# Spa therapy in the treatment of knee osteoarthritis, a large randomised multicentre trial.

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*Ann Rheum Dis* published online 3 Sep 2009;
doi:10.1136/ard.2009.113209

**ARD Online First, published on September 3, 2009 as 10.1136/ard.2009.113209**

ANNRHEUMDIS/2009/113209 revised 20jul09

# Spa therapy in the treatment of knee osteoarthritis, a large randomised multicentre trial.

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**Key words**: spa therapy, knee osteoarthritis, balneotherapy, Zelen randomisation

**Word Count** (main text only): 2447

## ABSTRACT

**Objective:** To determine whether spa therapy, plus home exercises and usual medical treatment provides any benefit over exercises and usual treatment, in the management of knee osteoarthritis.

**Methods:** Large multicentre randomised prospective clinical trial of patients with knee osteoarthritis according to the American College of Rheumatology criteria, attending French spa resorts as outpatients between June 2006 and April 2007.

Zelen randomisation was used so patients were ignorant of the other group and spa personnel were not told which patients were participating. The main endpoint criteria were patient self-assessed. All patients continued usual treatments and performed daily standardised home exercises. The spa therapy group received in addition 18 days of spa therapy (massages, showers, mud and pool sessions).

**Main endpoint:** The number of patients achieving Minimal Clinically Important Improvement at six months, defined as ≥19.9 mm on the VAS pain scale and/or ≥9.1 points in a normalised WOMAC function score and no knee surgery.

**Results:** The intention to treat analysis included 187 controls and 195 spa therapy patients.

At 6 months, 99/195 (50.8%) spa group patients had Minimal Clinically Important Improvement and 68/187 (36.4%) of controls (chi2=8.05; df =1; p=0.005). However, no improvement in quality of life (SF36) or Patient Acceptable Symptom State was observed at 6 months.

**Conclusion:** For patients with knee OA a 3 week course of spa therapy together with home exercises and usual pharmacological treatments offers benefit after 6 months compared to exercises and usual treatment alone, and is well tolerated.

**Trial registration:** www.clinicaltrials.gov: n° NCT00348777.


Word count: 249

## INTRODUCTION

In Europe spa therapy is frequently prescribed for knee osteoarthritis (OA). Of the 403,381 patients receiving spa therapy for rheumatism in 2007 in France, nearly half presented knee OA. Spa therapy is reimbursed by the social security in France and in many other continental European countries.

Despite numerous small scale studies, high quality scientific evidence for the efficacy of spa therapy for knee OA is lacking. In a recent Cochrane systematic review, even those studies that met the selection criteria were found to be flawed.[1] Thus, spa therapy does not figure in the recommended treatments of the European league against rheumatism (EULAR)[2] or recent reviews.[3]

In this multicentre RCT we aimed to include enough patients to obtain sufficient statistical power to fill the gap in evidence based data of high quality evaluating the use of spa therapy for knee OA. Our primary objective was the therapeutic efficacy of spa therapy for knee OA at 6 months in patients following usual treatments and a home exercise programme (HEP) compared to a control group receiving usual treatments and HEP alone.

## PATIENTS AND METHODS

This study was carried out in the three largest spa therapy resorts in France, Aix-les-Bains, Balaruc and Dax. In 2007 respectively 29 000, 36 000 and 50 000 people attended these 3 resorts for spa therapy. Patients were recruited locally, such that they could attend the centre on a daily basis, by advertisements in the regional press and posters in pharmacies and surgery waiting rooms.[4] Recruitment notices referred to treatment for knee OA but did not specify spa therapy.

Patients were enrolled by a trained examining physician in private practice outside and independent of the spa setting and with no vested interest in the spa. Osteoarthritis was confirmed by physical examination and the presence of osteophytes on the X rays.

Inclusion criteria followed the definitions of the American College of Rheumatology: painful knee OA plus either age >50 years and/or morning stiffness lasting more than 30 minutes and/or articular crepitation.[5] Required evidence were a knee X-ray examination in the last 3 years including antero-posterior, schuss, lateral and skyline views to grade the severity of osteoarthritis, and pain intensity of ≥30mm on the Visual Analogue pain Scale (VAS pain).[6]

Non-inclusion criteria were: osteoarthritis limited to the patello-femoral joint; severe depression or psychosis; a contra-indication (immune deficiency, evolving cardiovascular conditions, cancer, infection) or intolerance to any aspect of spa treatment; professional involvement with a spa resort; spa treatment within the previous 6 months; knee intra-joint corticosteroid injection within the last 3 months; massages, physiotherapy or acupuncture in the last month; a NSAID within the last 5 days or other analgesic drug in the previous 12 hrs, or change in symptomatic slow acting drugs in OA (SYSADOA) in the last 3 months.

### Intervention

At inclusion the examining physician orally explained the home exercise programme to all patients and the importance of performing all 4 exercises, each 6 times, 3 times a day.[7,8] All patients were given a booklet about knee OA with details of the HEP [see supplementary file N° 1 online] and continued their usual treatments (analgesics, NSAIDS, SYSADOAs, physiotherapy). The self-assessment forms were completed without assistance in the waiting room.

In addition, the spa therapy group received 18 days of therapy over 3 weeks. The standardised knee OA therapy programme was designed by experienced spa therapy physicians. Spa mineral water and treatments are approved and controlled by the French authorities. Treatment included: mineral hydro-jet sessions at 37°C for 15 minutes, manual massages of the knee and thigh under mineral water at 38° by a physiotherapist for ten minutes, applications of mineral matured mud at 45° to the knees for fifteen minutes and supervised general mobilisation in a collective mineral water pool at 32°C in groups of 6 patients for 25 minutes.

Attendance, tolerance and proper performance of the various treatments were checked by an independent physician (general practitioner, rheumatologist or physiatrist) during consultations at the start, middle and end of the 3 week therapy period. Study patients were mixed with the general public and the centre personnel were not informed which patients were taking part in the clinical trial.

Patients in the control group were offered a 3 day wellness package at their local spa resort following the 6 month follow up visit.

### Follow-up and Data Collection

Follow up was at 1, 3 and 6 months, by a visit to the examining physician who completed the electronic case report form, enquired whether the patient was doing the exercises and insisted on their importance. At each visit, but not in the presence of the physician, the patients filled in self-assessment of: their average level of pain over the previous 7 days on the VAS pain scale,[6] the Western Ontario and McMaster Universities OA Index (WOMAC)[9] and the quality of life (QOL) questionnaire, SF36,[10] without assistance. At 9 months these forms were completed at home and returned to the coordination centre by post.

The primary endpoint was achievement of Minimal Clinically Important Improvement (MCII)[11] defined as ≥19.9 mm on the VAS pain[6] scale and/or ≥9.1 points on the WOMAC function subscale normalised to a 0-100 score,[9] and no knee surgery, at 6 months. For WOMAC we used a five point Likert scale for each item and higher scores indicate greater severity.[11]

Secondary endpoints were: "Patient Acceptable Symptom State" (PASS),[12] VAS pain ≤32 mm, normalised WOMAC function subscale ≤31 points; knee flexion, effusion and swelling; associated treatments; the overall opinions of the patient and the examining physician, and QOL.

All items collected by the examining physician at baseline and during follow-up visits are listed in table 1 and online tables (supplementary file N° 2) respectively. All adverse events were recorded**.**

**Design**

The sample size was determined using an open preliminary study with 13 consecutive patients from which we calculated that 50% would be improved in the spa group and estimated 25% improved in the control group. The agreed alpha risk was 5%, and the beta risk 20%. Thus the number of patients was 58 per group per centre, or 67 allowing for 15% loss to follow up.

The randomisation technique of Zelen was used.[13,14] Eligible patients were randomly assigned to spa therapy or to the control group using a centralised computer programme. Randomisation was stratified by centre and in blocks of 8 with random order. Concealment was assumed by a protected computer file.

The Zelen randomisation method [14] implied that patients were not informed of the existence of two groups. If the patient refused to participate as randomised, they were proposed the other treatment, but remained in their assigned group for intention to treat analysis.

In order to conceal the existence of the other group,[14] randomisation was performed before written informed consent was obtained. Patients were told only about the group to which they had been assigned and given one of the two possible patient information documents with the consent form. In addition, delocalisation of the consultation away from the spa setting was done with the intention of keeping patients ignorant of the other group.

**Statistics**

Analysis was performed in intention to treat. Categorical variables were expressed as frequency and percentage; continuous variables as mean and standard deviation. The main endpoint was tested using an uncorrected Chi-square test. Relative Risk with CI95%, Odds Ratio and CI95%, Number Needed to Treat, and effect size with CI95%, were calculated.

Secondary qualitative endpoints were analysed using the same principles. For continuous variables, an ANOVA analysis was performed for repeated data, assuming sphericity, (comparison M0-M6 and M0-M3-M6-M9) with a treatment factor and an interaction analysis (repetitions*treatment). Between group comparisons at 6 months used Student t test. For WOMAC and VAS pain, the effect size is equal to the mean change in score from baseline to six months, divided by the standard deviation of the baseline score.

For sub-group analyses a Mantel-Hanzel test of homogeneity was used. For the WOMAC and SF36 scores, missing data for each subscale were replaced by the mean of all the patients who had replied to at least half the questions in that subscale, according to the recommendations for SF36.[10]

Two-sided P values <0.05 were considered statistically significant. Analyses were performed using STATA software (version 10.0; Stata Corp, College Station, Texas).

The trial protocol was passed favourably by the regional ethics committee (Lyon A) in April 2006 and registered on www.clinicaltrials.gov with n° NCT00348777. Study coordination, monitoring visits to each centre, data management, data entry from patient questionnaires and data analysis were performed by the Grenoble Clinical Research Centre.

## RESULTS

Overall flow of patients included between June 2006 and April 2007 is shown in figure 1. In total, 7.2% (16/223) patients changed from control to spa group, and 10.5% (24/228) changed from the spa group to control group. Thirteen patients in the spa group withdrew consent to participate before starting the sessions. Of 12 who dropped out, mainly for health or family reasons, only two had started spa sessions. In the control group 17 patients withdrew consent and another 10 failed to attend study visits.

**Table 1: Baseline characteristics of participants**

| CHARACTERISTIC | CONTROL | SPA THERAPY |
|---|---|---|
| Male, n/N (%) | 119/223 (53.4%) | 118/228 (51.8%) |
| age, mean +/- SD (n) | 64.3 +/- 10.4 (n=223) | 63.0 +/- 9.1 (n=228) |
| **History of treatment for the knee** | | |
| Medication, n/N (%) | 187/223 (83.9%) | 195/228 (85.5%) |
| Massage, n/N (%) | 70/223 (31.4%) | 73/228 (32.0%) |
| Intra-articular injection, n/N (%) | 51/223 (22.9%) | 59/228 (25.9%) |
| Hyaluronic acid treatment, n/N (%) | 92/223 (41.3%) | 95/228 (41.7%) |
| Surgery, n/N (%) | 82/223 (36.8%) | 81/228 (35.5%) |
| Previous spa therapy n/N (%) | 74/218 (33.9%) | 61/227 (26.9%) |
| Other physical treatment, n/N (%) *(brace, traction, manipulation or physiotherapy in the last 3 months)* | 10/223 (4.5%) | 10/228 (4.4%) |
| **Prognostic factors** | | |
| Length of present episode(months), mean+/SD (n) | 63.9 +/- 73.3 (n=223) | 60.5 +/- 72.0 (n=228) |
| Number of acute episodes, mean+/-SD (n) | 7.8 +/- 10.5 (n=223) | 8.6 +/- 16.9 (n=228) |
| Family history of osteoarthritis, n/N (%) | 116/223 (52.0%) | 117/228 (51.3%) |
| Body mass index, mean+/-SD (n) | 29.0 +/- 4.6 (n=223) | 30.7 +/- 5.9 (n=228) |
| **Knee Examination** | | |
| Knee joint swelling, n/N (%) | 94/223 (42.2%) | 96/228 (42.1%) |
| Knee joint effusion, n/N (%) | 62/223 (27.8%) | 58/228 (25.4%) |
| Knee joint crepitation on active motion, n/N (%) | 107/223 (48.0%) | 107/228 (46.9%) |
| **Radiological severity (**Kellgren & Lawrence)n/N(%) | | |
| grade 1 | 53/223 (23.8%) | 54/228 (23.7%) |
| grade 2 | 70/223 (31.4%) | 73/228 (32.0%) |
| grade 3 | 83/223 (37.2%) | 82/228 (36.0%) |
| grade 4 | 17/223 (7.6%) | 19/228 (8.3%) |
| **WOMAC pain score (0-100)** mean+/-SD (n) | 42.0 +/- 18.1 (n=223) | 45.1 +/- 17.8 (n=224) |
| **WOMAC function score (0-100)**, mean+/-SD (n) | 38.9 +/- 17.1 (n=218) | 42.6 +/- 19.7 (n=214) |
| **VAS pain (0-100 mm)**, mean+/-SD (n) | 45.7 +/- 19.0 (n=223) | 49.9 +/- 20.2 (n=225) |
| **Patient Acceptable Symptom State**, n/N (%) | 36/223 (16.1%) | 27/225 (12.0%) |
| **SF-36 scores** | | |
| PHYSICAL, mean+/-SD (n) | 38.6 +/- 7.5 (n=216) | 37.4 +/- 7.7 (n=216) |
| PSYCHOLOGICAL, mean+/-SD (n) | 46.6 +/- 10.0 (n=216) | 46.2 +/- 11.5 (n=216) |
| **Medication (at the time of inclusion)** | | |

| | | |
|---|---|---|
| At least one medication, n/N (%) | 110/223 (49.3%) | 117/228 (51.3%) |
| NSAID, n/N (%) | 33/223 (14.8%) | 37/228 (16.2%) |
| SYSADOA n/N (%) | 58/223 (26.0%) | 52/228 (22.8%) |
| Analgesic, n/N (%) | 49/223 (22.0%) | 62/228 (27.2%) |
| Hyaluronic acid, n/N (%) | 1/223 (0.4%) | 1/228 (0.4%) |

VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities OA Index; NSAID Non-Steroidal Anti-Inflammatory Drug; SYSADOA: symptomatic slow acting drug in OA
Patient Acceptable Symptom State is the value beyond which patients can consider themselves well. It is composed of the VAS pain (cut-off ≤ 32mm), the WOMAC function scores (cut-off ≤ 31) and the patient's global self assessment of disease.

**Main Endpoint**

The difference in MCII at 6 months is statistically significant (chi2=8.05; df =1; p=0.005) in favour of spa therapy (Table 2). Three patients in the spa group and one in the control group achieved MCII but underwent knee prosthesis surgery during the study. They were considered as treatment failures. The relative risk of MCII is 1.4 [1.1; 1.8] for the spa group versus control, the odds ratio: 1.8 [1.2; 2.8], and the number needed to treat is 6.9 patients.

**Table 2: Number (%) of patients achieving MCII at 3, 6 and 9 months.**

| Visit | Control | Spa therapy | p |
|---|---|---|---|
| 3 months | 70/179 (39.1%) | 107/183 (58.5%) | |
| **6 months** | **68/187 (36.4%)** | **99/195 (50.8%)** | **0.005** |
| *details :* | | | |
| Improvement of VAS pain [+] | 36/186 (19.4%) | 63/193 (32.6%) | |
| Improvement of WOMAC function[x] | 49/172 (28.5%) | 75/179 (41.9%) | |
| 9 months | 62/173 (35.8%) | 93/173 (53.8%) | |

[+] 3 missing values for VAS pain
[x] 31 missing values for WOMAC function
MCII is defined as ≥19.9 mm on the VAS painscale and/or ≥9.1 points on the WOMAC function subscale normalised to a 0-100 score, and no knee surgery.

**Secondary endpoints**

The secondary endpoint results are internally coherent with the effect size found for the components of the main endpoint (Tables 3 and 4 and further details online in supplementary file N° 2).

**Table 3: Change in VAS pain and WOMAC scores (completed by the patient)**

| | **Difference: 6 months –inclusion** | | | | |
|---|---|---|---|---|---|
| | **Control** | | **Spa therapy** | | |
| | | **Effect Size [CI 95%]** | | **Effect Size [CI 95%]** | **P** |
| **VAS pain mean+/-SD** [+] | **-4.0 +/- 22.8** (n=186) | *0.21* [0.01 – 0.42] | **-11.4 +/- 24.9** (n=193) | *0.55* [0.35 – 0.75] | 0.003 |
| **WOMAC function mean+/-SD** [x] | **-3.0 +/- 15.4** (n=172) | *0.17* [-0.04 – 0.38] | **-8.5 +/- 14.7** (n=179) | *0.43* [0.22 – 0.64] | < 0.001 |
| [+] 3 missing values for VAS pain<br>[x] 31 missing values for WOMAC | | | | | |

VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities OA Index

**Table 4: Opinions of the patient and the physician at 6 months**

| | Control | Spa therapy | P |
|---|---|---|---|
| **Opinion of the patient** | | | |
| **Worse** | 23/175 (13.1%) | 12/180 (6.7%) | *p < 0.001* |
| **Neither worse nor better** | 100/175 (57.1%) | 70/180 (38.9%) | *chi2=22.8 ; df=2* |
| **Better** | 52/175 (29.7%) | 98/180 (54.4%) | |
| **Opinion of the examining physician** | | | |
| **Worse** | 12/175 (6.9%) | 8/180 (4.4%) | *p < 0.001* |
| **Neither worse nor better** | 109/175 (62.3%) | 74/180 (41.1%) | *chi2=20.2 ; df=2* |
| **Better** | 54/175 (30.9%) | 98/180 (54.4%) | |

**Planned Sub-group analyses, sensitivity analysis and unplanned Post-hoc analyses**
See online supplementary file N° 2

**Adverse events**
One patient in the spa group was hospitalised for urinary lithiasis, no other unexpected serious adverse event was reported. For adverse events see online supplementary file N° 2.

## DISCUSSION

This study demonstrates that an intensive course of spa therapy with HEP and usual treatment provides medium-term benefit over HEP and usual treatment alone in the management of knee OA

To our knowledge this is the first multicentre RCT of spa therapy for knee OA. The study size attains the number of patients (498) combined from seven smaller heterogeneous studies in a recent systematic Cochrane review.[1].

We used the Zelen randomisation method to blind patients in one group to the existence of the other group, and to limit the level of drop out. 1t allowed patients assigned to spa therapy who did not want the constraint of having to attend a spa for 3 weeks, to change to the control group. The possibility to change could potentially reduce the difference between the two treatments as the intention to treat analysis was performed according to randomisation status.

We did not attempt to assess the efficacy of spa therapy alone, but only in combination with HEP and usual medical treatment. Thus both groups adhered to the current recommendations for treatment of knee OA.[3,15,16] We minimised a 'placebo' effect in the control group, who were followed up in the same way as the spa group.[17] The use of a qualitative endpoint measure, the MCII, may also reduce the influence of a potential 'placebo effect'.[18]

Our main endpoint, MCII, is clinically relevant to the patient, comprising change in the WOMAC function subscale and VAS pain measurement, both recognized validated endpoint measures.

According to the recommendations for non-pharmacologic trials,[19] we used Zelen randomisation, employed examining physicians independent of the spa setting, and patient self-assessed primary endpoint measures.

The amplitude of our result is in line with our hypothesis when we calculated the sample size needed for this study. Our effect sizes are similar to those for other treatments of knee OA including hyaluronic acid, paracetamol and NSAIDS.[20-22]

Whilst only 3 patients were completely lost to follow-up, 52 patients withdrew consent or dropped out early on and 14 patients failed to return the questionnaires at 6 months, leading to a reduced number of patients or data in the main endpoint analysis at 6 months.

Our three centres receive about 30%, of patients attending a spa in France. The standardised therapy delivered to OA patients is similar to treatments delivered in other European spa settings.

The effect of spa therapy might be explained by that of a holiday. This was not the case here, patients had to drive daily to the spa, unlike those in a recent study by Karagulle.[23] In France 26% of patients attend spa therapy on an outpatient basis, the rest staying on site for the duration of the course.
In general our results confirm those already observed in other studies of smaller size undertaken in a spa setting with natural hot mineral waters. Comparisons between the various studies are difficult as the baseline profiles of the patients are heterogeneous, the interventions differ in type, intensity and in length [24-33], the methods used for the assessment of efficacy vary and patients have been assessed at different time points after therapy.
At inclusion the severity of OA in our patients is comparable to patients in the study advocating the use of MCII as an endpoint measure.[11] ).
This study attempts to assess the medium-term effect of spa therapy rather than simply short term relief. Significant relief from pain at shorter time points after therapy, compared to control is reported in other studies.[27,28,32,34] Our encouraging results obtained at 6 months appear to persist at least until 9 months.
What is the place of thermal spa therapy in the management of knee OA? A recent high quality RCT demonstrated that arthroscopy of the knee, has no lasting effect on knee OA.[35] Likewise, acupuncture plus a course of advice and HEP showed no significant effect of real acupuncture at 6 months follow up.[36] Spa therapy appears to provide some benefit.
A physical exercise regimen has been shown to be effective for knee OA. Nevertheless, it is well known that unsupervised HEPs often have limited efficacy over time due to progressive lack of compliance, even in the context of therapeutic trials with consecutive visits and that are motivating for the patients.[4,37] Thus a course of spa therapy may enhance patient compliance to HEP.
In conclusion, this RCT argues in favour of a clinical effect of spa therapy, as practised in France, for patients with knee OA who continue their usual medical treatment and are encouraged to do regular exercises at home. In addition spa therapy is well tolerated.

**ACKNOWLEDGEMENTS**
We thank Sandrine Massicot for data monitoring and Wainer Tabone, Eric Vignon and Claudine Rouffet for their suggestions. We also thank the examining physicians: Drs Y Attal, JC Perronnard and L Mendiharrat; the spa physicians and the secretaries in each centre, and the OA group of the French Society for Rheumatology for their support (in particular Dr Michel Lequesne and Prs Serge Poiraudeau, Jean-François Maillefert and Xavier Chevalier).

**Contributors**

- R Forestier (rheumatologist): Initiated the project, wrote the protocol, organised data collection, and wrote the article
- H Desfour (rheumatologist): organised data collection and contributed to writing the article
- J-M Tessier (rheumatologist): organised data collection contributed to writing the article
- A Françon (rheumatologist): contributed to the writing of the protocol and the article.
- A Foote (medical writer and translator): translated, reviewed data interpretation, critically revised and edited the article.
- C Genty (statistician): performed the statistical analyses and critically read the article
- C Rolland (study coordinator): managed the study and critically read the article
- C-F Roques (professor of physical medicine and rehabilitation): contributed to writing the article
- JL Bosson (professor of medical statistics and coordinator of Clinical Research Centre): contributed to the writing the protocol, supervised the statistical analysis, and contributed to writing the article.

**Participating Physicians working with the Spas**
Aix les Bains: Drs Bernard, Gerrud, Guillemot, Joly, Palmer, Souchon; Balaruc Les Bains: Drs Ballini-Cammal, Calas-Vedel, Cammas, Cassanas, Cros, Rivalland-Lentz, Rousseau, Tuffery, Vidil-Roux; Dax: Drs Doppia, Karrasch, J Lavielle, V Lavielle, Fretille, Grillon, Lacoste, Pale, Boniol-Maurel, Labaste, Guchan, Le Poncin, Delest, Soullard, Legros, Reau-Legros, Maligne, Petit, Chicoye, Prothery.

**Competing interest statement**

All authors declare no conflicts of interest

The study sponsors did not participate in the study design, in the collection, analysis, or the interpretation of data.

**Funding**

This study was funded by The French Society for Spa research (Association Française pour la Recherche Thermale, AFRETH) a non-profit organisation, the Rhone-Alpes regional council and the County Council of Savoie.

**Licence Statement**

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## 1. Secondary Outcome Results

**Table 1.1 VAS pain and WOMAC function scores at all visits (components of Minimal Clinically Important Improvement, the main outcome)**

| b) VAS pain and WOMAC function scores at each visit | | | | |
|---|---|---|---|---|
| **VAS pain mean+/-SD** | | **Control** (n=151) | **Spa therapy** (n=158) | **P** |
| | **M0** | **44.6 (+/-18.5)** | **48.4 (+/-20.7)** | **0.005** |
| | **M3** | **38.4 (+/-21.0)** | **37.7 (+/-22.7)** | |
| | **M6** | **39.7 (+/-21.7)** | **36.1 (+/-24.4)** | |
| | **M9** | **41.5 (+/-24.3)** | **36.5 (+/-24.0)** | |
| **WOMAC function, mean+/-SD** | | **Control** (n=121) | **Spa therapy** (n=139) | **P** |
| | **M0** | **38.4 (+/-17.9)** | **41.1 (+/-20.8)** | **0.02** |
| | **M3** | **33.7 (+/-18.5)** | **32.8 (+/-20.3)** | |
| | **M6** | **34.3 (+/-18.5)** | **32.5 (+/-22.3)** | |
| | **M9** | **35.2 (+/-19.8)** | **33.0 (+/-21.5)** | |
| The beneficial effect of spa therapy (MCII) was seen at the 3 month visit and seemed to persist until at least 9 months.<br>*VAS: Visual Analogue Scale;*<br>*WOMAC: Western Ontario and McMaster Universities OA Index*<br>Both these criteria were self-assessed by the patient | | | | |

**Table 1.2 Patients with an Acceptable Symptom State (PASS) data at all follow-up visits**

| Visit | Control | Spa therapy | p |
|---|---|---|---|
| inclusion | 36/223 (16.1%) | 27/225 (12.0%) | |
| 3 months | 50/179 (27.9%) | 63/183 (34.4%) | |
| **6 months** | **53/187 (28.3%)** | **64/195 (32.8%)** | **0.34** |
| 9 months | 56/173 (32.4%) | 70/174 (40.2%) | |
| PASS is the value beyond which patients can consider themselves well. It is composed of the VAS pain (cut-off ≤ 32mm), the WOMAC function scores (cut-off ≤ 31) and the patient's global self assessment of disease.<br>The number of Patients with an Acceptable Symptom State appears in general to be higher in the spa therapy group. However, at 6 months the PASS results were not significant, chi2=0.90; df =1; p=0.34. | | | |

**Table 1.3 Opinion of the examining physician and the patient** (see table 3 in main text)

**Table 1.4 Other secondary outcomes at 6 months (last visit with examining physician)**

| | Control | Spa therapy | |
|---|---|---|---|
| Right knee flexion | 127.8 (+/- 10.4) | 127.9 (+/- 11.9) | p=0.96 (t=-0.05; df=353) |
| Left knee flexion | 127.0 (+/- 10.9) | 126.9 (+/- 10.7) | p=0.95 *(t=0.06; df=353)* |
| **Medication** | | | |
| NSAID, n/N (%) | 20/175 (11.4%) | 23/180 (12.8%) | p=0.70 (chi2=0.15; df=1) |
| Δ NSAID (between 0 and 6 months) | -25.9% | -25.8% | |
| SYSADOA n/N (%) | 38/175 (21.7%) | 33/180 (18.3%) | p=0.43 (chi2=0.63; df=1) |
| Analgesics, n/N (%) | 12/175 (6.9%) | 26/180 (14.4%) | p=0.02 (chi2=5.3; df=1) |
| Δ analgesics (between 0 and 6 months) | -67.6% | -50.0% | |
| Hyaluronic acid, n/N (%) | 13/175 (7.4%) | 8/180 (4.4%) | *p=0.23 (chi2=1.4; df=1)* |
| Joint corticosteriod injection, n/N (%) | 2/175 (1.1%) | 1/180 (0.6%) | p=0.62 (fisher exact: chi2=0.37; df=1) |
| **Physical Treatments** | | | |
| massage, brace etc, n/N (%) | 6/175 (3.4%) | 5/180 (2.8%) | p=0.72 (chi2=0.13; df=1) |

At first sight there appears to be some difference between the groups in the consumption of analgesics at baseline and at 6 months. Our sensitivity analysis reveals that if one excludes those patients taking analgesics because they have a lot of pain, then the level of analgesic consumption is similar in the two groups, both at inclusion and at 6 months

*NSAID: Non-Steroidal Anti-Inflammatory Drug*

*SYSADOA: symptomatic slow acting drug in OA*

**Table 1.5 Quality of Life scores (SF36) at each visit and for all the patients for whom data is available**

| a) Control group | M0 | M3 | M6 | M9 |
|---|---|---|---|---|
| **Combined scores** | | | | |
| PHYSICAL | 38.6 +/- 7.5 (n=216) | 39.8+/-8.1 (n=174) | 40.6+/-8.1 (n=177) | 39.3+/-9.1 (n=159) |
| PSYCHOLOGICAL | 46.6 +/- 10.0 (n=216) | 48.5+/-9.8 (n=174) | 48.4+/-9.4 (n=177) | 47.3+/-9.7 (n=159) |
| **8 dimensions of SF36** | | | | |
| PF *(physical activity)* | 55.8 +/- 21.8 (n=223) | 56.6+/-22.2 (n=180) | 57.7+/-23.8 (n=186) | 52.0+/-24.2 (n=172) |
| RP *(limitations due to physical state)* | 46.3 +/- 39.1 (n=220) | 59.7+/-40.3 (n=180) | 60.6+/-39.2 (n=183) | 53.1+/-42.2 (n=168) |
| BP *(physical pain)* | 44.2 +/- 16.8 (n=223) | 48.9+/-18.8 (n=179) | 50.8+/-19.5 (n=185) | 50.6+/-21.0 (n=170) |
| GH *(perception of health)* | 61.0 +/- 17.7 (n=219) | 61.5+/-17.6 (n=176) | 61.3+/-18.3 (n=186) | 59.6+/-19.8 (n=167) |
| VT *(vitality)* | 53.1 +/- 17.6 (n=222) | 54.9+/-15.7 (n=180) | 54.9+/-17.1 (n=187) | 52.3+/-17.4 (n=170) |
| SF *(social aspects)* | 67.8 +/- 21.8 (n=222) | 72.8+/-19.9 (n=179) | 71.3+/-20.9 (n=182) | 68.2+/-22.9 (n=169) |
| RE *(limitations due to psycological state)* | 56.4 +/- 42.7 (n=222) | 68.2+/-40.6 (n=179) | 67.3+/-41.2 (n=183) | 60.0+/-43.1 (n=168) |
| MH *(mental health)* | 64.8 +/- 16.2 (n=222) | 65.8+/-16.4 (n=180) | 66.2+/-15.3 (n=187) | 64.5+/-16.7 (n=170) |

| b) Spa Therapy group | M0 | M3 | M6 | M9 |
|---|---|---|---|---|
| **Combined scores** | | | | |
| PHYSICAL | 37.4 +/- 7.7 (n=216) | 40.7+/-8.5 (n=182) | 40.7+/-8.8 (n=190) | 39.9+/-8.5 (n=161) |
| PSYCHOLOGICAL | 46.2 +/- 11.5 (n=216) | 49.8+/-9.8 (n=182) | 47.8+/-10.9 (n=190) | 48.8+/-10.6 (n=161) |
| **8 dimensions of SF36** | | | | |
| PF *(physical activity)* | 53.6 +/- 23.4 (n=220) | 58.6+/-24.3 (n=183) | 57.2+/-24.6 (n=195) | 56.6+/-23.5 (n=175) |
| RP *(limitations due to physical state)* | 42.0 +/- 39.1 (n=222) | 61.7+/-39.7 (n=182) | 58.6+/-41.0 (n=194) | 56.1+/-40.1 (n=169) |
| BP *(physical pain)* | 41.4 +/- 19.5 (n=225) | 52.4+/-21.3 (n=183) | 51.9+/-21.4 (n=194) | 52.3+/-21.5 (n=169) |
| GH *(perception of health)* | 60.1 +/- 18.7 (n=219) | 63.8+/-17.9 (n=183) | 62.0+/-19.6 (n=193) | 60.9+/-19.7 (n=166) |
| VT *(vitality)* | 50.2 +/- 18.8 (n=224) | 57.0+/-18.6 (n=183) | 54.4+/-19.7 (n=193) | 55.7+/-19.2 (n=173) |
| SF *(social aspects)* | 66.0 +/- 24.8 (n=223) | 72.9+/-22.7 (n=183) | 70.5+/-22.9 (n=193) | 70.1+/-24.4 (n=168) |
| RE *(limitations due to psycological state)* | 54.4 +/- 43.4 (n=221) | 71.0+/-39.9 (n=182) | 65.8+/-41.8 (n=194) | 62.9+/-41.7 (n=170) |

| | | | | |
|---|---|---|---|---|
| MH *(mental health)* | 64.0 +/- 19.8 (n=224) | 69.4+/-16.4 (n=183) | 65.6+/-19.1 (n=193) | 68.5+/-18.3 (n=173) |
| There was no difference at 6 months in either the physical (p=0.14) or psychological (p=0.68) aspects of QOL assessed by SF36. In both groups, QOL scores did not change with time. | | | | |

**2. Sub-group analyses planned in the protocol**

**2.1 Analysis by centre**

There was no significant difference between the centres in MCII (Mantel-Hanzel test: chi2=0.12; df =2; p=0.94).

**2.2 Effect of previous spa treatment**

The effect of treatment is similar in patients who had previously received spa therapy and those who had not (Mantel-Hanzel test: chi2=0.15; df =1; p=0.70).

**2.3 Sensitivity analysis (post-hoc)**

We performed a sensitivity analysis to examine the possibility of a regression bias towards the mean greater in the spa than in the control group. If patients >75$^{th}$ percentile at inclusion for WOMAC are excluded then the difference remains significantly in favour of the spa group.

For analgesic consumption, if we exclude patients having a WOMAC score at inclusion >75$^{th}$ percentile, analgesic consumption is similar in the two groups, at inclusion (control 15.8%; spa 16.7%; p=0.83), and at 6 months (control 5.0%; spa 7.0%; p=0.47).

The proportion of improved patients is similar between the two genders (Mantel-Hanzel test chi2=0.55; df =1; p=0.46).

**4. Adverse events**

| Adverse Event | Spa therapy |
|---|---|
| Serious Adverse Event (Urinary lithiasis) | 1 |
| **Adverse events during period of Spa therapy** | |
| Painful knee episode | 4 |
| Lower back pain | 2 |
| Venous insufficiency (requiring interruption of spa therapy), | 1 |
| Haematuria (2 days) | 1 |
| Upper respiratory tract infection | 1 |
| Leg Erysipelas (responded favourably to antibiotics) | 1 |
| Severe asthenia (in a patient who continued to work) | 1 |
| **Control Group** | |
| No adverse events were reported in the control group | |

**5. Spa Therapy Compliance (from forms completed by the spa physician)**

A form recording patient compliance was completed by the physician at the beginning, middle and end of the course of spa therapy. It included the systolic and diastolic blood pressure, heart rate, the patient's weight, any adverse events and the patients' adaptation to the treatment.

Among the 195 patients in the spa therapy group included in the analysis at 6 months:

- 18 had changed group and were not subject to surveillance (analysis in ITT)
- 8 patients had no compliance form completed
- 169 had at least one compliance form completed during the course of spa therapy:
    * 163 patients with all 3 visits (beginning + middle + end)
    * 5 patients with 2 visits (beginning + end or beginning + middle)
    * 1 patient with 1 visit ((beginning)

**7. Home exercise programme (HEP)**

The exercises were derived from those developed for knee OA by O'Reilly [11] and evaluated by Ravaud [12]

**Details of the exercises to be performed at home are given in a separate file: (supplementary file 1)**