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# Interferential therapy for chronic constipation in adults: The CON-COUR randomized controlled trial

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## Abstract

**Background:** Chronic constipation (CC) is a frequent condition, and the first-line treatment includes dietary rules, the use of laxatives, and biofeedback for evacuation disorders. However, almost half of the patients are dissatisfied with their current treatment. We report the first double-blind randomized multicenter trial assessing the effectiveness of transabdominal electrical stimulation by interferential therapy (IFT) in the treatment of CC in adults.

**Methods:** A prospective, multicenter, randomized, double-blind, sham-controlled, parallel-group, phase 3 trial was conducted at 7 centers in France. The primary endpoint was 8-week efficacy as defined by the number of complete spontaneous bowel movements during the last 4 weeks of the 8-week stimulation period. Secondary endpoints included the evaluation of the effects of IFT on symptoms (Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM)), quality of life (QOL) (Patient Assessment of Constipation Quality of Life), Colonic transit time (CTT), anorectal manometry, and patient satisfaction.

**Results:** The proportion of 8-week responders was not significantly different between the two groups (73.2% in the IFT group vs. 67.1% in the sham group). After 8 weeks of stimulation, the mean overall PAC-SYM score and the mean reduction in the overall PAC-SYM score were significantly greater in the IFT group than in the sham group. No differences were observed concerning CTT, anorectal manometry, or patient satisfaction.

**Conclusions:** Although the primary endpoint was not reached, IFT can significantly alleviate the symptoms and improve the QOL of CC patients. It can be assumed that new treatments require different modes of evaluation and that the assessment of patient-reported outcomes may become a priority among therapeutic targets of CC. Trial registration number NCT02381665.

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**KEYWORDS**

chronic constipation, double blind, interferential therapy, quality of life, randomized clinical trial, transabdominal electrical stimulation

**INTRODUCTION**

Chronic constipation (CC) is a frequent condition in adults and is more common in women than in men, with a prevalence of approximately 15% in Western countries.<sup>1,2</sup>

Two mechanisms of CC have been identified: (1) slow transit constipation (STC), characterized by impaired propulsion of stool, and (2) evacuation disorders, characterized by the inability to achieve or difficulty with stool expulsion.<sup>3</sup>

Regardless of the mechanism, CC has a significant negative impact on quality of life (QOL) and is a considerable burden on healthcare resources, with high levels of loss of work productivity (including absenteeism and overall work impairment) as well as more healthcare consumption and emergency room visits.<sup>4,5</sup>

This impact on QOL may be partly due to differences in the definition of CC between patients and physicians, leading to incomplete management. Physicians usually define CC only as a reduction in bowel movements, whereas patients define CC as a series of complaints, including multiple symptoms (reduction in bowel movements, straining, incomplete evacuation, hard stools, bloating, abdominal discomfort) and associated psychological and social morbidities, including increased somatization, decreased sexual satisfaction, social exclusion, anxiety, and depression.<sup>6-8</sup>

The first-line treatment for CC is based on dietary rules, bowel habits, the use of different laxatives, and biofeedback for evacuation disorders.<sup>9</sup>

However, up to 28% of patients with CC are often dissatisfied with their current treatment because of efficacy and safety concerns, and the extent of dissatisfaction may be associated with the type of laxative they are taking with a significant impact on QOL.<sup>10,11</sup> Moreover, practitioners are conscious of the impact of this symptom and both patients and physicians are interested in any new treatments.<sup>11,12</sup> An ideal treatment would be effective, well tolerated, noninvasive, and largely available.

Interferential therapy (IFT) was first described to treat STC in children and the results were promising based on a small number of patients.<sup>13-15</sup> In 2013, we published the first pilot study assessing the effectiveness and impact of IFT on QOL in adult patients and reported significant success with alleviating symptoms, improving QOL scale results and decreasing Colonic transit time (CTT).<sup>16</sup> More recently, in a single-blind randomized study in 33 patients, Moore et al. reported the significant efficacy of IFT on CC.<sup>17</sup> This promising nondrug technique has the advantage of being an alternative treatment that is easy to use, noninvasive, and very well tolerated. To date, despite encouraging results, the level of evidence remains low regarding the effectiveness of IFT in the treatment of CC.

Here, we report the first double-blind randomized multicenter trial assessing IFT effectiveness in the treatment of CC in adults. The

**Key Summary****Summary of the established knowledge on this subject**

- Chronic constipation significantly impacts the quality of life (QOL) of many patients.
- The first-line treatment includes dietary rules and the use of laxatives, but many patients are dissatisfied with their current treatment.

**What are the significant and/or new findings of this study?**

- Transabdominal electrical stimulation by interferential therapy (IFT) is a new promising device for the treatment of CC.
- It offers a new concept in the treatment of this disorder.
- Future studies should evaluate which patients will benefit most from this new treatment and how to combine it with other therapeutic strategies.

primary objective was to assess IFT efficacy based on the number of complete spontaneous bowel movements (CSBMs) at the end of an 8-week stimulation period. The secondary objectives were (i) to assess the effect of IFT on constipation symptoms, QOL, CTT, and anorectal manometry, and (ii) to explore factors associated with IFT efficacy.

**METHODS****Study design**

A prospective, multicenter, randomized, double-blind, sham-controlled, parallel-group, phase 3 trial was conducted at 7 centers in France. The study protocol was designed using the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement. The sponsor of the study was the Assistance Publique - Hôpitaux de Marseille (AP-HM, France). The central pharmacy of AP-HM oversaw the assignment, allocation, and delivery of the devices. This trial was supported by institutional grants from the French 2013 National Program of Clinical Research (Program Hospitalier de Recherche Clinique National).

**Eligibility of patients**

Patients were included if they met the following criteria: adult patients (> or = 18 years of age) of either sex; with a history of CC defined as 1. Two or fewer CSBMs per week for a minimum of 6 months before the screening visit, and/or 2. A sensation of incomplete evacuation or straining during at least 25% of bowel movements (according to the

consensual definition of constipation); CC lasting for more than 6 months; CC refractory to medical treatment for at least 3 months (failure or intolerance of medical treatment); affiliation with or beneficiary of a social security system; and a signature on the written informed consent form. Patients could continue their usual baseline treatment for CC and were allowed, in case of absence of bowel movements for three or more consecutive days, to take up 10 mg of bisacodyl (Opella Healthcare, France) as a rescue medication.

Patients were ineligible if they met any of the following criteria: minors or pregnant or breast-feeding women; CC secondary to anorectal malformations, including colorectal or anal organic lesions or a pelvic floor disorder, considered by the investigator as necessitating surgical treatment (rectal prolapse exteriorized, rectocele, enterocele); implanted electrical devices, including cardiac pacemakers, defibrillators, cardiac pumps, or spinal stimulators; CC secondary to drugs or to neurologic, endocrine, or metabolic disorders; history of partial colectomy; megacolon, megarectum, or colonic inertia; skin lesions preventing implantation of the electrodes; women without effective contraception (hormonal or intrauterine device); inability to understand written and spoken French; or participation in another biomedical research protocol.

NB: Failure of “medical” treatment included biofeedback therapy: all patients suffering from anismus were included if they previously had 10 to 20 biofeedback sessions without significant clinical success.

were asked to report weekly CSBMs in a bowel diary during the first 2-week observational period. After this 2-week period, at visit 1 (V1), the patients were randomized into one of the two treatment groups and instructions for device use were provided. The patients were asked to report CSBMs without the use of the device during a second 2-week period. During this period, the patients underwent CTT and anorectal manometry measurements. At visit 2 (V2), the patients began stimulation. They were assessed at 4 (mid-term evaluation, visit 3, V3) and 8 weeks (stimulation and evaluation, visit 4, V4) after V2. After the 8-week period of stimulation, the patients were assessed at visits 5 (V5) and 6 (V6), corresponding to 12 (+/- 2) and 24 weeks (+/-2) after the beginning of stimulation.

### Randomization

At V1, patients were randomized into one of the two treatment groups. Computer-generated randomized lists were drawn up at the beginning of the study using a permuted block design under the direction of the clinical research unit (AP-HM). The randomization was stratified by center (1:1 allocation ratio). The allocation sequence was sequentially numbered. Prior to and during the entire study period, the participant, the treating medical staff, and the investigators were blinded to the allocation.

### General organization

The diagram of the general organization is presented in Figure 1. After completing the consent form (visit 0, V0), the included patients

### Effective or sham device

The device procedure (effective or sham) was blinded; neither the patient nor the physician responsible for the prescription was informed

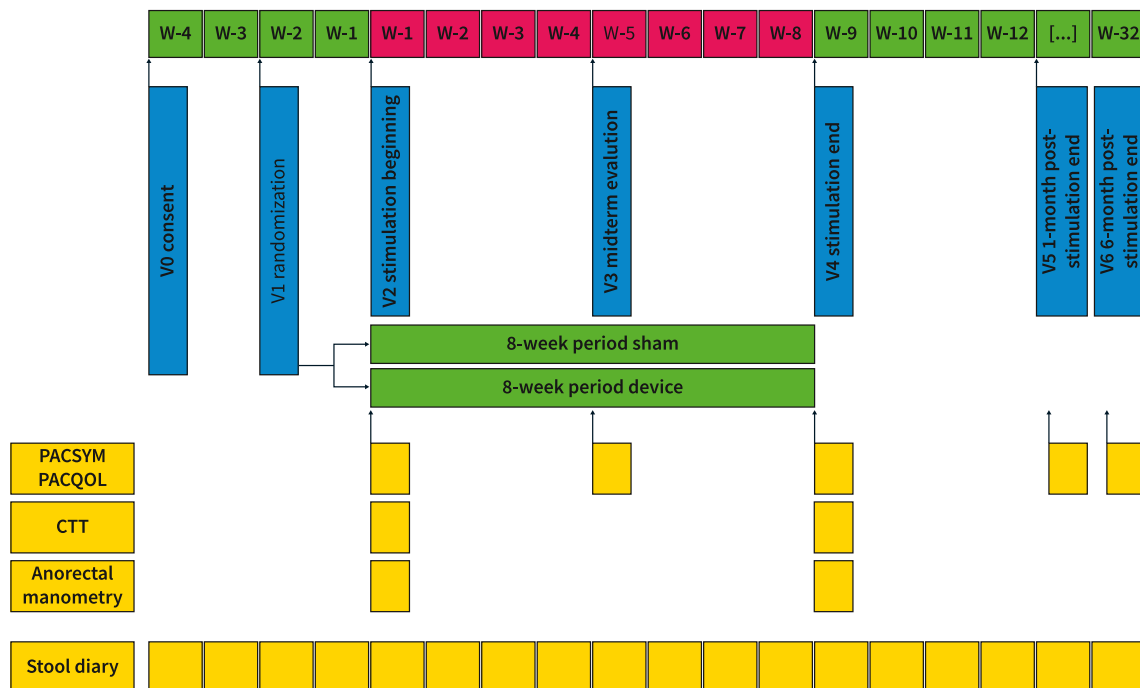


FIGURE 1 Diagram of the study design.

of the nature of the device. Regardless of the group (control or experimental), the patients followed the same procedures, received devices that looked the same, and had the same follow-up. The practitioner who gave the instructions concerning the use of the device was the only person aware of the sham or effective stimulation. The instructions were exactly the same for each patient in both groups.

In the interferential-experimental, effective stimulation group, patients received stimulation 1 h per day every day at home for 8 weeks. There was no "dose adjustment" if the stimulation was not well tolerated; it was stopped in accordance with the practitioner's decision. The stopping criteria were as follows: severe pain or neurological symptoms (paresthesia, burn, or shaking). Unblinding of the treatment could be conducted by contacting the coordinating investigator.

In the sham-control group, the exact same protocol was applied, except that the device did not deliver any stimulation. Thus, no side effects or poor tolerance was expected. However, if a side effect was reported, its use was stopped in accordance with the criteria detailed below. Unblinding of the treatment could be conducted by contacting the coordinating investigator.

### Concomitant permitted and prohibited medications

In the absence of bowel movements for three or more consecutive days, the patients were allowed to take up to 10 mg of bisacodyl (Opella Healthcare, France) as a rescue medication. All other new laxative drugs were forbidden during the study.

### Medical device

The IFT device uses a 6-V battery-operated interferential stimulating machine (Flexitim IF Tenscare, Fuji Dynamics, Honk Kong, CE mark 0473, Market authorization December 2009). The device is marketed in France by A-Legrand (<http://www.a-legrand.com>). Interferential treatment delivers a 4-kHz carrier frequency, a beat frequency of 80–160 Hz, and an intensity of less than 33 mA. The stimulation was performed according to the procedure described by Ismail et al.<sup>18</sup> This technique uses four adhesive surface electrodes, two abdominal (placed below the costal margin) and two paraspinal (placed between T9 and L2), producing two sinusoidal currents crossing the body. To ensure the proper placement of the electrodes, the first stimulation was administered in the presence of the practitioner. During the 8-week treatment period, the stimulation protocol was home-based and self-applied by the patient for 1 h per day every day.

### Endpoints

#### Primary endpoint

The primary endpoint was the 8-week efficacy defined by three or more CSBMs per week during the last 4 weeks of the 8-week

stimulation period (from W5 CSBM to W8 CSBM). A patient was classified as 1) a responder when she or he had three or more CSBMs per week during the last 4 weeks and 2) a nonresponder in other cases. In the case of missing data (MD) for one or more of the 4 weeks, the individual was not classified.

This primary endpoint was chosen according to data from previously randomized trials on severe CC.<sup>19</sup>

#### Secondary endpoints

- The efficacy was determined by the following definitions: (i) the response (three or more CSBM per week) during W7 and W8; (ii) the response (three or more CSBM) during W8; (iii) the response (three or more CSBM) during W4 (fourth week after the stimulation beginning); (iv) the mean CSBM from W5 to W8; from W7 to W8, at W8; and (v) the CSBM difference from W1 to W8.
- Constipation symptoms were assessed using the Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM).<sup>20</sup> This questionnaire included 12 constipation-related symptoms, providing a total score and three subscores: stool, abdominal, and rectal symptoms. For the total score and for each subscore, scores ranged from 0 (no symptoms) to 4 (very severe symptoms). Scores and subscores at W8, change scores from baseline (W1) to W8, at 4 weeks poststimulation end (W12) and scores at 24 weeks poststimulation end (W32) were compared between groups.
- The patients' QOL was assessed using the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL).<sup>21</sup> This self-report questionnaire includes 28 items related to the effects of constipation on daily life. One total score and four subscores are provided: physical discomfort, psychosocial discomfort, worries and concerns, and satisfaction. For each item, scores can range from 0 to 4 with lower scores indicating a better QOL. Scores and subscores at W8, scores from baseline (W1) to W8, and scores at 4 weeks post-stimulation end (W12) and 24 weeks post-stimulation end (W32) were compared between groups.
- CTT was measured according to the Bouchoucha et al.<sup>22</sup> technique. With this technique, the subjects ingested 10 markers per day 6 consecutive days. A plain film of the abdomen was obtained on the seventh day. The number of persistent markers was analyzed in each area of interest (colonic segment). The total and segmental transit times were calculated by multiplying the number of markers by segment by 2.4. A slow transit time is defined by a total transit time greater than 91.2 h for women and 76.8 h in men. CTT was measured during the 2 weeks before the beginning of the treatment (W1-2 weeks) and at W8.
- Anorectal manometry was performed according to each center's usual procedure. The following parameters were collected: resting pressure and increment in the voluntary contraction measured in mmHg, maximal rectal tolerable volume in ml, and presence of anismus. Ano-rectal manometry was performed during the 2 weeks before the beginning of the treatment (W1-2 weeks) and at W8.

- Patient satisfaction with the efficacy of the treatment was assessed with the response to one question: "On an analogical visual scale (AVS) of 0–5, how satisfied are you with the device?" Responses ranged from 0 (not satisfied at all) to 5 (completely satisfied). AVS was assessed at W4, W8, W12, and W32.
- Tolerance was assessed with data on the following items: pain (local, ventral or dorsal) or neurological symptoms such as paresthesia, burn, or shaking.
- Bisacodyl use was assessed at W4 and W8.
- Long-term efficacy was assessed at W12 and W32
- Treatment compliance: Treatment compliance at W4 and W8 was assessed among a subgroup of patients,  $n = 70$ . Compliance was defined as daily use of the device during the 8 weeks as noted by the patients on a paper diary (self-administered questionnaires), and noncompliance was defined as all other cases.

## Pharmaceutical aspects

Devices (both effective or sham) and electrodes were labeled and numbered according to the randomization list and sent to the dispensing pharmacist of each investigating center under the direction of the Hospital Pharmacy at AP-HM. At the end of the study, the devices were returned to the sponsor's coordinating pharmacy.

## Statistical analysis

### Sample size

Based on previous reports, the estimated proportion of responders at 8 weeks was 15% in the control group.<sup>19,23</sup> To detect an absolute difference of 20 points (35% of responders in the experimental group), considering a potential 15% loss to follow-up at 8 weeks (primary endpoint), a 5% alpha risk, and 80% power, a total of 95 subjects per group was needed (a total of 190 subjects). To take into account follow-up losses, a total of 200 subjects (100 in each arm) were planned for inclusion (Power Analysis and Sample Size Software Version 2008, Utah, USA). No interim analysis was planned.

### Data analysis

The data were analyzed using SPSS version 17.0 software. The analysis was performed on the intention-to-treat population. The baseline parameters were described per group ('control' C and 'experimental' E).

The proportions of treatment response at 8 weeks (primary endpoint) were compared between groups using the  $\chi^2$  test or Fisher's exact test (primary analysis); the result was presented as proportions, difference D (experimental minus control) and the 95% confidence interval 95% CI. No imputation data were obtained.

As a secondary analysis, adjustment for the mechanism of constipation (increased CTT and/or anismus) and baseline severity of constipation was performed using logistic regressions; variables were selected based on their clinical significance.

The secondary endpoints were compared between groups using the  $\chi^2$  test or Fisher's exact test for categorical variables (anismus) and Student's test or the Mann-Whitney test for continuous variables (PAC-SYM and PAC-QOL scores).

The association between efficacy (primary endpoint) and the following 3 parameters was independently tested: prestimulation anismus (absence-presence), prestimulation CTT (short-long; 72 min for men and 91 min for women<sup>22</sup>), and baseline CSBM ( $\leq 2 / > 2$ ). Three logistic regression models were performed (the group was systematically entered in the models). The results were expressed as odds ratios, 95% CIs, and  $p$  values.

## Ethical aspects, laws, and regulations

The study was conducted in accordance with the Declaration of Helsinki and French laws and regulations (*Code de la Santé Publique, article L.1121-1/Loi de Santé Publique n°2004-806 du 9 août 2004 relative à la politique de Santé Publique et ses décrets d'application du 27 août 2006*) and the International Conference on Harmonization E6 Guideline for Good Clinical Practice. Regulatory monitoring was performed by the sponsor. The sponsor needed the approval of the French authorities, including the French ethics committee (*Comité de Protection des Personnes Sud Méditerranée, reference number 14 89; 08 December 2014*) and the French drug and device regulation agency (Agence Nationale de Sécurité du Médicament, reference number DMTCOS/DMCOSM/SV/2014-A01359-38), before beginning the study. The [ClinicalTrials.gov](https://clinicaltrials.gov) identifier is NCT02381665. Informed consent was obtained from all subjects.

## RESULTS

### Enrollment and baseline characteristics of patients

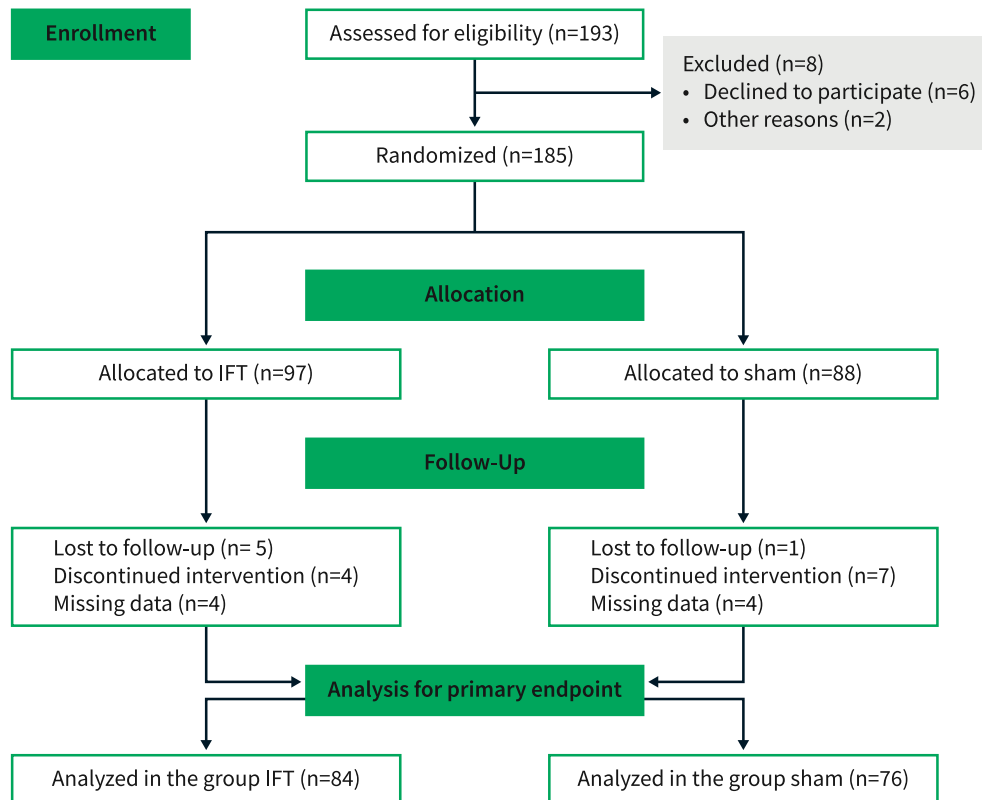
From November 2015 to December 2020, among 300 patients eligible for the study, 193 patients were included. A total of 185 patients were randomized, 88 in the sham group and 97 in the IFT group. The flow chart is presented in Figure 2.

The baseline characteristics are presented in Table 1.

### Primary endpoint

The proportions of 8-week responders, according to the definition detailed above (having three or more CSBMs per week during the last 4 weeks of the 8 weeks of stimulation), were 73.2% (60 of 82 patients) in the IFT group versus 67.1% (51 of 76 patients) in the sham group (D (E-C) 6.1%, 95% CI [-8%; 20.0%],  $p = 0.405$  (Table 2)).





**FIGURE 2** Flow-chart.

### Secondary endpoints

Other definitions were derived from the primary endpoint: the response (three or more CSBMs per week) during W7 and W8, the response (three or more CSBMs) during W8, the response (three or more CSBMs) during W4, the means of CSBM from W5 to W8, from W7 to W8, and at W8, and the CSBM difference from W1 to W8. No difference was found between the groups. All the results are presented in Table 2.

### Mid-term evaluation

At W4, no significant difference was observed between the two groups except for the PAC-SYM abdominal subscore, which was better in the IFT group (Supplementary Appendix).

### Constipation symptoms (Patient Assessment of Constipation Symptoms questionnaire scores)

After 8 weeks of stimulation, the mean overall PAC-SYM score and the mean reduction in the mean overall PAC-SYM score were significantly greater in the IFT group than in the sham group. Two of

the three PAC-SYM subscores, abdominal and rectal subscores, differed between groups, with significantly better scores and improvement in the IFT group. The improvement in the PAC-SYM score was not maintained at W12 and W32 (Table 3).

### Quality of life (Patient Assessment of Constipation Quality of Life scores)

After 8 weeks of stimulation, the mean PAC-QOL improvement was significantly greater in the IFT group than in the sham group (Table 4). Changes between baseline and W8 were significantly higher for the IFT group than those for the sham group for 3 subscores: worries, physical discomfort, and psychological discomfort. The PAC-QOL subscore satisfaction was significantly better in the IFT group. The improvement in the PAC-QOL score was not maintained at W12 and W32 (Table 3).

### Colonic transit time

After 8 weeks of stimulation, the mean colonic transit time (CCT) and the mean difference in CCT between baseline and W8 were not significantly different between the two groups (Table 4).

**TABLE 1** Baseline characteristics of the patients.

| Group                                   |           | Sham<br>N = 88   | IFT<br>N = 97    |
|---|-----------|------------------|------------------|
| Sex                                     |           |                  |                  |
| Male                                    | N (%)     | 8 (9.1)          | 5 (5.2)          |
| Female                                  | N (%)     | 80 (90.9)        | 92 (94.8)        |
| Age, years                              | Mean (SD) | 52.06 (15.01)    | 49.36 (16.11)    |
| BMI, kg/m <sup>2</sup>                  | Mean (SD) | 23.27 (4.48)     | 22.19 (4.44)     |
| Constipation symptoms (PAC-SYM scores)  |           |                  |                  |
| Total <sup>a</sup>                      | Med (IQR) | 2.42 (1.75–3.08) | 2.18 (1.83–2.92) |
| Abdominal <sup>a</sup>                  | Med (IQR) | 2.75 (2.00–3.50) | 2.50 (2.00–3.25) |
| Stool <sup>a</sup>                      | Med (IQR) | 1.33 (0.67–2.67) | 1.33 (0.67–2.00) |
| Rectal <sup>a</sup>                     | Med (IQR) | 2.80 (2.00–3.40) | 2.60 (1.60–3.40) |
| Quality of life (PAC-QOL scores)        |           |                  |                  |
| Total <sup>b</sup>                      | Med (IQR) | 2.60 (2.05–3.04) | 2.54 (2.07–2.96) |
| Worry <sup>b</sup>                      | Med (IQR) | 2.58 (2.08–3.17) | 2.67 (2.08–3.08) |
| Physical discomfort <sup>b</sup>        | Med (IQR) | 2.75 (2.25–3.25) | 2.75 (2.25–3.25) |
| Psychol. Discomfort <sup>b</sup>        | Med (IQR) | 2.00 (1.13–2.88) | 1.88 (1.38–2.75) |
| Satisfaction <sup>b</sup>               | Med (IQR) | 3.50 (2.75–4.00) | 3.75 (2.75–4.00) |
| Colonic transit time, hours             | Med (IQR) | 94 (48–137)      | 97 (54–126)      |
| Anal resting pressure, mmHg             | Med (IQR) | 65 (45–78)       | 68 (48–84)       |
| Voluntary contraction (increment), mmHg | Med (IQR) | 122 (85–170)     | 131 (100–184)    |
| Maximal tolerable volume, ml            | Med (IQR) | 200 (150–280)    | 180 (150–240)    |
| Anismus                                 |           |                  |                  |
| Presence                                | N (%)     | 59 (72.0)        | 55 (59.8)        |
| Absence                                 | N (%)     | 23 (28.0)        | 37 (40.2)        |

Abbreviations: BMI, body mass index; Med (IQR), medians (interquartile range); N (%), number (percent); PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; SD: standard deviation.

<sup>a</sup>from 0 (no symptoms) to 4 (very severe symptoms).

<sup>b</sup>from 0 (highest) to 4 (lowest QOL).

## Ano-rectal manometry

No significant difference was observed after 8 weeks of stimulation for any of the parameters collected (resting pressure, increment in the voluntary contraction, maximal rectal tolerable volume, or presence of anismus) (Table 4).

## Patient satisfaction with the efficacy of treatment

No significant difference between the two groups was observed at any evaluation time point (Table 4).

## Tolerance

No side effects or unexpected effects, such as pain (local, ventral, or dorsal) or neurological symptoms, such as paresthesia, burn, or shaking, were reported during the study.

## Bisacodyl use

The frequency of one-time bisacodyl use was not significantly different between the two groups during the stimulation period (Table 4).



**TABLE 2** Primary and secondary endpoints on number of stools.

| Group   |           | Sham          | IFT           | p value |
|---|-----------|---------------|---------------|---------|
| 1. Primary endpoint <sup>a</sup>                      |           |               |               |         |
| Response ( $\geq 3$ CSBM from W5 to W8)               | N (%)     | 51 (67.1)     | 60 (73.2)     | 0.405   |
| Nonresponse   | N (%)     | 25 (32.9)     | 22 (26.8)     |         |
| 2. Secondary endpoints                                |           |               |               |         |
| $\geq 3$ CSBM at W7+W8                                | N (%)     | 44 (59.6)     | 53 (68.8)     | 0.230   |
| $\geq 3$ CSBM at W8                                   | N (%)     | 49 (66.2)     | 59 (76.6)     | 0.157   |
| Number of stools at W8                                | Med (IQR) | 4.0 (2.0–6.3) | 4.0 (3.0–7.0) | 0.405   |
| Number of stools at W7+W8                             | Med (IQR) | 4.0 (2.5–5.5) | 4.5 (2.8–6.8) | 0.240   |
| Number of stools at W5–W8                             | Med (IQR) | 3.8 (2.3–5.7) | 4.5 (2.8–6.8) | 0.223   |
| Mean difference in number of stools between W1 and W8 | Mean (SD) | 0.24 (2.51)   | 0.11 (3.56)   | 0.490   |

Abbreviations: CSBM, spontaneous, complete bowel movements; Med (IQR), median (interquartile range); Wi, week-*i*; N (%), number (percent); from W5 to W8, from fifth to eighth stimulation period.

<sup>a</sup>The primary endpoint was the 8-week efficacy defined as CSBMs during the last 4 weeks (from W5 to W8) of the 8-week stimulation period (from the 5-week CSBM to the 8-week CSBM). A patient was classified as a responder if she or he had three or more CSBMs per week during the last 4 weeks of the 8-week stimulation period and a nonresponder in other cases. In the case of MD for one or more of the 4 weeks, the individual was not classified.

### Long-term efficacy at 1 (W12) and 6 (W32) months after the end of stimulation

At W12 and W32, there were no significant differences between the two groups for CSBMs, PAC-SYM, PAC-QOL, and AVS (Tables 3 and 4).

### Compliance

Compliance at W8 was not significantly different between the two groups (Table 4).

### Factors associated with interferential therapy efficacy

After adjusting for the group, the presence of prestimulation anismus (model 1), having a normal prestimulation CTT (model 2), and having more than 2 baseline CSBMs (model 3) were independently associated with the 8-week IFT efficacy. The results are provided in the Supplementary Tables 1 and 2.

## DISCUSSION

We report the results of the first double-blind randomized multicenter trial assessing IFT effectiveness in the treatment of CC in adults. The proportion of patients achieving the primary endpoint was not significantly different between the IFT group and the sham group. However, the rate of clinical response in both groups was unusually high. It can be hypothesized that it may be related to the choice of the primary endpoint. Moreover, we chose the average number of CSBMs at the end of the treatment period as the primary

endpoint. Data from the literature suggest that the assessment of the change in the number of stools from baseline is a better criterion, but in our study, there was no significant difference between the two groups.

The selection and clinical characteristics of our population were comparable to those usually observed in studies including constipated patients, and only the mean baseline total PAC SYM score, which was between 2.27 (IFT group) and 2.28 (sham group), was slightly higher than what was reported in an integrated analysis of 6 clinical trials, in which it was 1.9.<sup>24</sup> However, as usually described in the literature, we also had a high rate of anismus in both groups since the most prevalent form of constipation encountered in specialist referral centers is represented by pelvic floor dysfunction.<sup>25,26</sup> Our choice to include patients with both mechanisms of constipation may appear questionable. Nevertheless, in practice, in most severe patients, both mechanisms are involved, anismus is an important complaint for patients, and we wanted to first propose this treatment to all patients and then associate the mechanism with the analysis of the results. Moreover, in a secondary analysis, after adjusting for the group, a link between the mechanism and the severity of CC was observed. This result may appear surprising because of the supposed, but still little-known, mechanism of action of IFT on the colon. The therapeutic use of IFT was developed by Nemeč who argued that two currents of slightly different frequencies interfere in tissues and that there is maximum stimulation in the region at which the two current paths intersect.<sup>27</sup> Different hypotheses may be suggested to explain the effects of IFT. It has been proposed that the improvement of STC by IFT could be explained by the stimulation of parasympathetic fibers or a direct block of sympathetic nerve fibers inducing a blockade of inhibition. It is possible that neural blockade may occur through a direct conduction block of the nerve fibers.<sup>28,29</sup> As suggested by Chase et al, electrical stimulation during IFT may activate vagal

**TABLE 3** Constipation symptoms (Patient Assessment of Constipation Symptoms questionnaire (PAC-SYM) scores) and quality of life (QOL) (Patient Assessment of Constipation Quality of Life (PAC-QOL) scores) at 8, 12, and 32 weeks post-stimulation initiation.

|   | Group sham<br>Med (IQR) | MD | Group IFT<br>Med (IQR) | MD | p value      |
|---|-------------------------|----|------------------------|----|--------------|
| Constipation symptoms (PAC-SYM scores)      |                         |    |                        |    |              |
| W8-total <sup>a</sup>                       | 2.33 (1.75–2.92)        | 14 | 1.92 (1.31–2.67)       | 11 | <b>0.013</b> |
| W8-abdominal <sup>a</sup>                   | 2.75 (1.75–3.25)        | 14 | 2.25 (1.25–2.81)       | 11 | <b>0.015</b> |
| W8-stool <sup>a</sup>                       | 1.33 (0.66–2.42)        | 14 | 1.00 (0.33–2.00)       | 11 | <b>0.057</b> |
| W8-rectal <sup>a</sup>                      | 2.60 (1.75–3.25)        | 14 | 2.20 (1.40–3.00)       | 11 | <b>0.020</b> |
| DeltaW1-W8-total <sup>a</sup>               | 0.00 (–3.00–0.30)       | 35 | –0.33 (–0.90–0.00)     | 26 | <b>0.003</b> |
| DeltaW1-W8-abdominal <sup>a</sup>           | 0.00 (–0.50–0.25)       | 34 | –0.50 (–1.00–0.00)     | 26 | <b>0.009</b> |
| DeltaW1-W8-stool <sup>a</sup>               | 0.00 (–0.30–0.50)       | 35 | –0.30 (–1.00–0.33)     | 26 | 0.109        |
| DeltaW1-W8-rectal <sup>a</sup>              | 0.20 (–0.50–0.40)       | 35 | –0.20 (–1.00–0.20)     | 26 | <b>0.009</b> |
| W12-total <sup>a</sup>                      | 2.00 (1.41–2.75)        | 26 | 2.21 (1.58–2.58)       | 27 | 0.481        |
| W12-abdominal <sup>a</sup>                  | 2.75 (1.50–3.06)        | 26 | 2.25 (1.50–3.00)       | 27 | 0.177        |
| W12-stool <sup>a</sup>                      | 1.00 (0.33–2.00)        | 26 | 1.00 (0.33–2.08)       | 27 | 0.601        |
| W12-rectal <sup>a</sup>                     | 2.20 (1.55–3.00)        | 26 | 2.60 (1.75–3.25)       | 27 | 0.147        |
| W32-total <sup>a</sup>                      | 2.25 (1.77–2.67)        | 38 | 2.25 (1.58–2.75)       | 42 | 0.830        |
| W32-abdominal <sup>a</sup>                  | 2.37 (1.50–3.00)        | 38 | 2.50 (1.50–3.25)       | 42 | 0.990        |
| W32-stool <sup>a</sup>                      | 1.33 (0.58–2.67)        | 38 | 1.33 (0.33–2.00)       | 42 | 0.500        |
| W32-rectal <sup>a</sup>                     | 2.77 (2.00–3.40)        | 38 | 2.80 (1.80–3.40)       | 42 | 0.740        |
| Quality of life (PAC-QOL scores)            |                         |    |                        |    |              |
| W8-total <sup>b</sup>                       | 2.41 (1.83–2.95)        | 16 | 2.19 (1.43–2.69)       | 13 | 0.075        |
| W8-worries <sup>b</sup>                     | 2.41 (1.83–2.95)        | 16 | 2.25 (1.66–2.87)       | 13 | 0.439        |
| W8-phys. Discomfort <sup>b</sup>            | 2.75 (2.00–3.31)        | 16 | 2.25 (1.50–3.00)       | 13 | <b>0.003</b> |
| W8-psychol. Discomfort <sup>b</sup>         | 1.75 (1.00–2.59)        | 16 | 1.62 (0.75–2.37)       | 13 | 0.222        |
| W8-satisfaction <sup>b</sup>                | 3.50 (2.25–4.00)        | 16 | 3.00 (1.75–4.00)       | 13 | <b>0.039</b> |
| DeltaW1-W8-total <sup>b</sup>               | –0.05 (–0.34–0.32)      | 36 | –0.37 (–0.82–0.04)     | 26 | <b>0.001</b> |
| DeltaW1-W8-worries <sup>b</sup>             | 0.00 (–0.35–0.25)       | 26 | –0.33 (–0.75–0.08)     | 32 | <b>0.006</b> |
| DeltaW1-W8-phys. Discomfort <sup>b</sup>    | 0.00 (–0.50–0.50)       | 34 | –0.25 (–1.00–0.25)     | 26 | <b>0.006</b> |
| DeltaW1-W8-psychol. Discomfort <sup>b</sup> | –0.12 (–0.47–0.36)      | 36 | –0.41 (–0.75–0.12)     | 26 | <b>0.002</b> |
| DeltaW1-W8-satisfaction <sup>b</sup>        | 0.00 (–0.81–0.75)       | 34 | 0.00 (–1.00–0.25)      | 26 | 0.086        |
| W12-total <sup>b</sup>                      | 2.36 (1.75–2.92)        | 26 | 2.32 (1.89–2.78)       | 26 | 0.700        |
| W12-worries <sup>b</sup>                    | 2.42 (1.25–2.92)        | 26 | 2.41 (1.83–3.08)       | 26 | 0.610        |
| W12-phys. Discomfort <sup>b</sup>           | 2.75 (1.75–3.25)        | 26 | 2.50 (1.50–3.00)       | 26 | 0.361        |
| W12-psychol. Discomfort <sup>b</sup>        | 1.56 (0.97–2.50)        | 26 | 1.75 (0.87–2.25)       | 26 | 0.706        |
| W12-satisfaction <sup>b</sup>               | 3.00 (2.00–4.00)        | 26 | 3.50 (2.50–4.00)       | 26 | 0.179        |
| W32-total <sup>b</sup>                      | 2.40 (1.68–2.83)        | 38 | 2.32 (1.70–2.78)       | 43 | 0.946        |
| W32-worries <sup>b</sup>                    | 2.42 (1.50–2.85)        | 38 | 2.42 (1.75–2.83)       | 43 | 0.612        |
| W32-phys. Discomfort <sup>b</sup>           | 2.50 (1.75–3.06)        | 38 | 2.25 (1.50–3.00)       | 43 | 0.471        |

(Continues)

**TABLE 3** (Continued)

|                                      | Group sham<br>Med (IQR) | MD | Group IFT<br>Med (IQR) | MD | p value |
|--------------------------------------|-------------------------|----|------------------------|----|---------|
| W32-psychol. Discomfort <sup>b</sup> | 1.81 (0.84–2.40)        | 38 | 1.69 (0.97–2.62)       | 43 | 0.797   |
| W32-satisfaction <sup>b</sup>        | 3.50 (2.94–4.00)        | 38 | 3.50 (2.50–4.00)       | 43 | 0.958   |

Note: Bold:  $p < 0.05$ .

Abbreviations: Delta Wi- W1, stimulation beginning; MD, missing data; Med (IQR), medians (interquartile range); Med (IQR): Wi, week-i; PAC-QOL, Patient Assessment of Constipation Quality of Life; PAC-SYM, Patient Assessment of Constipation Symptoms; W8, stimulation end; W12, 1-month poststimulation end; W32, 6-month poststimulation end.

Wy: change score between Wi and Wy.

<sup>a</sup>from 0 (no symptoms) to 4 (very severe symptoms).

<sup>b</sup>from 0 (highest) to 4 (lowest QOL).

**TABLE 4** Colonic transit time (CTT), anorectal manometry, and patient satisfaction.

|   |           | Group sham    | Group IFT     | p value |
|---|-----------|---------------|---------------|---------|
| CTT at W8, hours                              | Med (IQR) | 82 (46–127)   | 80 (38–114)   | 0.452   |
|   | MD        | 20            | 23            |         |
| DeltaW1-W8-CTT, hours                         | Med (IQR) | −2 (−22–15)   | −6 (−32–13)   | 0.349   |
|   | MD        | 22            | 24            |         |
| Anal resting pressure at W8, mmHg             | Med (IQR) | 58 (43–74)    | 65 (49–83)    | 0.057   |
|   | MD        | 22            | 14            |         |
| Voluntary contraction at W8, mmHg             | Med (IQR) | 131 (98–168)  | 146 (97–192)  | 0.365   |
|   | MD        | 23            | 16            |         |
| Maximal tolerable volume at W8, ml            | Med (IQR) | 185 (150–242) | 180 (135–240) | 0.720   |
|   | MD        | 26            | 17            |         |
| Presence of anismus at W8                     | N (%)     | 41 (68.3)     | 43 (59.7)     | 0.365   |
|   | MD        | 28            | 25            |         |
| Patient satisfaction at W4, AVS <sup>a</sup>  | Med (IQR) | 2 (0–3)       | 2 (0–3)       | 0.800   |
|   | MD        | 9             | 10            |         |
| Patient satisfaction at W8, AVS <sup>a</sup>  | Med (IQR) | 2 (0–3)       | 2 (0–3)       | 0.401   |
|   | MD        | 15            | 16            |         |
| Patient satisfaction at W12, AVS <sup>a</sup> | Med (IQR) | 2 (0–3)       | 1 (0–3)       | 0.373   |
|   | MD        | 22            | 25            |         |
| Patient satisfaction at W32, AVS <sup>a</sup> | Med (IQR) | 0.50 (0–2)    | 1.0 (0–2.5)   | 0.617   |
|   | MD        | 32            | 40            |         |
| Number of stools at W12                       | Med (IQR) | 4 (3–7)       | 4 (2–6)       | 0.366   |
|   | MD        | 33            | 37            |         |
| Number of stools at W32                       | Med (IQR) | 4 (2–7)       | 5 (2–7)       | 0.818   |
|   | MD        | 52            | 57            |         |
| Use of bisacodyl at W8                        | N (%)     | 21 (28.40)    | 16 (19)       | 0.167   |
|   | MD        | 14            | 13            |         |
| Treatment compliance at W8 (N = 69)           | N (%)     | 26 (78.80)    | 34 (94.40)    | 0.076   |

Abbreviations: AVS, analogical visual scale; CTT, Colonic transit time; Med (IQR), medians (interquartile range); Wi, week-i.

<sup>a</sup>from 0 (not satisfied at all) to 5 (completely satisfied).

sympathetic and parasympathetic nerves of the intestine but is unlikely to directly stimulate the pelvic floor and the external anal sphincter.<sup>13</sup> However, in the case of IFT, we can hypothesize that since transit constipation and anismus mechanisms may be linked, a direct or indirect beneficial effect on both can be observed. The fibers that are most likely to be affected by the stimulation are the large diameter B fibers since the stimulation is not painful excluding pain fibers C and without visible external motor response excluding Ab fibers. During IFT, the stimulation of somatic afferent fibers via somato-visceral reflexes may also be involved as previously demonstrated in cats by Vitton et al.<sup>30</sup> Direct stimulation of intrinsic excitatory neurons located in the intramural plexus can also be hypothesized.

Surprisingly, although the placebo response is well known, the one observed in our sham group was higher than that which is usually reported in the literature but remains in agreement with the placebo effect rate reported from some data for functional bowel disorders.<sup>19,31</sup> Moreover, as reported by some authors, this high rate of placebo effect may be linked to patients' expectations that are important in CC patients.<sup>31</sup> In the case of electrical stimulations, a significant effect of sham stimulation on symptoms and QOL scores has also been described. For this reason, the use of a sham control is very important.<sup>32</sup> In our study, patients in the control group did not receive any stimulation. In the literature, the choice of the "sham" in trials for constipation remains controversial. Indeed, sham stimulation is defined as a form of placebo control in which patients are delivered an inert stimulus in a blinded manner. However, in most randomized trials using stimulation (sacral nerve stimulation or electroacupuncture), the device was turned off, meaning that, as in our study, the patients did not receive any stimulation.<sup>32</sup> Moreover, in our study, the patients in the sham group did not perceive any stimulation, which should have induced a lesser placebo effect.

In addition, in both groups, the mean number of CSBMs improved during the baseline period only after inclusion. Although it is not easy to understand, there are at least two possible explanations. The first explanation may be that most patients with CC are dissatisfied with current treatment options and report safety-related concerns and adverse effects.<sup>11</sup> Patients and practitioners are waiting for a new innovative nonpharmacological treatment. Thus, it can be assumed that simply being included in the study may have had a positive impact on patients' symptoms, even before the stimulation began. The second explanation may be that the empathy of nurses and other practitioners listening and providing comprehensive care to patients, who often report that their symptoms are not taken seriously, had an impact.<sup>11,12</sup>

Our primary endpoint was chosen considering findings from most randomized trials assessing the treatment of constipation.<sup>19</sup> However, if the number of stools is often the criterion chosen by doctors, it does not correspond in practice to that of patients. The literature suggests that constipation has multifaceted symptoms and that straining is a more frequent concern than the self-reported frequency of stools. Thus, to better evaluate patients' symptoms, questionnaires such as PAC-SYM have been developed.<sup>20</sup> In our

study, a significant improvement in the total PAC-SYM score was observed in the IFT group at the end of the treatment period.

This improvement was particularly reflected in the abdominal and rectal subscores, and the abdominal subscores had already improved at the mid-term evaluation after 4 weeks of treatment.<sup>12</sup> These results are particularly relevant in clinical practice because they correspond to the main complaints of CC patients.<sup>6,7</sup> The impact of a treatment for CC on the QOL is also important to evaluate. For this purpose, we used the PAC-QOL score, which is largely validated and assessed in most randomized studies on CC. We observed a significant difference in the total mean improvement in the IFT group at the end of the stimulation period. It is interesting to note that changes between baseline and W8 were significant for the 3 subscores: worries, physical discomfort, and psychological discomfort. The satisfaction subscore was significantly better in the IFT group. The PAC-QOL score is particularly important because the authors describe it as the most reflective perceived improvement in CC symptoms.<sup>21</sup> However, for both PAC-SYM and PAC-QOL, no change was observed after 4 weeks of treatment, except for the PAC-SYM abdominal subscore, which was improved in the IFT group, indicating that an 8-week treatment is necessary to obtain stimulation efficiency. On the other hand, the beneficial effects of treatment were not maintained at 12 and 38 weeks. This may be due to a cessation of the effect of the stimulation, although with some electrical therapies a maintenance of the effect can still be observed after the cessation of the treatment. Nevertheless, it can also be explained by a placebo effect, which is frequent in this type of pathology. It may seem contradictory to not observe a significant improvement in the AVS. However, we can assume that, in our study, the question was confusing. Indeed, the question concerned satisfaction "with the device" and not with the overall improvement in symptoms.

In the first studies in children, IFT appeared to be a promising new and noninvasive treatment for CC.<sup>13-15</sup> These data were confirmed in trials with adults, not only in our first pilot study but also in the study by Moore et al.<sup>16,17</sup> In both studies, IFT improved not only the number of stools but also symptoms and QOL scores. However, although our pilot study and the study by Moore and colleagues were encouraging, both included a small number of patients (11 and 33, respectively) and were open or single-blinded trials. Unfortunately, our study, which is the first double-blind randomized multicenter trial, did not confirm the results for the primary endpoint. Among the secondary endpoints, no significant modification was observed in CTT, anorectal manometry parameters, AVS, or bisacodyl use. However, we did observe a significant effect on symptoms and QOL scores, which is particularly clinically relevant. In contrast, whereas an enduring effect of the stimulation has been reported by Chase and Moore, it was not confirmed in our trial since the improvement observed in PAC-SYM and PAC-QOL scores was not maintained at 1 month or 6 months after the end of the stimulation period. Our study has two main limitations. The first limitation is that we did not meet the primary endpoint. Nevertheless, on the one hand, clinically relevant scores were improved, and on the other hand, one may question the

validity of this endpoint when evaluating a stimulation device and not a drug. The second limitation is that the required number of subjects was not reached at the end of the study. Nevertheless, this study included a high number of patients and has, to date, the largest sample of patients for whom IFT is evaluated in the treatment of CC. Moreover, after adjustment for the mechanism of constipation and the baseline severity of constipation, there was an association with the IFT effect. This indicates that rigorous patient selection and subgroup analysis is fundamental. Our study confirms the difficulty of objectively assessing a functional disorder as complex as CC.

In conclusion, although the primary endpoint was not reached in this first double-blind controlled study, we showed that IFT can significantly alleviate the symptoms and improve the QOL of CC patients. It can be assumed that new treatments require different modes of evaluation and that the assessment of patient-reported outcomes may become a priority among therapeutic targets of CC.

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### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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## SUPPORTING INFORMATION

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

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