

## ORIGINAL ARTICLE

# The effect of the EXOPULSE Mollii Suit on pain and fibromyalgia-related symptoms—A randomized sham-controlled crossover trial

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## Abstract

**Background:** Fibromyalgia pain and related symptoms are poorly managed by approved pharmacological and alternative interventions. This trial aimed to evaluate the effects of the EXOPULSE Mollii Suit—a multisite transcutaneous electrical nerve stimulation device—on fibromyalgia pain, fatigue, affective symptoms, disease impact, and quality of life.

**Methods:** Adult patients with fibromyalgia were enrolled. Phase 1 implied a randomized, sham-controlled, cross-over, double-blind trial, applying daily 1 h sessions of active or sham intervention, over 2 weeks (2-week washout). In the open-label phase 2, all patients received daily active intervention for 4 weeks. Comparisons on pain, fatigue, disease impact, affective symptoms, quality of life, clinical impression, and comfort ratings were performed using Friedman, Wilcoxon signed rank, and Chi2 tests.

**Results:** Thirty-three patients completed the study (93.9% female, mean age: 51.3 years). Pain (primary endpoint assessed via a visual analog scale) was significantly reduced after the active (pre-active:  $6.9 \pm 1.4$ , post-active:  $5.9 \pm 1.8$ , pre-sham:  $6.8 \pm 1.4$ , post-sham:  $6.6 \pm 1.5$ ) versus the sham intervention ( $X^2 = 10.60$ ,  $p = 0.014$ ). This was also the case of other secondary endpoints (i.e., fatigue, anxiety, and disease impact), except depression and quality of life. The Clinical Global Impression of Change (CGI-C) was significantly different between the active and sham intervention periods ( $X^2 p = 0.035$ ), and the different proportions of categories were as follows: ‘worsening’ (sham: 18.2% vs. active: 0.0%), ‘improvement’ (sham: 48.5% vs. active 63.6%) or ‘no change’ (sham: 33.3% vs. active 36.4%) respectively. After phase 2, significant positive effects were observed for most of the outcomes, and 78.8% of patients reported improvement according to CGI-C.

**Conclusions:** This study suggests the clinical benefits of the EXOPULSE Mollii Suit in alleviating pain and fibromyalgia-related fatigue, emotional symptoms, and disease impact. It is worth noting that the study has several limitations

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related to the low number of participants, the short-term analysis of effects in the first blinded and controlled phase, and the open-label nature of phase 2. Future studies with a larger cohort and longer protocol treatment are needed, to further confirm the current results, and evaluate the long-term effects of this technique.

**Significance:** Patients with fibromyalgia suffer from pain as well as fatigue, sleep impairment, emotional disturbances, and altered quality of life. Transcutaneous electrical nerve stimulation might help manage those symptoms, but the available systems are limited by the fact that they could be applied at best over two sites. This randomized controlled study is the first to apply a multi-site transcutaneous electrical nerve stimulation device, the EXOPULSE Mollii Suit, with significant effects on fibromyalgia pain and related symptoms.

## 1 | INTRODUCTION

Fibromyalgia is a multifactorial and complex syndrome characterized by chronic and widespread pain affecting the musculoskeletal system, pressure sensitivity, and a low threshold to noxious stimuli (Fillingim et al., 2014; Treede et al., 2015). Besides pain, patients could suffer from several symptoms, including fatigue, sleep disturbance, as well as somatic, affective, and cognitive symptoms, and an altered quality of life (Burwinkle et al., 2005; Wolfe et al., 2014, 2015).

The aetiology of fibromyalgia is far from being uncovered. The interplay between some factors might be incriminated such as genetic predisposition, immune components, stressful life events, oxidative stress, neurotransmission, central sensitization, as well as emotional and cognitive mechanisms (Clauw et al., 2024; Pinto et al., 2023). Several central mechanisms have been proposed: a hyperactive nociceptive system, and/or a defective antinociceptive pain inhibitory system, possibly due to a GABAergic/glutamatergic imbalance (Schmidt-Wilcke & Clauw, 2011; Schmidt-Wilcke & Diers, 2017), and/or implication of the serotonergic and dopaminergic systems (Okifuji & Hare, 2013; Wolfe et al., 2014). Peripheral mechanisms have also been suggested, such as reduced blood flow, muscle hypoxia, and metabolic defects at the muscular level (Okifuji & Hare, 2013).

Despite the available diagnostic criteria (Macfarlane et al., 2017; Wolfe et al., 2010), setting the diagnosis remains a clinical challenge (Häuser et al., 2019). Its prevalence range from 0.2 to 6.6% and seems to increase with female sex, increasing age, comorbidities, and a family history of this condition (Heidari et al., 2017; Marques et al., 2017; Queiroz, 2013; Wolfe et al., 2013).

Fibromyalgia ranks in the third position among the most frequent musculoskeletal conditions (Sarzi-Puttini et al., 2020), rendering its management a public health concern. More than 40 molecules have been tested and

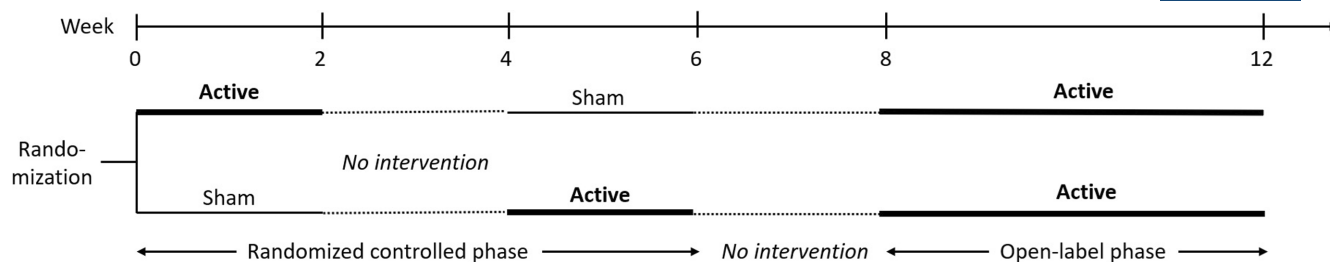
resulted in different benefits and side-effects profiles (Schmidt-Wilcke & Clauw, 2011; Schmidt-Wilcke & Diers, 2017). Current approved pharmacological treatments consist of antidepressants and antiepileptic drugs, but monotherapy rarely yields satisfactory management, with only 10%–25% of patients exhibiting meaningful pain reduction (Johnson et al., 2017; Taylor et al., 2019). In this context, a wide range of non-pharmacological methods have also been proposed.

Here, transcutaneous Electrical Nerve Stimulation (TENS) yielded promising results according to recent reviews and meta-analyses (Coskun Benlidayi, 2020; García-López et al., 2024). However, ‘classical’ TENS devices can only target a limited number of body sites (two to four sites), which does not address the widespread pain encountered in fibromyalgia. To overcome this issue, a multisite device might be of help in this context. EXOPULSE Mollii Suit, a full-body garment (jacket and pants) with 58 integrated electrodes, can transcutaneously stimulate 40 body sites, using a low-intensity electric current. EXOPULSE Mollii Suit appears to have promising effects when applied over a single one-hour session, in a few preliminary reports (Riachi et al., 2023; Rubio-Zarapuz et al., 2023, 2024). However, randomized controlled trials, with repeated sessions, are needed, to draw formal conclusions on the specific effects of this device, on pain and other symptoms, in patients suffering from this disease, as well as to assess the long-term effects of this intervention. This was the aim of the current study.

## 2 | METHODS

### 2.1 | Study design

The study consisted of two phases (Figure 1). The first one is a randomized, sham-controlled, double-blind, cross-over study, in which each participant was randomly



**FIGURE 1** Study design. During active and sham intervention periods, patients had daily 1 h sessions with the EXOPULSE Mollii Suit at home.

assigned to receive daily 1 hour active, or sham, stimulation. Stimulation conditions lasted 2 weeks each and were separated by a two-week washout interval. Randomization was performed by a research technician using a randomization list from the online tool Research Randomizer ([randomizer.org](http://randomizer.org)). Patients were randomized 1:1 to one or the other intervention sequence, with no further stratification criteria. The randomization list was blinded from anyone involved in informing potential study participants. The treatment allocation codes (referring to the stimulation conditions) were then put into sealed envelopes which remained closed until the end of the study. A research technician, trained to use EXOPULSE Mollii Suit, and not involved in any other step of the protocol, programmed control units for active and sham stimulation, both being strictly identical in their aspect and use, allowing double-blinding, both for investigators as well as participants.

The second phase is an open-label phase, that started at least 2 weeks following the end of the last stimulation session of phase 1, meaning that a washout interval of at least 2 weeks was respected between both phases. All participants received daily one-hour active stimulation sessions for four consecutive weeks.

## 2.2 | Study product and intervention

The EXOPULSE Mollii Suit (EXONEURAL NETWORK AB, Danderyd, Sweden) is made of two combined CE-marked medical devices: (i) body garments (jacket and pants, class I according to Regulation EU 2017/745), which contain embedded electrodes, conductive wires, and connectors, and (ii) a control unit (active class IIa), which is a battery-powered electrical device, that delivers low energy electric pulses through connectors to the body garments (Figure S1). The suit comes in 37 sizes (ranging from 104 cm up to 5XL) for women and men. The whole system provides non-invasive electro-stimulation, to key nerves and corresponding muscle groups, throughout the body (Figure S2). As stated previously, during both two-week intervention periods, the participants were

instructed to use the medical device 1 h per day and to perform the stimulation at rest. During active sessions, the device delivered an electric current, with a constant voltage of 20 V and a frequency of 20 Hz. During the sham sessions, the device delivered the same electric current for 1 minute only, then switched off automatically, enabling cutaneous sensations, that mimicked the active stimulation and maintained blinding. Patients can only turn the device on and off, but they cannot change the stimulation parameters.

Patients received a training session on EXOPULSE Mollii Suit usage, with instructions (paper and electronic format) provided as backup. Afterward, they were given the suit, with a control unit programmed for active or sham intervention, according to the sequence allocation, to perform home-based daily sessions for two consecutive weeks. Patients were instructed to return the material (suit and control unit) at the end of the first stimulation period. Following a washout interval of at least 2 weeks, they were given another set of materials (suit and control unit), to be returned at the end of the second stimulation period. Finally, an EXOPULSE Mollii Suit, and an active control unit, were provided for the open-label phase.

## 2.3 | Population

The study took place at the Clinical Neurophysiology Department of Henri Mondor Hospital (Créteil, France). Eligible patients were adults (18–75 years old), with a definite diagnosis of fibromyalgia, according to the American College of Rheumatology (ACR) 2010 criteria (Wolfe et al., 2010), for at least 1 month before inclusion, and suffered from pain, whose intensity was  $\geq 4$  on a visual analog scale ( $VAS_{\text{pain}}$ ) over the last week before inclusion (Jensen et al., 2003). Participants could not be included if they (i) had medical contraindications to wearing the suit (e.g., uncontrolled epilepsy, arrhythmias, cardiac stimulator, a ventriculoperitoneal shunt, intrathecal baclofen pump, pregnancy, and/or body mass index above 35 kg/m<sup>2</sup>), (ii) were suffering from other somatic diseases (i.e.,

other diseases causing osteoarticular and muscular pain) or psychiatric pathology (other than anxiety and depression), (iii) were included in another biomedical research protocol, (iv) were unable to submit to the medical follow-up of the study for geographical or social reasons, (v) or had changed their pharmacological treatment over the last 3 months. Pregnant women were also not eligible for inclusion.

Participants were screened for eligibility by one of the study investigators, who provided oral and written information about the study protocol. After a reflection period of at least 1 week, following the screening visit, patients were called by the investigator to confirm their willingness to participate in the study, then schedule baseline visits to finalize inclusion (i.e., verification of eligibility criteria, informed consent signature, baseline measures, and randomization). Apart from the screening visit, the protocol consisted of six visits: one at the beginning and one at the end of each of the three intervention periods (i.e., active and sham periods of phase 1 and the open-label phase 2).

Patients did not receive any compensation (financial or medical device) for their participation. They returned the medical device in question at the end of the study.

## 2.4 | Demographic and clinical data

Clinical and demographic data were collected from each participant, including age, sex, BMI, disease duration, pharmacological treatments, non-pharmacological approaches, the Widespread Pain Index (WPI) which measures the number of painful body regions (range: 0–19) and the Symptom Severity (SS) scale which assesses the severity of three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) from 0-no problem to 3-severe, and the extent of somatic symptoms in general from 0-no symptoms to 3-a great deal of symptoms. The SS scale score sums up these symptoms (range: 0 to 12).

## 2.5 | Study objectives

The study outcomes were assessed using questionnaires and scales that are validated in French, previously employed in French cohorts, and with good psychometric properties.

The primary objective of this study was to evaluate the short-term impact of EXOPULSE Mollii Suit on pain in adult patients with fibromyalgia. We hypothesized that using this device would reduce pain, as per  $VAS_{\text{pain}}$  measured at the end of the intervention periods of the randomized phase.  $VAS_{\text{pain}}$  consists of a 10cm horizontal

line over which the patient could place a mark between 0 (none) and 10 (unbearable) (Hayes & Patterson, 1921; Jensen et al., 2003; Perrot et al., 2010).

Secondary objectives aim to assess the effects of EXOPULSE Mollii Suit on fatigue, anxiety, depression, and quality of life, assuming a clinical benefit. The Brief Pain Inventory (BPI) was used to evaluate pain severity (4 items) and pain interference (7 items) (Brasseur, 1997). Each BPI item is rated on a 10-point scale ranging from 0 (no pain/does not interfere) to 10 (pain as bad as you can imagine/interferes completely) (Cleeland & Ryan, 1994; Sullivan et al., 1995).

The Pain Catastrophizing Scale (PCS) was employed to assess the presence and severity of feelings or thoughts that emerge when experiencing pain (13-item scale, each rated on a 5-point Likert scale ranging from 0—not at all to 4—all the time) (French et al., 2005).

$VAS_{\text{fatigue}}$ , a 10cm horizontal line used like  $VAS_{\text{pain}}$ , was adopted to evaluate the effects of this intervention on fatigue (Lee et al., 1991; Perrot et al., 2010).

The Fibromyalgia Impact Questionnaire (FIQ) was also used. It is an 11-item scale that assesses health status and functional disability, by exploring the impact of fibromyalgia on work, well-being, fatigue, sleep, stiffness, anxiety, and depression (Burckhardt et al., 1991; Perrot et al., 2003). FIQ total score and subscores range from 0 to 100, with higher scores reflecting worse health status.

The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety (7 items) and depression (7 items) (Boc er an & Dupret, 2014). Scores range from 0 to 21 on each subscale, with higher scores indicating worse symptomatology.

Quality of life was assessed via the Short Form 36 health survey (SF-36), which provides scores for eight dimensions (physical functioning, role-physical, role-emotional, bodily pain, general health, vitality, social functioning, and mental health), and a remaining item on the perception of health change. Each score ranges from 0 to 100, with a higher score implying better health status (Perneger et al., 1995; Ware & Gandek, 1998).

In order to account for potential day-to-day pain fluctuation, patients daily filled in  $VAS_{\text{pain}}$  over 1 week prior to each stimulation condition (average daily pain reporting at the end of the day over 1 week pre-sham and pre-active of phase 1 and 1 week pre-open label phase) and throughout the stimulation conditions (days 1–14 of each condition in phase 1, days 1–28 of phase 2). This yielded an average  $VAS_{\text{pain}}$  measure. In addition, to test the acute effects of the intervention on  $VAS_{\text{pain}}$ , the scale was completed before and after the first session of active and sham interventions.

In both phases, all the remaining questionnaires (except  $VAS_{\text{pain}}$ ) were completed before and after each

intervention period (before the first stimulation session and at the end of each condition of phase 1, before the first session and at the end of phase 2). In addition, the Clinical Global Impression of Change (CGI-C) was evaluated after each intervention period (Le Gal et al., 2010). It consists of a 7-point scale, ranging from 1-“very much improved since the initiation of treatment” to 7-“very much worse since the initiation of treatment” (Busner & Targum, 2007). Improvement was considered from 1 to 3, worsening from 5 to 7, and no change if 4. Participants were also asked to guess the type of stimulation received, active or sham at the end of each stimulation condition of phase 1, to assess blinding integrity, and were rated as follows: correct guess, wrong guess, and unable to guess.

## 2.6 | Statistical analysis

Considering the pilot nature of this work and the lack of previous studies applying EXOPULSE Mollii Suit in patients with fibromyalgia, sample size calculation did not rely on previous data. Sample size calculation was performed using G\*Power Software (version 3.1.9.6, Faul et al., 2007). When adopting the following parameters (medium effect size of 0.25, two-tailed significant difference of  $\alpha = 0.05$ , estimated power of 80%) and taking into account the risk of dropouts, a sample size of 34 was considered. Data were collected using a case report form (investigator) and self-questionnaires (patient), then entered in an electronic database (Excel file) for further statistical analysis performed using IBM SPSS Statistics for Windows (Version 29.0.2.0 Armonk, NY: IBM Corp). All endpoints collected during the randomized phase were compared, considering the intervention (active versus sham), and the time points (baseline versus end of each period). For the open-label phase, long-term effects were assessed, by comparing data at the start and end of the active intervention period. Since quantitative data did not follow a normal distribution (Shapiro–Wilk test), comparisons for the randomized phase were performed using Friedman's tests, using a covariate with four categories: active pre-intervention, active post-intervention, sham pre-intervention, and sham post-intervention. These were followed by post-hoc Dunn's tests with a Bonferroni p-value adjustment. In order to check if the patients who guessed the sham condition had different results from those who did not, the percentage of improvement for the primary outcome ( $VAS_{\text{pain}}$ ) was calculated following active and following sham conditions, and the percentage of improvement of the sham condition was subtracted from the active condition as previously described in the literature (Lefaucheur et al., 2011).  $\%VAS_{\text{pain}}(\text{active} - \text{sham}) = 100 \times \frac{VAS_{\text{preactive}} - VAS_{\text{postactive}}}{VAS_{\text{preactive}}}$

$-(100 \times \frac{VAS_{\text{presham}} - VAS_{\text{postsham}}}{VAS_{\text{presham}}})$ .  $\%VAS_{\text{pain}}(\text{active} - \text{sham})$  was compared between patients who guessed or not the sham condition. In a similar manner,  $\%VAS_{\text{pain}}(\text{active} - \text{sham})$  was compared between patients who received at least one treatment versus those who did not receive any medical treatment, as well as between those who received non-pharmacological interventions versus those who did not. The same analysis was repeated for each medication and nonpharmacological category using Mann–Whitney test when appropriate (i.e., analysis applied in the groups with at least 15% of the sample size under a specific medication or nonpharmacological therapy).

Wilcoxon signed-rank tests were used for the open-label phase. Significance was set at 0.05. The estimation of effect size was based on Kendall's coefficient of concordance  $W$  (randomized phase) and  $r = Z/\sqrt{N}$  (open-label phase). Categorical endpoints (CGI-C, and blinding integrity) were compared in phase 1 (active versus sham conditions) with the Chi-2 test. For all analyses, the effect size was classified as small ( $<0.3$ ), moderate ( $\geq 0.3$  and  $<0.5$ ) or large ( $\geq 0.5$ ). Quantitative variables are described with mean  $\pm$  standard deviation.

## 2.7 | Ethical approval and information

This clinical trial was prospectively registered on [clinicaltrials.gov](https://clinicaltrials.gov) as ‘EXOPULSE Mollii Suit and Fibromyalgia (EXOFIB)’ (NCT 05361577). The study was conducted in accordance with the ISO 14155 standard (Clinical investigation of medical devices for human subjects – Good clinical practice), and the European Union Regulation on medical devices (2017/745). The protocol was approved by an independent ethics committee (COMITÉ DE PROTECTION DES PERSONNES « EST IV ») on November 5, 2021. Following French legislation and regulatory requirements, the approval was sent for information to the French health authority (*Agence Nationale de sécurité du médicament et des produits de santé*, Saint-Denis, France) before the inclusion of the first participant. Written informed consent was obtained from all participants before enrollment into the study. Financial compensation was provided only for travel costs to study visits.

## 3 | RESULTS

Overall, 42 patients were screened initially. After the screening visits, 34 patients were recruited. The study took place between March 1, 2022, and July 31, 2023. The participation flow chart is presented in [Figure 2](#).

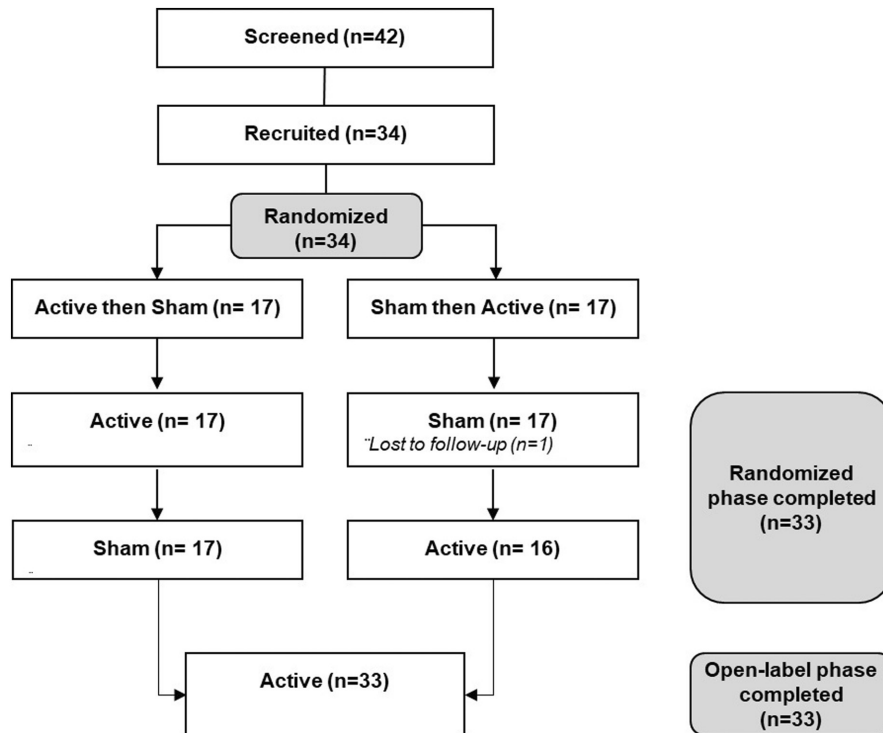


FIGURE 2 Participation flow chart.

### 3.1 | Clinical and demographic characteristics

Thirty-three patients completed both study phases ( $n=1$  dropout in the sham condition). 31 (93.90%) were female, and the mean age was  $51.33 \pm 8.99$  years. The mean BMI was  $26.55 \pm 5.42$  Kg/m<sup>2</sup>. At the time of inclusion, disease duration was  $8.94 \pm 10.74$  years. The WPI was  $14.15 \pm 3.36$  and the SS scale score was  $8.0 \pm 2.38$ . All patients had diffuse pain, and only two reported predominant pain in specific body regions (the lower limbs ( $n=1$ ), left hemibody ( $n=1$ )). No patients had pain-related surgery. There was no missing data.

The patients had the following controlled medical comorbidities: arterial hypertension ( $n=8$ ), migraine ( $n=8$ ), tension headache ( $n=2$ ), diabetes mellitus type 2 ( $n=2$ ), thyroid disease ( $n=6$ ), asthma ( $n=2$ ), polycystic ovary syndrome ( $n=2$ ), obstructive sleep apnea ( $n=2$ ), glaucoma ( $n=1$ ), atopic dermatitis ( $n=1$ ), fatty liver disease ( $n=1$ ), hepatitis B ( $n=1$ ) and endometriosis ( $n=1$ ).

With regards to medication profile, 84.85% of patients received at least 1 pharmacological treatment and only 15.15% did not receive any medication. Patients were receiving antiepileptics ( $n=6$ ), antidepressants ( $n=18$ ), anxiolytics ( $n=6$ ), opioids analgesics ( $n=5$ ), combined opioids and acetaminophen medications ( $n=10$ ), anti-inflammatory ( $n=9$ ), acetaminophen ( $n=13$ ), nefopam ( $n=5$ ), baclofen ( $n=2$ ), lidocaine transdermal patch ( $n=4$ ), and cannabinoids ( $n=3$ ). Physical therapy ( $n=20$ ) and other nonpharmacological methods [hypnosis ( $n=4$ ),

physical exercise ( $n=4$ ), auriculotherapy ( $n=2$ ), yoga and meditation ( $n=2$ ), osteopathy ( $n=2$ ), acupuncture ( $n=1$ ), and music therapy ( $n=1$ )] were also adopted.

There were no missing days of treatment based on patients' reporting.

### 3.2 | Randomized phase

Blinding integrity was preserved, as the rates of guessing the intervention type did not differ between active and sham conditions ( $X^2=0.792$ ;  $p=0.673$ ): wrong guess (18.20% vs. 12.10%; respectively), correct guess (48.50% vs. 45.50%, respectively), and unable to guess (33.33% vs. 42.4%, respectively). When adopting forced guessing for patients who were unable to guess, the differences remained nonsignificant ( $X^2=0.580$ ;  $p=0.447$ ): wrong guess (42.40% in active vs. 33.33% in sham) and correct guess (57.60% vs. 66.67%, respectively).

When comparing %VASpain (active – sham) between who guessed or not the sham condition (correct guess 45.59% vs. wrong guess 12.10% vs. unable to guess 42.40%), Kruskal-Wallis test was nonsignificant ( $p=0.593$ ). The same results were obtained when running Mann-Whitney test on data obtained with forced guessing (correct guess 66.67% vs. wrong guess 33.33%,  $p=0.721$ ).

The CGI-C distribution was significantly different between the active and sham intervention periods ( $p=0.035$ ): clinical worsening was reported for 0% versus 18.18% of participants ( $p<0.05$ ), clinical improvement for

63.64% versus 48.48% ( $p > 0.05$ ), and no change for 36.36% versus 33.33% of participants ( $p > 0.05$ ) respectively, for active versus sham stimulation.

Results from the randomized phase for efficacy endpoints are detailed in Table 1. With regards to the primary endpoint (VAS<sub>pain</sub>), Friedman's test of differences was statistically significant ( $p = 0.014$ ). The posthoc Dunn's test

revealed a significant decrease in VAS<sub>pain</sub> after the active intervention period (pre-active VAS<sub>pain</sub>:  $6.85 \pm 1.36$ ; post-active VAS<sub>pain</sub>:  $5.91 \pm 1.83$ , Dunn's  $p = 0.029$ ) (Figure 3). No significant difference was observed between pre-and post-VAS<sub>pain</sub> for the sham intervention, nor between the active and sham interventions for pre-VAS<sub>pain</sub> (Dunn's  $p = 1.000$ ). The results were also significant right after the first active

**TABLE 1** Summary of efficacy endpoints before and after each two-week intervention period (randomized phase).

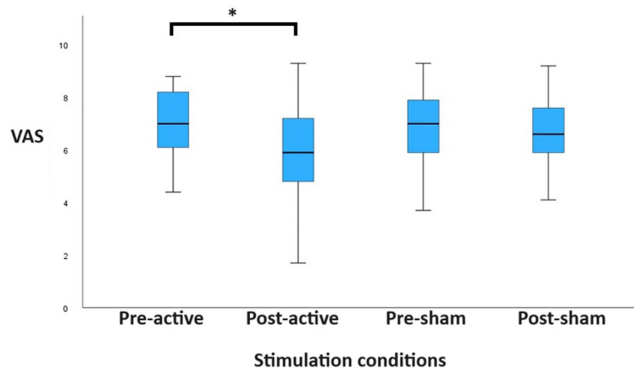
Efficacy endpoints	Active intervention		Sham intervention		p-value <sup>a</sup>	Effect size <sup>b</sup>
	Pre-score	Post-score	Pre-score	Post-score		
VAS <sub>pain</sub> (average)	<b>6.85 ± 1.36</b>	<b>5.91 ± 1.83</b>	6.80 ± 1.44	6.63 ± 1.45	<b>0.014</b>	0.11
VAS <sub>pain</sub> (1st session)	<b>6.59 ± 2.13</b>	<b>4.91 ± 2.33</b>	6.47 ± 1.77	6.47 ± 2.06	<b>0.001</b>	0.16
VAS <sub>fatigue</sub>	6.87 ± 1.89	6.50 ± 1.81	6.89 ± 1.65	6.62 ± 1.80	0.120	0.06
BPI <sub>total</sub>	5.97 ± 1.57	5.20 ± 1.99	5.72 ± 1.46	5.34 ± 1.83	0.157	0.05
BPI <sub>pain severity</sub>	5.84 ± 1.54	5.33 ± 1.94	5.91 ± 1.17	5.75 ± 1.61	0.417	0.03
BPI <sub>pain interference</sub>	<b>6.11 ± 1.83<sup>#</sup></b>	<b>5.12 ± 2.38</b>	5.58 ± 2.05 <sup>#</sup>	5.75 ± 1.61	<b>0.005</b>	0.13
FIQ <sub>total</sub>	<b>52.11 ± 13.84</b>	<b>42.85 ± 17.78</b>	51.52 ± 13.15	45.26 ± 14.90	<b>&lt;0.001</b>	0.20
FIQ <sub>physical impairment</sub>	<b>5.45 ± 2.03</b>	<b>4.39 ± 2.23</b>	5.00 ± 1.96	5.09 ± 2.55	<b>0.003</b>	0.14
FIQ <sub>feel good</sub>	7.28 ± 3.08	6.62 ± 3.15	7.62 ± 2.13	6.66 ± 2.64	0.100	0.06
FIQ <sub>pain</sub>	<b>7.46 ± 1.82</b>	<b>6.18 ± 2.42</b>	7.30 ± 1.86	6.61 ± 1.92	<b>0.027</b>	0.09
FIQ <sub>fatigue</sub>	<b>7.59 ± 1.98</b>	<b>6.33 ± 2.32</b>	7.47 ± 2.00	6.73 ± 2.26	<b>0.045</b>	0.08
FIQ <sub>rested</sub>	<b>7.12 ± 2.39</b>	<b>5.52 ± 2.83</b>	7.42 ± 2.27	5.85 ± 2.53	<b>&lt;0.001</b>	0.17
FIQ <sub>stiffness</sub>	<b>6.60 ± 2.64</b>	<b>5.53 ± 2.84</b>	6.75 ± 2.70	5.93 ± 2.38	<b>0.018</b>	0.10
FIQ <sub>depression</sub>	4.68 ± 2.91	3.78 ± 2.99	4.40 ± 3.02	3.91 ± 2.92	0.241	0.04
FIQ <sub>anxiety</sub>	<b>5.95 ± 2.66</b>	<b>4.48 ± 2.95</b>	5.55 ± 2.86	4.47 ± 2.60	<b>0.002</b>	0.15
HADS <sub>depression</sub>	9.76 ± 4.60	9.45 ± 5.15	10.36 ± 4.26	10.06 ± 4.96	0.355	0.03
HADS <sub>anxiety</sub>	10.73 ± 4.38	9.33 ± 4.83	10.24 ± 4.17	9.42 ± 4.62	0.068	0.07
HADS <sub>total</sub>	20.48 ± 7.69	18.79 ± 9.00	20.61 ± 7.52	19.48 ± 8.57	0.340	0.03
PCS <sub>total</sub>	29.61 ± 12.56	23.82 ± 13.69	29.72 ± 11.58	27.06 ± 12.90	0.199	0.05
PCS <sub>ruminantion</sub>	10.09 ± 4.52	8.24 ± 4.64	10.12 ± 4.00	9.12 ± 4.86	0.667	0.02
PCS <sub>magnification</sub>	5.18 ± 3.14	4.55 ± 3.34	5.52 ± 3.39	4.94 ± 3.40	0.495	0.02
PCS <sub>helplessness</sub>	14.33 ± 6.15	11.03 ± 6.67	14.09 ± 5.72	13.00 ± 5.92	<b>0.048</b>	0.08
SF-36 <sub>physical functioning</sub>	39.09 ± 21.23	43.48 ± 24.57	42.42 ± 19.61	42.12 ± 23.25	0.436	0.03
SF-36 <sub>role physical</sub>	29.55 ± 35.61	33.33 ± 34.04	16.67 ± 29.76	18.18 ± 28.83	<b>0.012</b>	0.11
SF-36 <sub>role emotional</sub>	31.31 ± 39.91	50.41 ± 40.98	32.32 ± 41.24	42.42 ± 41.90	<b>0.017</b>	0.10
SF-36 <sub>vitality</sub>	<b>21.52 ± 16.61</b>	<b>31.53 ± 32.24</b>	21.23 ± 13.38	26.41 ± 20.79	<b>0.004</b>	0.14
SF-36 <sub>mental health</sub>	45.39 ± 18.95	51.21 ± 22.63	44.64 ± 21.77	50.97 ± 23.04	0.326	0.04
SF-36 <sub>social functioning</sub>	42.67 ± 24.89	49.24 ± 26.87	41.29 ± 26.05	46.59 ± 28.17	0.170	0.05
SF-36 <sub>bodily pain</sub>	<b>27.27 ± 22.56</b>	<b>40.14 ± 25.58</b>	23.48 ± 17.45	30.30 ± 18.77	<b>&lt;0.001</b>	0.23
SF-36 <sub>general health</sub>	35.38 ± 15.03	38.03 ± 20.11	31.85 ± 16.33	33.73 ± 16.71	0.144	0.06
SF-36 <sub>health change</sub>	38.64 ± 28.01	40.15 ± 32.44	31.33 ± 27.50	33.33 ± 27.00	<b>0.018</b>	0.10

Note: Data are mean ± standard deviation.

Abbreviations: BPI, brief pain inventory; FIQ, fibromyalgia impact questionnaire; HADS, hospital anxiety and depression scale; PCS, pain catastrophizing scale; SF-36, short-form 36 health survey; VAS, visual analog scale.

<sup>a</sup>p-value from Friedman's test comparing all four interventions (active/sham)\*time(pre-/post-) values.

<sup>b</sup>Kendall's W. Bolded values represent significant p-values (<0.05) for both Friedman's and post-hoc Dunn's tests. Some of Friedman's test p values were significant, but post hoc analysis did not reveal significant differences between pre-and post-active intervention. # Baseline scores comparison with post-hoc Bonferroni correction:  $p = 0.052$ .



**FIGURE 3** Pain scores before and after active and sham periods of stimulation (randomized phase). VAS, Visual Analog Scale (10 cm scale). \* $p=0.014$  for Friedman's test (global test) and 0.029 for the post-hoc Dunn's test (pre-active versus post-active values).

session compared to sham (Friedman's test  $p=0.001$ ;  $VAS_{\text{pain}}$  before the first active session:  $6.59 \pm 2.13$ ;  $VAS_{\text{pain}}$  after the first active session:  $4.91 \pm 2.33$ , Dunn's  $p=0.003$ ).

No statistically significant difference in the percentage of improvement ( $\%VAS_{\text{pain}}(\text{active} - \text{sham})$ ) between the patients who were receiving or not pharmacological treatments (treated vs. untreated). Similarly, the percentage of improvement in  $VAS_{\text{pain}}$  did not significantly differ between patients who were receiving alternative interventions compared to those who did not.

In addition, a significant reduction in pain was also observed following the active intervention (pre- versus post-values) when assessed via the BPI, FIQ, and SF-36 ( $BPI_{\text{pain interference}}$ ,  $FIQ_{\text{pain}}$ ,  $SF-36_{\text{bodily pain}}$ , respectively). However, no change was found in  $PCS_{\text{total}}$ , or in its subscales, which assess cognition related to pain (helplessness, rumination, and magnification).

Fatigue also significantly decreased following the active, but not the sham, intervention periods, as per  $FIQ_{\text{fatigue}}$ ,  $FIQ_{\text{rested}}$ , and  $SF-36_{\text{vitality}}$  but not  $VAS_{\text{fatigue}}$ . Similarly, a statistically significant (or almost significant) difference after active intervention periods only was found with regards to some anxiety-related endpoints (i.e.,  $FIQ_{\text{anxiety}}$  but not  $HADS_{\text{anxiety}}$ ) and to disease impact ( $FIQ_{\text{total}}$ ,  $FIQ_{\text{physical impairment}}$ ,  $FIQ_{\text{stiffness}}$ ). Conversely, depression-related endpoints ( $HADS_{\text{depression}}$ ,  $FIQ_{\text{depression}}$ ) were not significantly modified by any intervention. Lastly, no significant effects were observed on the remaining quality of life dimensions (SF-36 scores for physical functioning, role-physical, role-emotional, mental health, social functioning, general health, and health change).

For all endpoints that showed a benefit of the active intervention, the effect size was small, ranging from 0.08 to 0.23. The most important effect sizes were observed for  $SF-36_{\text{pain}}$  scores (0.23) and  $FIQ_{\text{total}}$  (0.20). The whole results are represented in Figure S3.

### 3.3 | Open-label phase

Results for efficacy endpoints from the open-label phase are detailed in Table 2. Improvement was reported for 78.8% of patients at the end of the 4-week active intervention period, as per the CGI-C. Following 1 month of intervention, the Wilcoxon signed rank tests yielded statistically significant effects for most of the study outcomes:  $VAS_{\text{pain}}$ ,  $VAS_{\text{fatigue}}$ ,  $BPI_{\text{total}}$  and both BPI subscales (pain severity and interference),  $PCS_{\text{total}}$  and all PCS subscales (rumination, magnification, and helplessness),  $HADS_{\text{anxiety}}$ ,  $HADS_{\text{depression}}$ ,  $FIQ_{\text{total}}$  and most FIQ subscales (physical impairment, feel good, pain, fatigue, rested, stiffness, and anxiety), and most of SF-36 scores (physical functioning, role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, and health change). Conversely,  $SF-36_{\text{general health}}$  and  $FIQ_{\text{depression}}$  did not change significantly following intervention. The effect sizes ranged from 0.25 (small) to 0.54 (large), with the highest reported for  $VAS_{\text{pain}}$ . Figure S4 provides a graphical representation of the whole results.

### 3.4 | Tolerance

All the stimulation sessions were well tolerated, and no serious adverse events were reported at any time.

## 4 | DISCUSSION

The present study is the first randomized controlled trial carried out to investigate the efficacy of EXOPULSE Mollii Suit in patients with fibromyalgia. It is also the first study to explore mid- and long-term treatment, made of repeated daily sessions (i.e., 2 weeks during the randomized phase, and 4 weeks in the open-label phase). This design suggests analgesic effects of the therapy, as reflected by the improvement in the primary outcome ( $VAS_{\text{pain}}$ ) after 2 weeks of active intervention compared to sham.

The present results are in line with previous data from studies on the acute effects of a single EXOPULSE Mollii Suit session in fibromyalgia (Riachi et al., 2023; Rubio-Zarapuz et al., 2023, 2024). The results of both phases converge to confirm the analgesic potential of EXOPULSE Mollii Suit, which is potent after two weeks and appears strengthened when the treatment lasts a longer time (i.e., four weeks). The mean  $VAS_{\text{pain}}$  decreased by almost 1 cm (on a 10cm scale) after two weeks, and by 1.7cm after four weeks of daily active sessions. Although we did not find in the literature any assessment of the minimal clinically important difference for this criterion in the context of fibromyalgia, the second change appears clinically

**TABLE 2** Summary of efficacy endpoints before and after the 4-week active intervention period (open phase).

Efficacy endpoints	Pre-score	Post-score	p-value <sup>a</sup>	Effect size <sup>b</sup>
VAS <sub>pain</sub>	6.73 ± 1.72	5.06 ± 2.35	<0.001	0.54
VAS <sub>fatigue</sub>	6.87 ± 1.90	5.60 ± 2.34	<0.001	0.45
BPI <sub>total</sub>	5.78 ± 1.98	4.79 ± 2.15	<b>0.003</b>	0.36
BPI <sub>pain severity</sub>	5.84 ± 1.84	4.88 ± 2.27	<b>0.007</b>	0.31
BPI <sub>pain interference</sub>	5.74 ± 2.31	4.74 ± 2.36	<b>0.002</b>	0.38
FIQ <sub>total</sub>	48.83 ± 15.05	38.78 ± 18.16	<0.001	0.48
FIQ <sub>physical impairment</sub>	5.22 ± 2.27	4.62 ± 2.22	<b>0.017</b>	0.29
FIQ <sub>feel good</sub>	7.14 ± 2.28	5.37 ± 3.29	<b>0.006</b>	0.33
FIQ <sub>pain</sub>	6.87 ± 2.17	5.15 ± 2.55	<0.001	0.46
FIQ <sub>fatigue</sub>	7.19 ± 2.14	5.76 ± 2.46	<0.001	0.47
FIQ <sub>rested</sub>	6.54 ± 2.54	5.36 ± 2.68	<b>0.002</b>	0.38
FIQ <sub>stiffness</sub>	6.45 ± 2.55	5.27 ± 2.76	<b>0.002</b>	0.38
FIQ <sub>depression</sub>	4.31 ± 3.25	3.50 ± 3.04	0.091	0.21
FIQ <sub>anxiety</sub>	5.10 ± 2.78	3.75 ± 2.84	<b>0.012</b>	0.31
HADS <sub>depression</sub>	10.09 ± 5.60	8.91 ± 5.37	<b>0.038</b>	0.26
HADS <sub>anxiety</sub>	9.94 ± 4.44	8.54 ± 4.50	<b>0.006</b>	0.34
HADS <sub>total</sub>	20.03 ± 9.14	17.45 ± 9.20	<b>0.003</b>	0.37
PCS <sub>total</sub>	24.67 ± 14.98	20.36 ± 14.02	<b>0.004</b>	0.35
PCS <sub>ruminantion</sub>	8.27 ± 5.17	6.85 ± 4.66	<b>0.009</b>	0.32
PCS <sub>magnification</sub>	4.91 ± 3.68	3.67 ± 3.28	<b>0.004</b>	0.35
PCS <sub>helplessness</sub>	11.48 ± 7.07	9.85 ± 6.89	<b>0.039</b>	0.25
SF-36 <sub>physical functioning</sub>	41.51 ± 21.60	47.73 ± 22.64	<b>0.025</b>	0.28
SF-36 <sub>role physical</sub>	17.42 ± 26.13	45.45 ± 39.75	<0.001	0.46
SF-36 <sub>role emotional</sub>	25.25 ± 38.22	48.48 ± 40.05	<b>0.011</b>	0.31
SF-36 <sub>vitality</sub>	24.85 ± 18.56	38.33 ± 23.14	<0.001	0.44
SF-36 <sub>mental health</sub>	47.34 ± 22.99	54.30 ± 23.83	<b>0.017</b>	0.29
SF-36 <sub>social functioning</sub>	46.21 ± 28.04	55.68 ± 30.47	<b>0.004</b>	0.36
SF-36 <sub>bodily pain</sub>	32.35 ± 21.47	41.27 ± 22.44	<b>0.043</b>	0.25
SF-36 <sub>general health</sub>	34.73 ± 18.26	36.18 ± 19.99	0.128	0.19
SF-36 <sub>health change</sub>	37.12 ± 29.40	50.00 ± 34.80	<b>0.002</b>	0.38

Note: Data are mean ± standard deviation.

Abbreviations: BPI, brief pain inventory; FIQ, fibromyalgia impact questionnaire; HADS, hospital anxiety and depression scale; PCS, pain catastrophizing scale; SF-36, short-form 36 health survey; VAS, visual analog scale.

<sup>a</sup>p-value from the Wilcoxon signed rank test comparing pre-/post-intervention values.

<sup>b</sup>(Z/√N). Bolded values represent endpoints that are statistically significantly different ( $p < 0.05$ ) prior to and after the active intervention.

relevant, by analogy with chronic musculoskeletal pain, measured on a numerical rating scale (Fleagle et al., 2024; Salaffi et al., 2004). VAS has good psychometric properties for assessing pain (Campbell & Lewis, 1990; Kahl & Cleland, 2005) a high sensibility and sensitivity, and a good discriminative power in patients with fibromyalgia (80%, 80% and 0.864, respectively) (Marques et al., 2008). Investigating the acute effects of EXOPULSE Mollii Suit on 50 patients with fibromyalgia, Riachi et al. found a change in VAS<sub>pain</sub> immediately after a single one-hour

session, and the change was still significant 24 hours later (Riachi et al., 2023).

Furthermore, our results suggest that the multisite stimulation delivered by EXOPULSE Mollii Suit also improved fatigue during the controlled phase, and more during the open-label phase. Analgesic and anti-fatigue effects were associated with an improvement in fibromyalgia-related stiffness and anxiety and a better perception of health change. Depression scores, some pain-induced behaviours, and several quality-of-life

domains did not significantly improve during the randomized phase. Still, most of them did after the open-label phase of the study. Comparing the higher number of significantly improved endpoints observed during the four-week intervention to those from the two-week intervention, it can be inferred that applying a long-term treatment might help increase the clinical improvement. It can also be hypothesized that longer treatment periods would durably improve mood disorders and quality of life. However, it is worth stating that, in the absence of a control condition, the results of the open-label phase should be interpreted with caution as it is not possible to rule out sham effects.

A multimodal treatment approach for fibromyalgia is needed since pathophysiological mechanisms interact with the psychological ability of individuals to cope with this chronic disease in a long-term perspective, and since no isolated strategy has so far proven its effectiveness (Sarzi-Puttini et al., 2020). Non-invasive electrotherapy techniques provide promising results in alleviating pain while causing negligible side effects (Coskun Benlidayi, 2020). Further research on EXOPULSE Mollii Suit protocols is required to optimize the benefits of treatment, together with the acceptability and adherence of patients: duration and frequency of sessions, overall duration, daily schedule, association with pharmacological or alternative strategies, adjustments based on individual's response, etc. (Perpetuini et al., 2023). The protocol chosen in this trial—one-hour daily sessions—was very well tolerated. Future studies on larger samples and with longer-term treatment should be planned to guide the therapeutic use of EXOPULSE Mollii Suit in fibromyalgia.

The mechanisms involved in the analgesic efficacy of this method remain to be elucidated. To start, transcutaneous electrical stimulation could exert effects at the peripheral (impulse blockade), segmental (spinal), and extra-segmental (supraspinal descending inhibition) levels (Johnson, 2021).

The rationale for using transcutaneous electrical stimulation for pain relief primarily refers to gate control theory, according to which, stimulation of large proprioceptive fibres would inhibit the nociceptive information transmitted by small fibres (Melzack & Wall, 1965). In this work, EXOPULSE Mollii Suit effects could have resulted from this mechanism. In addition, its impact may have arisen from other peripheral mechanisms (e.g., involving muscular, vascular, and immune factors). For instance, a case report and a randomized controlled trial performed on fibromyalgia found that a unique one-hour session of this device triggered a drastic increase in muscle oxygenation documented using near-infrared

spectroscopy (a device that measures muscle oxygen saturation (SmO<sub>2</sub>), total haemoglobin (tHb), oxygenated haemoglobin (O<sub>2</sub>Hb) and deoxygenated haemoglobin (HHb)) (Rubio-Zarapuz et al., 2023, 2024). Indeed, the impairment of muscle oxygen utilization could lead to muscular fatigue, and reduced exercise tolerance, as observed in fibromyalgia (Shang et al., 2012), while pain could result from muscle ischemia and local vasoconstriction (Katz et al., 2007). Also, while oxidative stress has been incriminated in fibromyalgia pathophysiology, antioxidative strategies might have some benefit in this condition (Assavarittirong et al., 2022). Therefore, EXOPULSE Mollii Suit might improve fibromyalgia pain and fatigue by reversing the abnormalities mentioned above. Moreover, previous works have suggested a reduction in the level of pro-inflammatory cytokines (i.e., interleukin-6) in patients with pain, which might also apply in the case of EXOPULSE Mollii Suit and fibromyalgia (Johnson, 2021).

Besides peripheral mechanisms, EXOPULSE Mollii Suit might have effects at the central level, as found in previous studies evaluating transcutaneous electrical nerve stimulation. For instance, in some works, transcutaneous electrical nerve stimulation resulted in changes in several metabolites in the cerebrospinal fluid (glutamate, aspartate, enkephalins, and endorphins) and cortical electrical waves (Ong Sio et al., 2023).

Finally, the effects of EXOPULSE Mollii Suit, on other fibromyalgia symptoms and impact, could be discussed and explained in the light of the biopsychosocial model of fibromyalgia, which consists of sensory, immune, emotional, cognitive, and social factors, among others (Clauw et al., 2024; Popkirov et al., 2020). The model implies bidirectional interaction among these factors involved in pain processing, perception, psychobehavioral, and social factors. The effects of EXOPULSE Mollii Suit might be exerted on one or several components of this model. For instance, analgesic effects per se (as per pain scales) might subsequently result in, or be associated with, less fatigue, less anxiety/stress, more ability to engage in social activities, and less disease impact. This is in line with the positive results observed in the first phase of the study, and the additional improvement noted following a longer treatment period, as shown in the open-label phase of the trial.

When discussing pain, it is important to mention the sensory (nociceptive), cognitive, and emotional components of its so-called matrix (Bushnell et al., 2013; Garcia-Larrea & Peyron, 2013). While the nociceptive component has improved following phase 1, pain-related cognitive processes (i.e., catastrophizing) and emotional experience (i.e., namely depression) might

require more time to reach statistically significant improvement, as observed at the end of phase 2. Here, it is noteworthy that some authors have applied functional brain neuroimaging and raised the hypothesis supporting the influence of catastrophizing on pain perception, via the modulation of cognitive and emotional responses to pain (Gracely et al., 2004). This was supported by an association between pain catastrophizing and increased activity in cerebral areas, involved in pain attention and anticipation (frontal, cerebellar, cingulate regions), and emotional aspect of pain (claustrum) (Gracely et al., 2004). In this context, EXOPULSE Mollii Suit might have yielded delayed effects on catastrophizing and depressive symptoms, which in turn, might have further increased the analgesic response and quality of life. This could be reflected by the additional clinical improvement reported at the end of phase 2 in terms of pain scores, clinical global impression of change, and quality of life.

While this study was the first randomized controlled trial carried out on the EXOPULSE Mollii Suit, some limitations can be highlighted. For instance, the trial was conducted in a single center, so the global care of patients cannot be extrapolated to the general population. In addition, the study is performed in a relatively small sample and over only two weeks per stimulation condition and four weeks in the open-label phase. Therefore, the current results merit to be replicated in larger cohorts and a longer follow-up duration. In addition, as previously stated, the one cannot rule out a potential placebo effects in the open-label phase. Also, only 6.1% of males were included in the cohort, which corresponds to the rate of males referred with fibromyalgia in clinical practice. Still, it is far lower than data from unbiased studies (>40%), which suggests a dramatic underdiagnosis of men (Wolfe et al., 2018). Moreover, although the blinding test yielded nonsignificant results between active and sham, some patients were able to guess the type of stimulation. Furthermore, there was no tracking system to monitor how long the suit was being used per day, or whether the stimulation duration was limited to once per day. Therefore, future studies would benefit from replicating the results with a trackable and controllable version of the medical device. However, despite the mentioned limitations, it is important also to note that the recruited cohort consisted of patients with chronic fibromyalgia (mean and median disease duration: 8.9 and 5 years, respectively) and who were already receiving pharmacological and non-pharmacological interventions (i.e., analgesics, antidepressants, anxiolytics, physical therapy, and other alternative interventions). This could emphasize the

potential beneficial effects of EXOPULSE Mollii Suit in patients with chronic fibromyalgia, suffering from insufficient response to the available management options.

## 5 | CONCLUSION

In conclusion, we observed the benefit of daily one-hour sessions of EXOPULSE Mollii Suit to alleviate pain and related-symptoms, in adult patients with fibromyalgia, after 2 weeks of intervention. This strategy appears promising, in the context of debilitating and difficult-to-manage diseases, such as fibromyalgia. Its potential utility in the management of fibromyalgia symptoms merits further exploration.

### AUTHOR CONTRIBUTIONS

J.G.M., M.A.C, M.S., J.P.L., S.S.A: Design and conceptualization of the study. M.A.C. and J.P.L: Statistical analysis and visualization. J.G.M: Data collection. G.N.A.L: Data curation. S.S.A: Supervision and project administration. J.G.M., M.A.C, N.O., J.L.G., J.P.L, G.N.A.L, S.S.A: Data interpretation. J.G.M., M.A.C, S.S.A: Writing- Original draft preparation. J.G.M, M.A.C., N.O, M.S., J.L.G., J.P.L., G.N.A.L., S.S.A: Writing- Reviewing and Editing. All authors read, commented on, and approved the final version of the manuscript.

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SA declares having received compensation from Sanofi Aventis, France; Novartis, France; Exoneural Network AB, Sweden and Ottobock, France. MC declares having received compensation from Janssen Global Services LLC, Exoneural Network AB, Sweden, and Ottobock, France. The remaining authors declare no conflicts of interest.

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## REFERENCES

- Assavarittirong, C., Samborski, W., & Grygiel-Górniak, B. (2022). Oxidative stress in fibromyalgia: From pathology to treatment. *Oxidative Medicine and Cellular Longevity*, 2022, 1582432.
- Bocéréan, C., & Dupret, E. (2014). A validation study of the hospital anxiety and depression scale (HADS) in a large sample of French employees. *BMC Psychiatry*, 14, 354.
- Brasseur, L. (1997). *Traitement de la Douleur*. Doin.
- Burckhardt, C. S., Clark, S. R., & Bennett, R. M. (1991). The fibromyalgia impact questionnaire: Development and validation. *The Journal of Rheumatology*, 18(5), 728–733.
- Burwinkle, T., Robinson, J. P., & Turk, D. C. (2005). Fear of movement: Factor structure of the Tampa scale of kinesiophobia in patients with fibromyalgia syndrome. *The Journal of Pain*, 6(6), 384–391.
- Bushnell, M. C., Ceko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience*, 14(7), 502–511.
- Busner, J., & Targum, S. D. (2007). The clinical global impressions scale. *Psychiatry*, 4(7), 28–37.
- Campbell, W. I., & Lewis, S. (1990). Visual analogue measurement of pain. *The Ulster Medical Journal*, 59(2), 149–154.
- Clauw, D., Sarzi-Puttini, P., Pellegrino, G., & Shoenfeld, Y. (2024). Is fibromyalgia an autoimmune disorder? *Autoimmunity Reviews*, 23(1), 103424.
- Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: Global use of the brief pain inventory. *Annals of the Academy of Medicine, Singapore*, 23(2), 129–138.
- Coskun Benlidayi, I. (2020). The effectiveness and safety of electrotherapy in the management of fibromyalgia. *Rheumatology International*, 40(10), 1571–1580.
- Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G\*power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), 175–191.
- Fillingim, R. B., Bruehl, S., Dworkin, R. H., Dworkin, S. F., Loeser, J. D., Turk, D. C., Widerstrom-Noga, E., Arnold, L., Bennett, R., Edwards, R. R., Freeman, R., Gewandter, J., Hertz, S., Hochberg, M., Krane, E., Mantyh, P. W., Markman, J., Neogi, T., Ohrbach, R., ... Wessellmann, U. (2014). The ACTION-American pain society pain taxonomy (AAPT): An evidence-based and multidimensional approach to classifying chronic pain conditions. *The Journal of Pain*, 15(3), 241–249.
- Fleagle, T. R., Post, A. A., Dailey, D. L., Vance, C. G. T., Zimmerman, M. B., Bayman, E. O., Crofford, L. J., Sluka, K. A., & Chimenti, R. L. (2024). Minimal clinically important change of movement pain in musculoskeletal pain conditions. *The Journal of Pain*, S1526-5900(24), 424.
- French, D. J., Noël, M., Vigneau, F., French, J. A., Cyr, C. P., & Evans, R. T. (2005). L'Échelle de dramatisation face à la douleur PCS-CF: Adaptation canadienne en langue française de l'échelle «Pain Catastrophizing Scale». [PCS-CF: A French-language, French-Canadian adaptation of the Pain Catastrophizing Scale.]. *Canadian Journal of Behavioural Science / Revue Canadienne des Sciences Du Comportement*, 37(3), 181–192.
- García-Larrea, L., & Peyron, R. (2013). Pain matrices and neuro-pathic pain matrices: A review. *Pain*, 154(Suppl 1), S29–S43.
- García-López, H., Calle-Ortega, F., García-Robles, P., Del-Rey, R. R., Obrero-Gaitán, E., & Cortés-Pérez, I. (2024). Effectiveness of transcutaneous electrical nerve stimulation improves pain intensity, disability and quality of life in patients with fibromyalgia syndrome: A systematic review with meta-analysis. *Disability and Rehabilitation*, 1–11. <https://doi.org/10.1080/09638288.2024.2331069>
- Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A., Petzke, F., Williams, D. A., & Clauw, D. J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain: A Journal of Neurology*, 127(Pt 4), 835–843.
- Häuser, W., Sarzi-Puttini, P., & Fitzcharles, M.-A. (2019). Fibromyalgia syndrome: Under-, over- and misdiagnosis. *Clinical and Experimental Rheumatology*, 37 Suppl 116(1), 90–97.
- Hayes, M. H. S., & Patterson, D. G. (1921). Experimental development of the graphic rating method. *Psychological Bulletin*, 18, 98–99.
- Heidari, F., Afshari, M., & Moosazadeh, M. (2017). Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatology International*, 37(9), 1527–1539.
- Jensen, M. P., Chen, C., & Brugger, A. M. (2003). Interpretation of visual analog scale ratings and change scores: A reanalysis of two clinical trials of postoperative pain. *The Journal of Pain*, 4(7), 407–414.
- Johnson, M. I. (2021). Resolving Long-standing uncertainty about the clinical efficacy of transcutaneous electrical nerve stimulation (TENS) to relieve pain: A comprehensive review of factors influencing outcome. *Medicina (Kaunas, Lithuania)*, 57(4), 378.
- Johnson, M. I., Claydon, L. S., Herbison, G. P., Jones, G., & Paley, C. A. (2017). Transcutaneous electrical nerve stimulation (TENS) for fibromyalgia in adults. *The Cochrane Database of Systematic Reviews*, 10(10), CD012172.
- Kahl, C., & Cleeland, J. A. (2005). Visual analogue scale, numeric pain rating scale and the McGill pain questionnaire: An overview of psychometric properties. *Physical Therapy Reviews*, 10(2), 123–128.
- Katz, D. L., Greene, L., Ali, A., & Faridi, Z. (2007). The pain of fibromyalgia syndrome is due to muscle hypoperfusion induced by regional vasomotor dysregulation. *Medical Hypotheses*, 69(3), 517–525.
- Le Gal, M., Mainguy, Y., Le Lay, K., Nadjar, A., Allain, D., & Galissié, M. (2010). Linguistic validation of six patient-reported outcomes instruments into 12 languages for patients with fibromyalgia. *Joint, Bone, Spine*, 77(2), 165–170.
- Lee, K. A., Hicks, G., & Nino-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Research*, 36(3), 291–298.
- Lefaucheur, J. P., Ménard-Lefaucheur, I., Goujon, C., Keravel, Y., & Nguyen, J. P. (2011). Predictive value of rTMS in the identification of responders to epidural motor cortex stimulation therapy for pain. *The Journal of Pain*, 12(10), 1102–1111.
- Macfarlane, G. J., Kronisch, C., Dean, L. E., Atzeni, F., Häuser, W., Fluß, E., Choy, E., Kosek, E., Amris, K., Branco, J., Dincer, F.,

- Leino-Arjas, P., Longley, K., McCarthy, G. M., Makri, S., Perrot, S., Sarzi-Puttini, P., Taylor, A., & Jones, G. T. (2017). EULAR revised recommendations for the management of fibromyalgia. *Annals of the Rheumatic Diseases*, 76(2), 318–328.
- Marques, A. P., Assumpção, A., Matsutani, L. A., Pereira, C. A. B., & Lage, L. (2008). Pain in fibromyalgia and discrimination power of the instruments: Visual analog scale, Dolorimetry and the McGill pain questionnaire. *Acta Reumatológica Portuguesa*, 33(3), 345–351.
- Marques, A. P., Santo, A. d. S. d. E., Berssaneti, A. A., Matsutani, L. A., & Yuan, S. L. K. (2017). Prevalence of fibromyalgia: Literature review update. *Revista Brasileira de Reumatologia*, 57(4), 356–363.
- Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. *Science (New York, N.Y.)*, 150(3699), 971–979. <https://doi.org/10.1126/science.150.3699.971>
- Okifuji, A., & Hare, B. D. (2013). Management of fibromyalgia syndrome: Review of evidence. *Pain and therapy*, 2(2), 87–104.
- Ong Sio, L. C., Hom, B., Garg, S., & Abd-Elseyed, A. (2023). Mechanism of action of peripheral nerve stimulation for chronic pain: A narrative review. *International Journal of Molecular Sciences*, 24(5), 4540.
- Perneger, T. V., Leplège, A., Etter, J. F., & Rougemont, A. (1995). Validation of a French-language version of the MOS 36-item short form health survey (SF-36) in young healthy adults. *Journal of Clinical Epidemiology*, 48(8), 1051–1060.
- Perpetuini, D., Russo, E. F., Cardone, D., Palmieri, R., De Giacomo, A., Pellegrino, R., Merla, A., Calabrò, R. S., & Filoni, S. (2023). Use and effectiveness of Electrosuit in neurological disorders: A systematic review with clinical implications. *Bioengineering (Basel, Switzerland)*, 10(6), 680.
- Perrot, S., Bouhassira, D., Fermanian, J., & CEDR (Cercle d'Etude de la Douleur en Rhumatologie). (2010). Development and validation of the fibromyalgia rapid screening tool (FiRST). *Pain*, 150(2), 250–256.
- Perrot, S., Dumont, D., Guillemin, F., Pouchot, J., Coste, J., & French Group for Quality of Life Research. (2003). Quality of life in women with fibromyalgia syndrome: Validation of the QIF, the French version of the fibromyalgia impact questionnaire. *The Journal of Rheumatology*, 30(5), 1054–1059.
- Pinto, A. M., Luís, M., Geenen, R., Palavra, F., Lumley, M. A., Ablin, J. N., Amris, K., Branco, J., Buskila, D., Castelhana, J., Castelo-Branco, M., Crofford, L. J., Fitzcharles, M. A., Häuser, W., Kosek, E., Mease, P. J., Marques, T. R., Jacobs, J. W. G., Castilho, P., & da Silva, J. A. P. (2023). Neurophysiological and psychosocial mechanisms of fibromyalgia: A comprehensive review and call for an integrative model. *Neuroscience and Biobehavioral Reviews*, 151, 105235.
- Popkirov, S., Enax-Krumova, E. K., Mainka, T., Hoheisel, M., & Hausteiner-Wiehle, C. (2020). Functional pain disorders—more than nociplastic pain. *NeuroRehabilitation*, 47(3), 343–353.
- Queiroz, L. P. (2013). Worldwide epidemiology of fibromyalgia. *Current Pain and Headache Reports*, 17(8), 356.
- Riachi, N., Chalah, M. A., Ahdab, R., Arshad, F., & Ayache, S. S. (2023). Effects of the TENS device, Exopulse Mollii suit, on pain related to fibromyalgia: An open-label study. *Neurophysiologie Clinique = Clinical Neurophysiology*, 53(4), 102863.
- Rubio-Zarapuz, A., Apolo-Arenas, M. D., Clemente-Suárez, V. J., Costa, A. R., Pardo-Caballero, D., & Parraca, J. A. (2023). Acute effects of a session with the EXOPULSE Mollii suit in a fibromyalgia patient: A case report. *International Journal of Environmental Research and Public Health*, 20(3), 2209.
- Rubio-Zarapuz, A., Apolo-Arenas, M. D., Tomas-Carus, P., Tornero-Aguilera, J. F., Clemente-Suárez, V. J., & Parraca, J. A. (2024). Comparative analysis of psychophysiological responses in fibromyalgia patients: Evaluating Neuromodulation alone, Neuromodulation combined with virtual reality, and exercise interventions. *Medicina (Kaunas, Lithuania)*, 60(3), 404.
- Salaffi, F., Stancati, A., Silvestri, C. A., Ciapetti, A., & Grassi, W. (2004). Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *European Journal of Pain (London, England)*, 8(4), 283–291.
- Sarzi-Puttini, P., Giorgi, V., Marotto, D., & Atzeni, F. (2020). Fibromyalgia: An update on clinical characteristics, aetiopathogenesis and treatment. *Nature Reviews Rheumatology*, 16(11), 645–660.
- Schmidt-Wilcke, T., & Clauw, D. J. (2011). Fibromyalgia: From pathophysiology to therapy. *Nature Reviews Rheumatology*, 7(9), 518–527.
- Schmidt-Wilcke, T., & Diers, M. (2017). New insights into the pathophysiology and treatment of fibromyalgia. *Biomedicine*, 5(2), 22.
- Shang, Y., Gurley, K., Symons, B., Long, D., Srikuea, R., Crofford, L. J., Peterson, C. A., & Yu, G. (2012). Noninvasive optical characterization of muscle blood flow, oxygenation, and metabolism in women with fibromyalgia. *Arthritis Research & Therapy*, 14(6), R236.
- Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). The pain catastrophizing scale: Development and validation. *Psychological Assessment*, 7(4), 524–532.
- Taylor, S. J., Steer, M., Ashe, S. C., Furness, P. J., Haywood-Small, S., & Lawson, K. (2019). Patients' perspective of the effectiveness and acceptability of pharmacological and non-pharmacological treatments of fibromyalgia. *Scandinavian Journal of Pain*, 19(1), 167–181.
- Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., ... Wang, S. J. (2015). A classification of chronic pain for ICD-11. *Pain*, 156(6), 1003–1007.
- Ware, J. E., & Gandek, B. (1998). Overview of the SF-36 health survey and the international quality of life assessment (IQOLA) project. *Journal of Clinical Epidemiology*, 51(11), 903–912.
- Wolfe, F., Brähler, E., Hinz, A., & Häuser, W. (2013). Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: Results from a survey of the general population. *Arthritis Care & Research*, 65(5), 777–785.
- Wolfe, F., Clauw, D. J., Fitzcharles, M.-A., Goldenberg, D. L., Katz, R. S., Mease, P., Russell, A. S., Russell, I. J., Winfield, J. B., & Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research*, 62(5), 600–610.
- Wolfe, F., Walitt, B., Perrot, S., Rasker, J. J., & Häuser, W. (2018). Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. *PLoS One*, 13(9), e0203755.

- Wolfe, F., Walitt, B. T., & Häuser, W. (2014). What is fibromyalgia, how is it diagnosed, and what does it really mean? *Arthritis Care & Research*, 66(7), 969–971.
- Wolfe, F., Walitt, B. T., Rasker, J. J., Katz, R. S., & Häuser, W. (2015). The use of Polysymptomatic distress categories in the evaluation of fibromyalgia (FM) and FM severity. *The Journal of Rheumatology*, 42(8), 1494–1501.

### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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