenberg et al., 2016). Lack of selection based on trialling and potential inclusion of patients that would not be a responder to the therapy, also introduces the possibility for underestimating the responder rate.

As this study needed to remain non-interventional, quality of life was assessed through one question as no validated questionnaire was used in routine practice across all sites. This limitation carries over to the medication assessment that was for the most part only qualitative (except for opioids we only provide data as to whether a molecule was used or not). This renders objective analysis and transfer of results difficult; it would be desirable in more advanced registries to use a standardized medication scale such as the Medication Quantification Scale (Gallizzi, Gagnon, Harden, Stanos, & Khan, 2008). Moreover, no pain diary was used and assessment was based on patient recollection of pain intensity.

This product registry was sponsored by Medtronic to report on the outcome of patients implanted with their devices. There is the potential for bias in any company sponsored research. This study utilized a scientific committee of physicians and statistician to develop the protocol and oversee study execution and reporting. There is also potential selection bias as some practitioners may desire and use specific equipment for certain patients.

This large registry has several strengths and included patients who were assessed by a multidisciplinary team as suffering from refractory chronic pain and were characteristic of patients that typically receive SCS therapy in France. The study also had a very low overall dropout rate (12%) compared to other registries, despite the 2-year follow-up period (Gatzinsky et al., 2017, 20%; Rosenberg et al., 2016, 37%; both at 1-year follow-up). Importantly, the 28 sites included

in this study were representative of implanting centres in France, with regard to activity, lead implantation method and status. The number of patients selected was comparable to the largest series published and these patients were not treated within the constraints of a randomized controlled trial but rather followed along their clinical path by a registry. No intervention was performed, and patients were treated according to the best judgement of their physician, providing results that are more reflective of a real-life setting compared to controlled studies or observation alone. The request of the French authority was issued at a time where the practice of SCS in France has not only reached maturity (over 30 years of experience) but is also extensive, with close to 100 implanting centres nationwide. Therefore, it is safe to assume that the results presented reflect the real-life results and workings of an entire healthcare system at a country level. Furthermore, this pertinent study comes at a time when stringency within the regulatory and reimbursement environment is increasing and more evidence that supports efficacy in a real-life setting is required.

This study shows that the long-term efficacy of SCS is excellent, with good stability of the treatment at 2 years and beyond. Future studies may aim to identify the predictors of success in order to improve patient selection for permanent implantation. Since the traditional SCS used in this study produce tonic waveforms, further studies are needed to explore alternative forms of stimulation (Deer et al., 2014) and potentially increase the efficacy of SCS in a real-life setting.

5 | CONCLUSION

This observational, prospective study following a large cohort of patients suffering from chronic pain and implanted with SCS in a real-life setting showed that tonic SCS was safe and effective in a representative sample of implanting sites in France. Key improvements seen in pain scores as well as in drug and non-drug pain treatments were reflected in high patient satisfaction scores. Long-term effectiveness is confirmed by the KM curve showing nearly 60% of patients retaining a significant pain reduction. Safety was in line with the literature and continues to support the use of SCS in refractory pain patients. Pain intensity at 2 years was similar for patients in the replacement group, supporting the stability and long-term effectiveness of SCS.

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The sponsor (Medtronic International Trading Sarl) monitored the data collected independently by the sites, performed data management, statistical analysis and wrote the study report.

The sponsor also provided input in the study design (including case report form development), interpretation of the data and this publication.

CONFLICT OF INTEREST

PPL and CVdA are employees of Medtronic; EC, DF, PM and MCD are all consultants for Medtronic. DF is also a consultant for St Jude-Abbott and Autonomic Technologies. AB is a graduate of the St Jude European Neuromodulation Fellowship Program 2017.

AUTHOR CONTRIBUTIONS

AB, PM and MCD participated in patient management and data collection. PPL performed analyses. Members of the Scientific Committee (DF, EC and MCD) participated in the development of the protocol and case report form, and the review of the study results. All authors discussed the study results and commented on the manuscript and CVdA coordinated publication activities.

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