



Original Reports

Spa Therapy for the Treatment of Fibromyalgia: An Open, Randomized Multicenter Trial

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Abstract: Fibromyalgia is a common chronic pain pathology with an incidence of 4.3 per 1,000 person-years. An open, randomized clinical trial of patients with fibromyalgia comparing an immediate vs. delayed 18-day spa therapy in five spa therapy care facilities in France enrolled 220 patients. Randomization was in blocks of four, stratified by center, severity of fibromyalgia and previous spa therapy. Patients continued usual treatment. The main endpoint was the number of patients achieving minimal clinically important difference at 6 months, defined as 14% change in their baseline fibromyalgia impact questionnaire score. The intention-to-treat analysis included 100 and 106 patients in the intervention and control groups, respectively. At 6 months, 45/100 (45.0%) and 30/106 (28.3%) patients in the intervention and control groups, respectively, achieved a minimal clinically important difference ($P = .013$). There was also a significant improvement in pain, fatigue, and symptom severity (secondary outcomes) in the intervention group but not for generic quality of life (QOL), sleep or physical activity. None of the 33 serious adverse events reported by 25 patients were related to the spa therapy. Our results demonstrate the benefit of spa treatment in patients with fibromyalgia.

Perspective: A 12-month, open, randomized clinical trial of 220 patients with fibromyalgia compared an immediate versus delayed (ie, after 6 months) 18-day spa therapy. The results showed a clinically significant improvement at 6 months for those who received immediate therapy which was maintained up to 12 months.

Trial registration number: *ClinicalTrials.gov*: NCT02265029

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Key Words: *Fibromyalgia, spa treatment, pain measurement, patient satisfaction, treatment outcome.*

Fibromyalgia syndrome is a common chronic pain condition, which is usually diagnosed in patients aged 30 and 50 years.^{10,39} The incidence of

physician-diagnosed fibromyalgia in the general population is 4.3 per 1,000 person-years (range = 0.33–18.8) with about seven-times more women than men being

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affected. The physiopathology is not fully understood and there are no specific somatic signs. The International Association for the Study of Pain and American College of Rheumatology define fibromyalgia as chronic widespread pain, lasting for at least three months, without any apparent tissue damage or inflammation.³⁸ However, recent research suggest that fibromyalgia pain could be due to central nervous system sensitization, peripheral small fiber neuropathy or impaired cell-mediated immunity.^{8,11,15,16,21,29,32,37}

The chronic pain is associated with fatigue, waking up without feeling rested, sleep disorders, cognitive disorders, other frequent general symptoms (eg, tension headaches, irritable bowel syndrome, pain in the temporomandibular joint), anxiety, and depression.⁹ Diagnostic criteria include these symptoms, and pain assessment. Diagnosis involves determining a global score combining the number of painful sites (widespread pain index, WPI) and a symptom severity (SS) score.³⁸

The fibromyalgia impact questionnaire (FIQ, score 0 to 100) is used to rate the severity of the fibromyalgia in the past week.⁶ See the online supplementary for more details. A FIQ score <39 corresponds to a mild form, a score of 39 to 58 corresponds to a moderate form and a score of 59 to 100 corresponds to a severe form. Overall, 12% of patients have mild disease, 69% have a moderate disease and 19% have severe disease.³⁵

The heterogeneous symptoms and poorly understood pathogenesis makes treatment for patients with fibromyalgia challenging.^{2,12} The European League Against Rheumatism (EULAR) evidence-based guidelines recommend personalized management with a graduated approach adapted to the symptoms of fibromyalgia, shared decision-making, and non-drug therapies as first-line treatment.²⁶ Physical exercise was the only non-drug therapy with a 'strong' recommendation and other non-drug therapies, including spa therapy, had 'weak' recommendations. Since these guidelines were published results from randomized clinical trials assessing cognitive therapeutic approaches (mindfulness-based stress reduction and attention bias modification), in addition to usual treatment suggest that there is some short-term benefit for pain reduction with these approaches, although the long-term benefit is less certain.^{7,31,34}

In Europe, spa therapy is frequently prescribed for patients with painful chronic diseases, such as osteoarthritis. Spa therapy, as practiced in France and other European countries, is a complex therapeutic intervention associating different hydrothermal treatments (such as hydromassage baths, hydro-mineral mud applications, body jet showers, and water affusion massages) with physiotherapy (such as supervised collective exercises in mineral water pools) and education (informal or organized in specific therapeutic programs). For example, the study Thermarthrose reported that a 3-week course of spa therapy together with home exercises and usual pharmacological treatments was beneficial at 6 months in patients with knee osteoarthritis compared with home exercises and usual pharmacological

Spa Therapy for the Treatment of Fibromyalgia treatments, without spa therapy.¹⁸ Several literature reviews have concluded that spa therapy could provide a small overall improvement in pain and health-related quality of life in patients with fibromyalgia, at least in the short-term, but the evidence is weak, particularly for long-term benefits.^{1,5,14,19,20,24,27,30} Therefore, high-quality studies assessing long-term maintenance of the beneficial effects with larger sample sizes are needed to confirm the therapeutic benefit of spa therapy. Here we report results from a randomized clinical trial that aimed to assess the medium- and long-term benefits of spa therapy in patients with fibromyalgia syndrome, using recognized diagnostic criteria.

Methods

Study Design

The trial protocol was approved by the South-East II Ethics Committee (Lyon) on 16 April 2014 (ID: 2014-A00184-43). Patients with fibromyalgia were recruited between September 2014 and September 2017 and randomized to receive immediate or delayed spa therapy in an open randomized clinical trial. Patients were treated in one of the five participating spa therapy care facilities located in Aix-les-Bains, Allevard-les-Bains, Bourbon-Lancy, Lamalou-les-Bains and Uriage-les-Bains in France. Patients were recruited throughout France, either during a consultation with a participating pain or rheumatology specialist (n = 11) in private practice or hospital, through patient associations (pre-screening and transfer to a study physician by the coordination center) or selected by the coordination center via press advertisement or posters in the spa therapy care facilities.

Randomization, prepared by an external organization (ClinInfo, Lyon France), was centralized via an electronic case report form (eCRF) using a fixed block size of 4, stratified for the spa therapy care facility, FIQ score at inclusion <59 or ≥ 59 , and first spa therapy or not.

Patients

Patients were eligible if they gave informed consent, had fibromyalgia for over a year, based on the American College of Rheumatology 2010 criteria,³⁸ had received stable medical treatment over the previous three months, had a FIQ score ≥ 39 (moderate to severe fibromyalgia), were aged >18 years, were available for the 3-week residential spa therapy within 6 weeks of inclusion (immediate group) or after the 6-month follow-up visit (delayed group), and were available for a 12-month follow-up visit. Exclusion criteria were contra-indication or intolerance to any aspect of the spa treatments (progressive cancer, behavioral disorders, immune deficiency, patient with psychosis on medication or not), rheumatology spa treatment in the current calendar year, changes in pain-related treatments in the previous three months, other known severe chronic diseases, such as severe asthma, severe cardiac, respiratory, hepatic or renal insufficiency, progressive inflammatory rheumatic disease and inflammatory colitis.

Intervention

Eleven investigator centers, located throughout France, not at the spa therapy care facilities, were responsible for recruiting and evaluating the patients. The patients were randomized to either the intervention group and received a 3-week spa therapy (6 d/wk, 18 days total) in one of the five participating spa therapy care facilities within 6 weeks of inclusion to the control group and received the same intervention after they had attended the 6-month study visit.

The spa therapy was standardized in the participating spa therapy care facilities. Each patient received 72 treatments during 2 hours in the morning for 18 days including the following:

1. Hydromassage baths
2. Hydro-mineral mud applications
3. Body jet showers with adjustment of the intensity of jets
4. Water affusion massages
5. Collective exercise in a mineral water pool under supervision of a state-registered physiotherapist

In addition, patients could attend a conference on their disease and weekly walking training sessions, but these activities were not mandatory. The walking training was given by a physical activity (APA) coach or a state-registered physiotherapist, with a progressive program over the 3 weeks. The content of both the conference and training was standardized at all centers. During the 3-week spa therapy the patients also had free access to on-site gym facilities.

The study patients were with other patients undergoing spa therapy. All patients continued to receive their usual treatments. The spa mineral water and treatments were approved and controlled by the French authorities. Attendance, tolerance, and correct use of the treatments was verified by a spa physician during consultations at the start, middle and end of the 3-week spa therapy.

The patients randomized to the delayed spa therapy group followed their usual treatment up to the 6-month follow-up visit when the primary outcome was evaluated. Then they received their 3-week spa therapy. This group was considered as the control group, since the primary outcome was evaluated at the 6-month follow-up visit before they had received the intervention.

Assessments

Efficacy

All patients were evaluated at baseline and followed-up at 3, 6, 9, and 12 months by the study physician who performed a clinical examination and completed the eCRF. At the same time as these visits, the coordinating center sent questionnaires (see below) directly to the patients, with a prepaid return envelope.

The primary endpoint was the percentage of patients with a minimal clinically important difference (MCID)

defined as a decrease of more than 14% in their FIQ score at 6 months compared with inclusion.^{3,23}

The secondary endpoints were: generic quality of life score measured by EQ-5D-3L¹³, patient global assessment (PGA) and investigator global assessment (not the staff at the spa therapy care facilities) (IGA) scales, VAS (visual analogue scale) for pain (score between 0 and 100), pain catastrophizing scale (French version, PCS-CF scale), number of pain points (WPI score), symptom severity (SS) score, sleep (Pittsburgh Sleep Quality Index) and sleepiness (Epworth scale), fatigue (Pichot scale), Hospital Anxiety and Depression Scale (HAD scale), ability to manage a stressful situation (Coping questionnaire), physical activity (Baecke questionnaire), body mass index (BMI), and drug treatment for fibromyalgia. A brief description of the instruments used and their interpretation is given in Table 1.

All questionnaire scores were collected at baseline, and at 3-months, 6-months, 9-months, and 12-months, except for the EQ-5D-3L and Coping questionnaires, which were collected at baseline, and 6- and 12-months.

The VAS pain results were collected every three months up to 12 months from the patients' diaries. These diaries, which were paper-based, were used by the patients to record their physical activity, their treatments and any medical events, as well as the VAS during the 12-month follow-up.

Safety

All serious adverse events (SAEs) were recorded and notified to the French clinical trials pharmacovigilance system.

Sample Size Calculation

We assumed that the success rate in the intervention group would be 50%, ie, that 50% of the patients would achieve a decrease of more than 14% in their FIQ score at 6 months compared with inclusion and that the success rate in the control group would be 30%.³ With an alpha risk of 5% and power of 80%, the number of patients needed was estimated to be 95 per group.³⁶ To allow for potential lost-to-follow-up, we included 220 patients, 110 per group.

Statistical Analysis

The statistician was not blinded to the treatment groups. Intention-to-treat analyses were performed. Categorical variables were expressed as frequencies and percentages and continuous variables as means and SDs, or medians and interquartile ranges (IQR; 25th and 75th percentiles). The primary endpoint was assessed using Chi² test. Risk ratios with 95% confidence intervals (CIs), odds ratios and 95% CIs, numbers needed to treat (NNT), and effect sizes were calculated. The Mantel-Haenszel test of homogeneity was used for subgroup analyses and results showing an interaction ($P < .20$) are presented here. Two-sided P values less than .05 were considered statistically significant. Analyses were

Table 1. Brief Description of Instruments Used for Primary and Secondary Endpoints

| <i>INSTRUMENT NAME (ABBREVIATION)</i> | <i>ASPECT MEASURED</i> | <i>SCORE(MIN – MAX)</i> | <i>INTERPRETATION</i> |
|---|---|-------------------------|--|
| Fibromyalgia impact questionnaire (FIQ) | Impact of fibromyalgia on current overall health status | 0 – 100 | Higher scores indicate greater impact |
| Baecke physical activity questionnaire | Evaluation of level of physical activity | 3 – 15 | Higher scores indicate higher levels of physical activities |
| Coping questionnaire - stress | Patient's ability to manage a stressful situation | 10 – 40 | Higher scores indicate greater difficult to manage a stressful situation |
| Coping questionnaire - emotions | Patient's ability to manage their emotions in a stressful situation | 9 – 36 | Higher scores indicate greater difficult to manage emotions in a stressful situation |
| Coping questionnaire - social support | Patient's need for social support to manage a stressful situation | 8 – 32 | Higher scores indicate greater need for social support to manage a stressful situation |
| Epworth sleepiness score | Evaluation of patient's sleepiness | 0 – 24 | Higher scores indicate more sleepiness |
| EQ-5D-3L score | Generic quality of life | -0.53 – 1 | Higher scores indicate better quality of life |
| EQ5D-3L perceived health | Generic quality of life | 0 – 100 | Higher scores indicate better perceived health status |
| Hospital anxiety and depression scale – anxiety (HADS– anxiety) | Evaluation of anxiety | 0 – 21 | Higher scores indicate higher anxiety |
| Hospital anxiety and depression scale – depression (HADS– depression) | Evaluation of depression | 0 – 21 | Higher scores indicate greater depression |
| Investigator global assessment (IGA) | Investigator-perceived overall health | 0 – 10 | Lower scores indicate good perception of overall health |
| Pain catastrophizing scale - French version (PCS-CF) | Quantification of an individual's pain experience | 0 – 52 | Higher scores indicate worse experience of pain |
| Pain visual analog scale (Pain VAS) | Overall evaluation of pain | 0 – 100 | Higher scores indicate worse pain |
| Patient global assessment (PGA) | Patient-perceived overall health | 0 – 10 | Lower scores indicate good perception of overall health |
| Pichot's fatigue scale | Evaluation of patient's fatigue | 0 – 32 | Higher scores indicate higher fatigue |
| Pittsburgh sleep quality index (PSQI): | Evaluation of sleep quality | 0 – 21 | Lower scores indicate better sleep quality |
| Symptom severity scale score | Evaluation of symptom severity | 0 – 12 | Higher scores indicate greater symptom severity |
| Widespread pain index (WPI) | Number of painful points | 0 – 19 | Higher scores indicate higher numbers of painful points |

performed using Stata software (version 15.0). More details can be found in the online supplementary material.

We performed an *a posteriori* analysis to assess the impact of residential therapy versus day therapy (where the patients went home daily after therapy) on the primary endpoint.

Results

Patients

Between September 2014 and September 2017, more than 400 patients were preselected and 220 patients were randomized to the immediate spa therapy (intervention) or delayed spa therapy (control) groups (Fig 1). Follow up was completed in October 2018. Two patients were excluded from the control group after randomization because their therapeutic management had varied substantially in the three months prior to inclusion. In the intervention group, 19 of the 110 patients could not be analyzed, therefore 91 were included in the ITT analysis; 98 patients received immediate spa therapy. In the control group, 10 of the 108 patients could not be analyzed, therefore 98 patients were included in the ITT analysis; 100 patients received delayed spa therapy. The patients' characteristics at enrollment are summarized in Table 2. The overall baseline scores for EQ-5D-3L and HADs were similar between the intervention and control groups. However, we observed that the scores were worse as the severity increased (Supplementary Table 1).

Compliance

The spa therapies prescribed and carried out are summarized in Supplementary Table 2. Five patients discontinued spa treatment before completion due to pain ($n = 2$), sprained ankle during the weekend ($n = 1$) and unknown ($n = 2$).

Efficacy

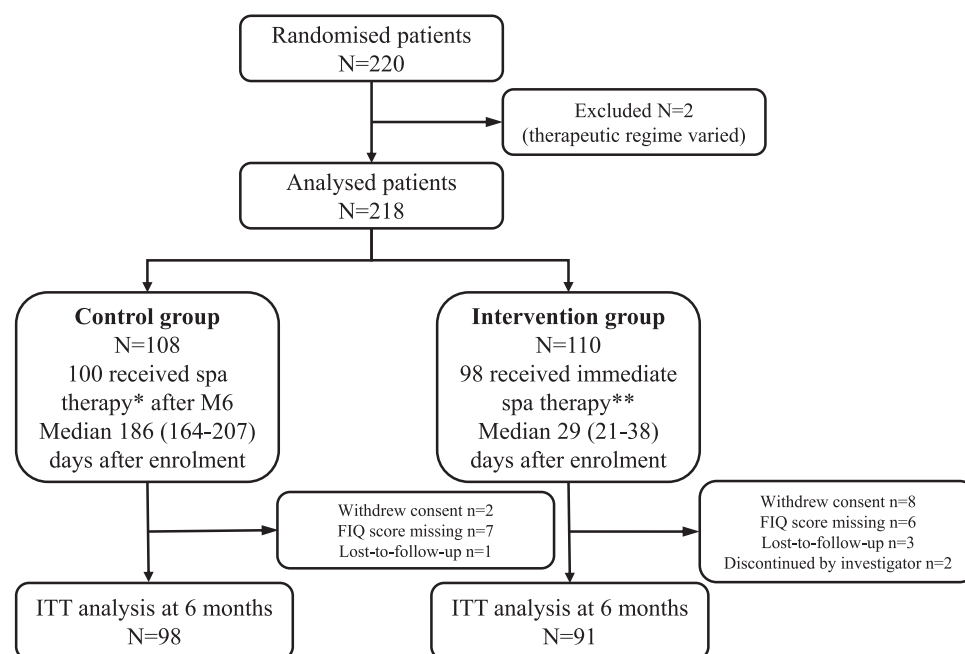
Primary Endpoint

The success rate at 6 months, ie, the percentage of patients with more than a 14% decrease in their FIQ score at 6 months compared with their inclusion score, was statistically significantly higher in the intervention group with or without replacement of missing values (45/100 (45.0%) vs 30/106 (28.3%), $P = .013$ and 41/91 (45.1%) vs 29/98 (29.6%), $P = .028$, respectively) (Table 3). The risk ratio for success was 1.59 (95% CI: 1.10 – 2.31), the odds ratio was 2.07 (95% CI: 1.16 – 3.69) and the NNT was 6 patients (values calculated with replacement of missing values).

The FIQ score decrease was between 15% and 30% for 20.9% and 17.4% of the patients in the intervention and control groups, respectively, between, 31% and 45% for 9.9% and 9.2%, respectively and greater than 45% for 14.3% and 3.1%, respectively.

Secondary Endpoints

The change in the FIQ score over 6 months was statistically significantly different between the 2 groups ($P = .001$), with an effect size of 0.49 (Fig 2). The FIQ



*Aix-les Bains n=30; Allevard-les-Bains n=22; Bourbon-Lancy n=12; Lamalou-les-Bains n=24;

Uriage-les-Bains n=20 median 22 (20-24) patients by spa resort (min=12; max=30)

**Aix-les Bains n=31; Allevard-les-Bains n=22; Bourbon-Lancy n=10; Lamalou-les-Bains n=26;

Uriage-les-Bains n=21 median 22 (21-26) patients by spa resort (min=10; max=31)

Figure 1. Study flow chart – Intention to treat (ITT) analysis.

Table 2. Baseline Characteristics of Participants

| | CONTROL GROUP(N=108) | INTERVENTION GROUP(N=110) | ALL(N=218) |
|---|--------------------------------|--------------------------------|--------------------------------|
| Female, n/N (%) | 99 (91.7) | 99 (90.0) | 198 (90.8) |
| Age, mean \pm SD | 49.2 \pm 8.8 | 50.4 \pm 8.9 | 49.8 \pm 8.8 |
| Spa therapy care facility, n (%) | | | |
| Aix-les-Bains | 30 (27.8) | 31 (28.2) | 61 (28.0) |
| Allevard-les-Bains | 22 (20.4) | 22 (20.0) | 44 (20.2) |
| Bourbon-Lancy | 12 (11.1) | 10 (9.1) | 22 (10.1) |
| Lamalou-les-Bains | 24 (22.2) | 26 (23.6) | 50 (22.9) |
| Uriage-les-Bains | 20 (18.5) | 21 (19.1) | 41 (18.8) |
| First time spa therapy, n (%) | 70 (64.8) | 73 (66.4) | 143 (65.6) |
| Professional status, n (%) | | | |
| Employed | 48 (44.4) | 36 (32.7) | 84 (38.5) |
| Sick leave | 27 (25.0) | 25 (22.7) | 52 (23.9) |
| Disability | 19 (17.6) | 28 (25.5) | 47 (21.6) |
| Retired | 8 (7.4) | 13 (11.8) | 21 (9.6) |
| Other | 6 (5.6) | 8 (7.3) | 14 (6.4) |
| Level of education, n (%) | | | |
| < Baccalaureate | 34 (31.5) | 35 (31.8) | 69 (31.7) |
| High school diploma (baccalaureate) | 33 (30.6) | 28 (25.5) | 61 (28.0) |
| University degree or higher* | 41 (38.0) | 47 (42.7) | 88 (40.4) |
| BMI, mean \pm SD | 27.7 \pm 5.8 <i>n=108</i> | 26.6 \pm 6.6 <i>n=107</i> | 27.2 \pm 6.2 <i>n=215</i> |
| Clinical history and comorbidities, n (%) (<i>more than one answer possible</i>) | <i>n=108</i> | <i>n=108</i> | <i>n=216</i> |
| Psychological trauma or prolonged stress | 71 (65.7) | 64 (59.3) | 135 (62.5) |
| Depression | 58 (53.7) | 64 (59.3) | 122 (56.5) |
| Irritable bowel syndrome | 54 (50.0) | 63 (58.3) | 117 (54.2) |
| Neurological disease | | | |
| Migraine | 37 (34.3) | 24 (22.2) | 61 (28.2) |
| Neuropathic pain | 15 (13.9) | 20 (18.5) | 35 (16.2) |
| Other neurological disease | 22 (20.4) | 21 (19.4) | 43 (19.9) |
| Menopause | 42 (38.9) | 49 (45.4) | 91 (42.1) |
| Rheumatic disease | 29 (26.9) | 33 (30.6) | 62 (28.7) |
| Sleep apnea | 15 (13.9) | 18 (16.7) | 33 (15.3) |
| Raynaud's disease | 7 (6.5) | 16 (14.8) | 23 (10.6) |
| Cancer | 2 (1.9) | 6 (5.6) | 8 (3.7) |
| Effort deconditioning | 18 (16.7) | 25 (23.1) | 43 (19.9) |
| Current medication for fibromyalgia n (%) (<i>more than one answer possible</i>) | <i>n=107</i> | <i>n=108</i> | <i>n=215</i> |
| Weak opioids (Codeine, Tramadol, Lamaline) | 59 (55.1) | 61 (56.5) | 120 (55.8) |
| Paracetamol | 55 (51.4) | 52 (48.1) | 107 (49.8) |
| Antidepressants (tricyclic, SNRIs, SRIs) | 47 (43.9) | 48 (44.4) | 95 (44.2) |
| NSAIDS | 20 (18.7) | 22 (20.4) | 42 (19.5) |
| Pregabalin | 12 (11.2) | 13 (12.0) | 25 (11.6) |
| Nefopam | 9 (8.4) | 6 (5.6) | 15 (7.0) |
| Other fibromyalgia therapies in the last three months, n (%) (<i>more than one answer possible</i>) | <i>n=107</i> | <i>n=109</i> | <i>n=216</i> |
| Use of health care system | 100 (93.5) | 107 (98.2) | 207 (95.8) |
| Physical exercise | 81 (75.7) | 76 (69.7) | 157 (72.7) |
| Psycho-behavioral therapy sessions | 54 (50.5) | 48 (44.0) | 102 (47.2) |
| Alternative and complementary medicine | 47 (43.9) | 54 (49.5) | 101 (46.8) |
| Dietary supplements, herbal medicines, or homeopathy | 47 (43.9) | 48 (44.0) | 95 (44.0) |
| FIQ, score, mean \pm SD | 70.5 \pm 10.1 | 69.0 \pm 12.5 | 69.7 \pm 11.4 |
| FIQ score < 59 (moderate), n (%) | 14 (13.0) | 23 (20.9) | 37 (17.0) |
| FIQ score \geq 59 (severe), n (%) | 94 (87.0) | 87 (79.1) | 181 (83.0) |
| Widespread pain index score, mean \pm SD | 13.8 \pm 2.8 | 14.3 \pm 3.0 | 14.0 \pm 2.9 |
| Symptom severity scale score, mean \pm SD | 9.8 \pm 1.6 | 10.0 \pm 1.5 | 9.9 \pm 1.6 |
| Time since first fibromyalgia signs (years), median [IQR] | 8 [5-14] | 10 [6-20] | 9 [5-16] |

(continued on next page)

Table 2. Continued

| | CONTROL GROUP(N=108) | INTERVENTION GROUP(N=110) | ALL(N=218) |
|---|-------------------------|---------------------------|-------------------------|
| Time since fibromyalgia diagnosis (years), median [IQR] | 4 [2-7] | 5 [3-8] | 4 [3-8] |
| EQ-5D-3L score, mean \pm SD | 0.25 \pm 0.24 (n=93) | 0.26 \pm 0.29 (n=93) | 0.26 \pm 0.27 (n=186) |
| EQ-5D-3L perceived health, mean \pm SD | 38.6 \pm 15.9 (n=96) | 42.8 \pm 18.3 (n=96) | 40.7 \pm 17.2 (n=192) |
| Patient global assessment, mean \pm SD | 7.4 \pm 1.6 (n=103) | 6.9 \pm 2.1 (n=104) | 7.1 \pm 1.9 (n=207) |
| Investigator global assessment, mean \pm SD | 6.0 \pm 2.0 (n=104) | 6.5 \pm 1.6 (n=103) | 6.3 \pm 1.8 (n=207) |
| Pain VAS (patient diary), mean \pm SD | 59.6 \pm 14.0 (n=96) | 61.4 \pm 17.1 (n=93) | 60.5 \pm 15.6 (n=189) |
| Pain Catastrophizing Scale (French) score, mean \pm SD | 30.8 \pm 11.4 (n=104) | 30.2 \pm 12.0 (n=106) | 30.5 \pm 11.7 (n=210) |
| Pittsburgh Sleep Quality Index score, mean \pm SD | 12.3 \pm 4.0 (n=104) | 12.3 \pm 4.1 (n=105) | 12.3 \pm 4.0 (n=209) |
| Epworth Sleepiness Scale score, mean \pm SD | 12.3 \pm 6.2 (n=103) | 12.7 \pm 5.8 (n=106) | 12.5 \pm 6.0 (n=209) |
| Pichot's Fatigue Scale score, mean \pm SD | 26.2 \pm 4.2 (n=103) | 25.3 \pm 4.7 (n=105) | 25.7 \pm 4.5 (n=208) |
| Hospital Anxiety and Depression Scale – Anxiety score, mean \pm SD | 12.2 \pm 4.0 (n=104) | 11.6 \pm 4.3 (n=105) | 11.9 \pm 4.2 (n=209) |
| Hospital Anxiety and Depression Scale – Depression score, mean \pm SD | 10.3 \pm 3.7 (n=104) | 9.8 \pm 4.1 (n=105) | 10.0 \pm 3.9 (n=209) |
| Coping Scale Score – Stress, mean \pm SD | 26.2 \pm 6.4 (n=96) | 26.7 \pm 6.1 (n=97) | 26.5 \pm 6.2 (n=193) |
| Coping Scale Score – Emotion, mean \pm SD | 23.7 \pm 5.7 (n=96) | 24.4 \pm 5.6 (n=97) | 24.1 \pm 5.7 (n=193) |
| Coping Scale Score – Social Support, mean \pm SD | 20.5 \pm 5.5 (n=97) | 21.8 \pm 5.3 (n=98) | 21.2 \pm 5.4 (n=195) |
| Baecke physical activity questionnaire score, mean \pm SD | 7.2 \pm 1.6 (n=99) | 7.2 \pm 1.6 (n=103) | 7.2 \pm 1.6 (n=202) |

*The number of women with a university degree or higher is slightly higher than the national average of 36.2% but was similar in both groups. BMI: body mass index; FIQ: fibromyalgia impact questionnaire; IQR: interquartile range; NSAIDs: nonsteroidal anti-inflammatory drugs; SNRIs: serotonin and norepinephrine reuptake inhibitors; SRIs: serotonin reuptake inhibitors; VAS: visual analogue scale

score at 6 months was <39 (mild impairment) for 6/98 (6.1%) and 17/91 (18.7%) patients in the control and intervention groups, respectively ($P = .008$).

The changes of the other scores over time are presented in Table 3. The evolution of the investigator's global impression of the disease activity was statistically different between the 2 groups ($P < .001$) with an improvement for the intervention group. No difference was seen for the patient's global impression ($P = .810$). The Pain VAS, PCS-CF, HADs (anxiety and depression), Pichot's Fatigue Scale and SS scores all showed a statistically significant improvement between inclusion and 6 months for the intervention group compared with the control group (Table 3).

The social support score in the Coping Scale was statistically significantly improved in the intervention group but not the stress and emotion scores. No statistically significant differences were observed for quality of life, sleep, physical activity, or BMI.

Paracetamol consumption at 6 months was lower in the intervention group (41.1% vs 57.3%, $P = .027$) and was the only drug or nondrug therapy that was statistically significantly different (Table 4).

The FIQ scores remained low at 9 and 12 months in the intervention group (Fig 3). Similar long-term persistence was observed for most of the other endpoints (Supplementary Table 3). In the control group, 90 of the 100 patients received their cure between month 6 and month 8. Their scores at month 9 and 12 were

similar those in the intervention group; 61.4 and 60.7, respectively.

Safety

During the study 33 SAEs were reported by 25 patients. In the intervention group 11 patients reported 13 SAEs, and in the control group 14 patients reported 20 SAEs. In the intervention group, six were fibromyalgia-related, three related to another pathology, 2 were trauma-related, and 2 were surgery-related. In the control group, eight SAEs were fibromyalgia-related, 5 were surgery-related, 4 related to another pathology, and 3 were trauma-related.

Planned Subgroup Analyses and Unplanned post-hoc Analyses

No statistically significant differences for the primary endpoint were observed in the subgroup analysis by spa therapy care facility (Mantel-Haenszel test $P = .618$), or for first-time vs. previous spa therapy status (Mantel-Haenszel test $P = .256$).

The baseline characteristics by severity at baseline are presented in Supplementary Table 1. The primary endpoint analyzed by the initial severity of the patient was not significantly different (Mantel-Haenszel test $P = .148$). The OR for success was 6.55 (95% CI: 1.19 – 36.0) for the 37 patients with moderately severe fibromyalgia

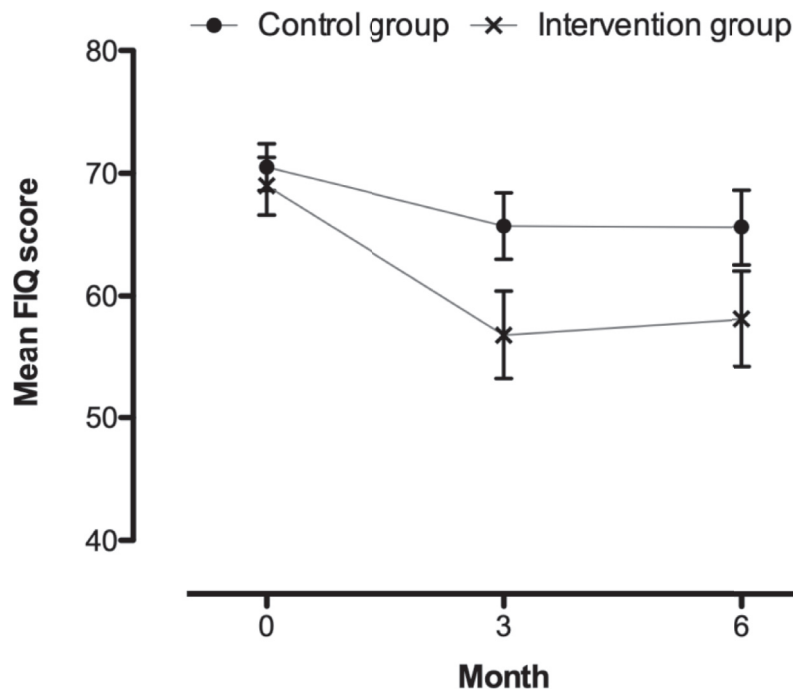
Table 3. Primary and Secondary Endpoints

| | | CONTROL GROUP | INTERVENTION GROUP | P VALUE* |
|--|----|-------------------------------|-------------------------------|--------------|
| Primary endpoint | | | | |
| MCID at six-months, n/N (%) | | 30/106 (28.3) | 45/100 (45.0) | 0.013 |
| Secondary endpoints | | | | |
| Investigator Global Assessment, mean \pm SD <i>n</i> | M0 | 6.0 \pm 2.0 <i>n</i> =104 | 6.5 \pm 1.6 <i>n</i> =103 | <0.001 |
| | M3 | 5.8 \pm 1.9 <i>n</i> =100 | 5.5 \pm 2.2 <i>n</i> =88 | |
| | M6 | 6.2 \pm 1.9 <i>n</i> =92 | 5.4 \pm 2.0 <i>n</i> =87 | |
| Patient Global Assessment, mean (\pm SD) <i>n</i> | M0 | 7.4 \pm 1.6 <i>n</i> =103 | 6.9 \pm 2.1 <i>n</i> =104 | 0.810 |
| | M3 | 7.0 \pm 1.7 <i>n</i> =94 | 6.3 \pm 2.1 <i>n</i> =90 | |
| | M6 | 7.0 \pm 1.9 <i>n</i> =96 | 6.4 \pm 2.1 <i>n</i> =89 | |
| Pain VAS (diary), mean (\pm SD) <i>n</i> | M0 | 59.6 \pm 14.0 <i>n</i> =96 | 61.4 \pm 17.1 <i>n</i> =93 | 0.013 |
| | M3 | 58.7 \pm 20.1 <i>n</i> =95 | 54.4 \pm 22.0 <i>n</i> =91 | |
| | M6 | 58.9 \pm 21.0 <i>n</i> =78 | 53.5 \pm 22.3 <i>n</i> =83 | |
| PCS-CF, mean \pm SD <i>n</i> | M0 | 30.8 \pm 11.4 <i>n</i> =104 | 30.2 \pm 12.0 <i>n</i> =106 | 0.031 |
| | M3 | 29.6 \pm 10.5 <i>n</i> =100 | 25.3 \pm 11.4 <i>n</i> =91 | |
| | M6 | 29.4 \pm 11.2 <i>n</i> =97 | 25.4 \pm 12.4 <i>n</i> =90 | |
| Widespread Pain Index Score, mean \pm SD <i>n</i> | M0 | 13.8 \pm 2.8 <i>n</i> =108 | 14.3 \pm 3.0 <i>n</i> =110 | <0.001 |
| | M3 | 13.1 \pm 3.7 <i>n</i> =102 | 11.4 \pm 4.3 <i>n</i> =93 | |
| | M6 | 13.2 \pm 3.7 <i>n</i> =96 | 11.8 \pm 4.5 <i>n</i> =90 | |
| Pichot's Fatigue Scale Score, mean \pm SD <i>n</i> | M0 | 26.2 \pm 4.2 <i>n</i> =103 | 25.3 \pm 4.7 <i>n</i> =105 | 0.014 |
| | M3 | 25.2 \pm 4.6 <i>n</i> =100 | 22.4 \pm 5.8 <i>n</i> =90 | |
| | M6 | 25.2 \pm 4.8 <i>n</i> =98 | 22.9 \pm 5.7 <i>n</i> =91 | |
| Symptom Severity Scale Score, mean \pm SD <i>n</i> | M0 | 9.8 \pm 1.6 <i>n</i> =108 | 10.0 \pm 1.5 <i>n</i> =110 | 0.002 |
| | M3 | 9.4 \pm 2.0 <i>n</i> =102 | 8.8 \pm 2.1 <i>n</i> =93 | |
| | M6 | 9.5 \pm 1.8 <i>n</i> =96 | 9.0 \pm 2.1 <i>n</i> =90 | |
| HADs anxiety, mean \pm SD <i>n</i> | M0 | 12.2 \pm 4.0 <i>n</i> =104 | 11.6 \pm 4.3 <i>n</i> =105 | 0.056 |
| | M3 | 12.1 \pm 4.4 <i>n</i> =100 | 10.3 \pm 4.3 <i>n</i> =90 | |
| | M6 | 11.7 \pm 4.6 <i>n</i> =98 | 10.8 \pm 4.6 <i>n</i> =91 | |
| HADs depression, mean \pm SD <i>n</i> | M0 | 10.3 \pm 3.7 <i>n</i> =104 | 9.8 \pm 4.1 <i>n</i> =105 | 0.050 |
| | M3 | 10.6 \pm 4.0 <i>n</i> =100 | 9.1 \pm 4.0 <i>n</i> =90 | |
| | M6 | 10.5 \pm 4.1 <i>n</i> =98 | 9.4 \pm 4.4 <i>n</i> =91 | |
| EQ-5D-3L score, mean \pm SD <i>n</i> | M0 | 0.25 \pm 0.24 <i>n</i> =93 | 0.26 \pm 0.29 <i>n</i> =93 | 0.801 |
| | M6 | 0.30 \pm 0.29 <i>n</i> =94 | 0.33 \pm 0.32 <i>n</i> =87 | |
| EQ-5D-3L Perceived Health Score, mean \pm SD <i>n</i> | M0 | 38.6 \pm 15.9 <i>n</i> =96 | 42.8 \pm 18.3 <i>n</i> =96 | 0.910 |
| | M3 | 43.0 \pm 19.4 <i>n</i> =96 | 47.1 \pm 21.5 <i>n</i> =90 | |
| | M6 | 43.0 \pm 19.4 <i>n</i> =96 | 47.1 \pm 21.5 <i>n</i> =90 | |
| Pittsburgh Sleep Quality Index Score, mean \pm SD <i>n</i> | M0 | 12.3 \pm 4.0 <i>n</i> =104 | 12.3 \pm 4.1 <i>n</i> =105 | 0.550 |
| | M3 | 11.8 \pm 4.3 <i>n</i> =99 | 11.5 \pm 3.7 <i>n</i> =91 | |
| | M6 | 11.7 \pm 4.5 <i>n</i> =98 | 11.8 \pm 3.8 <i>n</i> =90 | |
| Epworth Sleepiness Scale Score, mean \pm SD <i>n</i> | M0 | 12.3 \pm 6.2 <i>n</i> =103 | 12.7 \pm 5.8 <i>n</i> =106 | 0.432 |
| | M3 | 12.2 \pm 5.7 <i>n</i> =100 | 11.9 \pm 5.7 <i>n</i> =91 | |
| | M6 | 12.3 \pm 5.5 <i>n</i> =98 | 12.0 \pm 5.9 <i>n</i> =91 | |
| Baecke Physical Activity Questionnaire, mean \pm SD <i>n</i> | M0 | 7.2 \pm 1.6 <i>n</i> =99 | 7.2 \pm 1.6 <i>n</i> =103 | 0.796 |
| | M3 | 7.3 \pm 1.6 <i>n</i> =100 | 7.3 \pm 1.2 <i>n</i> =88 | |
| | M6 | 7.2 \pm 1.6 <i>n</i> =96 | 7.2 \pm 1.4 <i>n</i> =87 | |
| BMI, mean \pm SD <i>n</i> | M0 | 27.7 \pm 5.8 <i>n</i> =108 | 26.6 \pm 6.6 <i>n</i> =107 | 0.325 |
| | M3 | 28.0 \pm 5.9 <i>n</i> =102 | 26.9 \pm 6.8 <i>n</i> =92 | |
| | M6 | 28.1 \pm 5.9 <i>n</i> =96 | 26.8 \pm 6.9 <i>n</i> =90 | |
| Coping Scale Score – Stress, mean \pm SD <i>n</i> | M0 | 26.2 \pm 6.4 <i>n</i> =96 | 26.7 \pm 6.1 <i>n</i> =97 | 0.817 |
| | M6 | 25.3 \pm 6.4 <i>n</i> =93 | 26.2 \pm 7.0 <i>n</i> =82 | |
| Coping Scale Score – Emotion, mean \pm SD <i>n</i> | M0 | 23.7 \pm 5.7 <i>n</i> =96 | 24.4 \pm 5.6 <i>n</i> =97 | 0.333 |
| | M3 | 22.8 \pm 5.5 <i>n</i> =93 | 22.6 \pm 6.4 <i>n</i> =82 | |
| | M6 | 22.8 \pm 5.5 <i>n</i> =93 | 22.6 \pm 6.4 <i>n</i> =82 | |
| Coping Scale Score – Social Support, mean \pm SD <i>n</i> | M0 | 20.5 \pm 5.5 <i>n</i> =97 | 21.8 \pm 5.3 <i>n</i> =98 | 0.045 |
| | M6 | 20.5 \pm 5.1 <i>n</i> =93 | 19.9 \pm 6.6 <i>n</i> =82 | |

*p-value for the comparison of the change over 6 months of the scores in the intervention and control groups. BMI: body mass index; IGA: investigator global assessment; FIQ: fibromyalgia impact questionnaire; HADs: Hospital Anxiety and Depression Scale; MCID: Minimal Clinically Important Difference on FIQ; PCS-CF: Pain Catastrophizing Scale (French); PGA: patient global assessment; IQR: interquartile range; VAS: visual analogue scale

(FIQ at inclusion <59) and 1.71 (95% CI: 0.91 – 3.23) for the 169 patients with severe fibromyalgia (FIQ at inclusion \geq 59). In a *post-hoc* analysis, the difference for the success rate (primary endpoint) was not statistically significant between patients with severe fibromyalgia (FIQ

at inclusion 59-71, *n* = 86) and very severe patients (FIQ at inclusion \geq 72, *n* = 83) (Mantel-Haenszel test *P* = .438). In addition, no difference in the success rate was observed for patients who were resident during their therapy compared with those who were day patients



| | n = 110 | n = 92 | n = 91 |
|----------------------------|--|--|---|
| Immediate spa therapy X | 69.0 (95% CI: 66.6 - 71.3) | 56.8 (95% CI: 53.2 - 60.4) | 58.1 (95% CI: 54.2 - 62.0) |
| Deferred spa therapy ● | n = 108 70.5 (95% CI: 68.6 - 72.4) | n = 100 65.7 (95% CI: 63.0 - 68.4) | n = 98 65.6 (95% CI: 62.5 - 68.6) |

Figure 2. Evolution of the FIQ score over time.

(Pearson χ^2 $P = .20$). Lastly, for the primary endpoint in the intervention group, we looked at the impact of the number of treatments patients received. The median number of treatments was 64 (25%, 75% quartiles: 50, 72). There were no differences in the success rates for patients into when analyzed in subgroups based on the number of treatments received: <50, 50-63; 64-71 and >72 (Pearson χ^2 $P = .61$).

Discussion

We conducted an open RCT in five spa therapy care facilities in France. Patients were randomized to receive spa therapy immediately (intervention group, $N = 110$) or after primary outcome evaluation at six months (control group, $N = 108$). The characteristics of the study population were consistent with those previously

Table 4. Drug and Other Fibromyalgia Therapies Use at 6 Months

| | CONTROL GROUP (N=96) | INTERVENTION GROUP (N=90) | P VALUE |
|--|----------------------|---------------------------|---------|
| Drug consumption, n (%) | | | |
| Paracetamol | 55 (57.3) | 37 (41.1) | 0.027 |
| NSAIDS | 19 (19.8) | 20 (22.2) | 0.684 |
| Nefopam | 11 (11.5) | 7 (7.8) | 0.396 |
| Weak opioids (Codeine, Tramadol, Lamaline) | 55 (57.3) | 46 (51.1) | 0.398 |
| Pregabalin* | 8 (8.3) | 13 (14.4) | 0.188 |
| Antidepressants (tricyclic, SNRIs, SRIs) | 39 (40.6) | 39 (43.3) | 0.708 |
| Other fibromyalgia therapies, n (%) | | | |
| Use of health care system | 90 (95.7) | 83 (95.4) | 1.000 |
| Psycho-behavioral therapy sessions | 49 (52.1) | 41 (47.1) | 0.501 |
| Alternative and complementary medicine | 44 (46.8) | 37 (42.5) | 0.563 |
| Dietary supplements, herbal medicines, or homeopathy | 43 (45.7) | 47 (54.0) | 0.266 |

*Pregabalin was not indicated for fibromyalgia in France. NSAIDs: nonsteroidal anti-inflammatory drugs; SNRIs: serotonin and norepinephrine reuptake inhibitors; SRIs: serotonin reuptake inhibitors

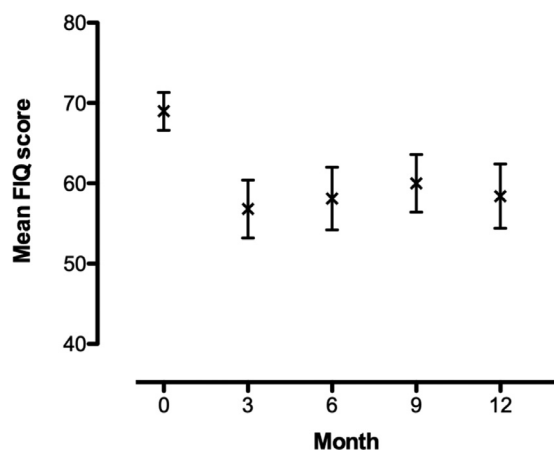


Figure 3. Long-term evolution of FIQ score for the intervention group.

reported in terms of age, gender, and symptoms and comorbidities.²⁵ All patients continued to receive their usual therapy. The spa therapy was standardized between the centers and the adherence was good with only four patients lost-to-follow-up. The success rate, ie, percentage of patients with a MCID, defined as >14% decrease in their FIQ score from baseline, was significant at 3 months, 6 months (primary outcome) and persisted up to 12 months. Improved scores were reported for most of the questionnaires and scales used showing the benefits for fibromyalgia symptoms. No significant center effect was observed. These results are consistent with those from a study that enrolled a total of 100 patients that provided evidence of effectiveness of spa therapy in controlling pain and improving functionality up to 6 months in patients with fibromyalgia.¹⁷ The estimated NNT was 6 and the effect size was 0.49. This is comparable to the NNT of between 4 and 16 reported for aerobic exercise training for patients with fibromyalgia in a Cochrane systematic review for improved quality of life (self-reported FIQ).⁴ The estimated NNT is also similar to that found for the spa therapy for patients with knee osteoarthritis in France.¹⁸

The longer-term benefit (up to 12 months) has rarely been reported.^{3,23,30} For example, in a meta-analysis evaluating the benefit of hydrotherapy and balneotherapy for fibromyalgia, the median follow-up was 2.5 and 3.5 months, respectively.³⁰ In another meta-analysis evaluating complementary and alternative exercise for fibromyalgia; the longest follow-up was six months, and many trials had no follow-up.²⁸

Our results showed a reduction in pain (EVA and WPI scores) and a decrease in paracetamol consumption (the only treatment self-managed by patients), while the consumption of other analgesics remained stable. We also observed significant benefits on severity and fatigue and borderline benefits for anxiety and depression. In contrast, spa therapy had no influence on the general quality of life, sleep, BMI, or physical activity. For physical activity, only 19% of patients participated in the weekly walking training, which is probably insufficient to have an impact after three weeks, and other physical activity was self-reported by the patients.

Although we observed a significant improvement in the IGA score for the intervention group, the PGA score was not significantly different between the groups. The lack of change in the PGA score may be because the patients suffer from a chronic illness. Our study failed to show an improvement in the general quality of life as measured using EQ-5D-3L. Spa therapy probably has, at most, only a very modest impact on the many psychosocial factors that influence the general quality of life. The EQ-5D-3L has been reported not to be very sensitive to changes in modest health states and to have a low sensitivity to detect clinical changes for some conditions.²² It is recommended to also use a disease-specific instrument, which was the FIQ in our study. The newly developed EQ-5D-5L is more sensitive and should be used in future studies, but it had not been validated at the time of the design of our study.²²

In addition, we demonstrated that spa therapy was safe for this population of patients with fibromyalgia. None of the SAEs were attributable to the spa therapy. It has been reported that there can be transient aggravation of pain when spa therapy starts but this is usually controlled by adapting the therapy. In a review of 33 randomized trials including 3,018 patients with chronic low back pain, knee osteoarthritis or fibromyalgia, only 1% of patients receiving spa therapy had to discontinue.³³

The patients in our study were mainly recruited in university hospital pain clinics and therefore the fibromyalgia was likely to be more severe than in patients followed elsewhere. The *post-hoc* analysis showed that the benefit from the spa therapy was significant for the 83 patients with a FIQ score ≥ 72 , although the benefit was lower than in patients with less severe fibromyalgia in our study.

One potential limitation of our study is the unblinded nature of the intervention. However, we compared immediate spa therapy (intervention group) with delayed spa therapy (control group) to enable all patients to receive spa therapy and therefore to limit the potential negative bias of patient disappointment. Although, the staff at the spa centers were not blinded, they were not involved in the evaluations, so it is unlikely that this introduced bias. Also, we cannot exclude that knowing they were going to go for a spa therapy, either immediately or after six months, had a positive effect on the patients or that the patients in the immediate spa therapy group felt stress because they had to organize their lives in a short time to be able to be available for the 3-week therapy. The data entry and analyses were not done under blind conditions as the dates of the therapy were available. However, the analyses were done independently of the data collection and after the database had been locked.

The primary endpoint was evaluated at six months, ie, before the control group had received the intervention, and long-term follow-up was assessed only for the intervention group. Although more patients withdrew in the intervention group than in the control group (8 vs 2), the reason was not related to the therapy but to difficulty to organize going away for the three-week spa therapy. Also, our pragmatic approach involved evaluating the

overall spa therapy and not the individual treatments. The treatments were standardized between the spa therapy care facilities and our aim was to evaluate the efficacy of the 3-week spa therapy with physiotherapy, since 19% of the patients also attended the weekly workshops for walking training. No structured therapeutic education program was included in the intervention. Compliance with the spa therapy was accurately recorded and was high. In addition, a *posteriori* analysis for resident versus day spa therapy showed no differences, suggesting that the de-stressing effect of being away from their normal environment was unlikely to have had an impact on the improvements observed.

Our results suggest that the indications for spa therapy could be extended to include prevention of progression to severe fibromyalgia in patients with moderate disease, ie, FIQ score between 39 and 58. In addition, the results from *post-hoc* analyses suggest that patients with severe fibromyalgia responded well. These results should be confirmed in randomized clinical trials.

In conclusion our results suggest that the assessed spa therapy provides a long-term beneficial clinical effect for patients suffering from moderate to severe fibromyalgia. Spa therapy can be considered as one of the

potential non-drug therapies in a multidisciplinary approach to the management of fibromyalgia.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2021.02.010>.

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