EXTENDED REPORT

# Randomised, controlled trial of avocado–soybean unsaponifiable (Piascledine) effect on structure modification in hip osteoarthritis: the ERADIAS study

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## ABSTRACT

**Objective** To assess the ability of avocado–soybean unsaponifiable—Expanscience (ASU-E) to slow radiographic progression in symptomatic hip osteoarthritis (OA).

**Methods** Prospective, randomised, double blind, parallel group, placebo controlled 3 year trial. Patients with symptomatic (painful ≥1 year, Lequesne Index between 3 and 10) hip OA (American College of Rheumatology criteria) and a minimum joint space width (JSW) of the target hip between 1 and 4 mm on a pelvic radiograph were randomly assigned to 300 mg/day ASU-E or placebo. Standing pelvis, target hip anteroposterior (AP) and oblique views were taken annually. The primary outcome was JSW change at year 3, measured at the narrowest point on pelvic or target hip AP view (manual measure using a 0.1 mm graduated magnifying glass). The full analysis dataset (FAS) included all patients having at least two successive radiographs. An analysis of covariance Mixed Model for Repeated Measurements with Missing at Random (for missing data) was performed to compare adjusted 3 year JSW changes (primary outcome) and the percentages of 'progressors' (JSW loss≥0.5 mm) between groups.

**Results** 399 patients were randomised (345 kept in the FAS), aged 62 (35–84) years, 54% women, mean body mass index 27 (SD 4) kg/m², mean symptom duration 4 (SD 5) years, 0–100 normalised Lequesne Index 30 (SD 9) and global pain visual analogue scale 37 (SD 23) mm. Mean baseline JSW was 2.8 (0.9) mm. There was no significant difference on mean JSW loss (−0.638 mm vs −0.672 mm, p=0.72, in the ASU-E and placebo groups, respectively) but there were 20% less progressors in the ASU-E than in the placebo group (40% vs 50%, respectively, p=0.040). No difference was observed on clinical outcomes. Safety was excellent.

**Conclusions** 3 year treatment with ASU-E reduces the percentage of JSW progressors, indicating a potential structure modifying effect in hip OA to be confirmed, and the clinical relevance requires further assessment.

**Trial registration number on ClinicalTrial.gov** NCT01062737

## INTRODUCTION

Osteoarthritis (OA) is the most common joint disease. It weights a heavy burden. Hip OA affects about 10% of the population aged 65–73 years.[1] Its prevalence dramatically increases with age.[2]

Each year, 150 000 total hip replacements (THR) are performed for OA in France and 100 000 in the UK. It accounts for nearly 50% of the economic cost of OA in France or in Australia.[3] [4] This burden is likely to dramatically increase[5]: by 2030, the demand for total hip arthroplasties for all conditions should grow by 174% in the USA and by 149% in The Netherlands.[6] [7]

At present, there is no specific therapy targeting the pathological process of OA.[8] Several treatment options are available.[9–11] Many symptom modifying therapies have been proposed with various levels of evidence.[12] However, we still lack an approved disease modifying therapy because no treatment has proven without doubt its efficacy in preventing, stopping or delaying the disease,[9–18] although glucosamine sulfate, chondroitin sulfate and very recently strontium ranelate have shown structure modifying properties in long term trials.[19] Most of the OA structure modifications trials have been performed in knee OA, but three conducted in hip OA had unconvincing efficacy.[20–22] The structural progression of OA is currently recommended to be assessed on plain radiographs by measuring joint space width (JSW) and joint space narrowing (JSN) over time,[13–26] as clearly restated by the European Medicines Agency in 2010.[26]

Avocado–soybean unsaponifiable—Expanscience (ASU-E) (Laboratoires Expanscience, Courbevoie, France) is made up of unsaponifiable fractions of one-third avocado and two-third soybean oils (ie, extracts) and has shown anti-OA properties in preclinical in vitro and in vivo works. It has an inhibitory effect on interleukin 1, a stimulating effect on collagen synthesis in articular chondrocyte cultures and a potential action on subchondral bone osteoblasts.[27–36] ASU-E demonstrated efficacy on symptoms in hip and knee OA in some trials,[37–39] which has been confirmed in a recent review and a meta-analysis.[40] [41] A pilot 2 year placebo controlled structure modification trial on 163 patients did not show any significant structure modifying effect, but identified a significant reduction in JSN in the most radiologically severe patients subgroup (baseline JSW<2.45 mm), in a post-hoc analysis.[21]

We decided to perform a long term randomised controlled trial to assess the structure modifying effect of ASU-E in a large sample of symptomatic hip OA patients.

## PATIENTS AND METHODS

### Patients
Outpatients, aged 45–75 years, were recruited by 122 French centres (52 private rheumatologists and 70 general practitioners) between February 2000 and January 2004.

### Definition of the disease
Patients were suffering from idiopathic hip OA, fulfilling the American College of Rheumatology clinicoradiographic criteria.[42]

### Symptom level at baseline
Patients were symptomatic (constant or intermittent pain) for at least 1 year, with pain being present half of the time at least of the 3 months preceding selection, with a Lequesne AlgoFunctional Index score (range 0–24)[43] for hip OA between 3 and 10, despite analgesics. In the case of bilateral complaints, the most symptomatic hip was chosen as the target hip.

### Radiographic severity at baseline
Radiographic criteria for selection were a localised superolateral or superomedial JSN with a minimal JSW (narrowest site) between 1 and 4 mm on the target hip anteroposterior (AP) view, or in case of a concentric global JSN, a JSW between 1 and 4 mm on this view and reduced by at least 1 mm compared with the contralateral hip on the front pelvic view. These values account for 20% (JSW reduced by 1 mm) and 80% (remaining joint space ≥1 mm) of a normal hip joint space of 5 mm on average.[44] Prior to randomisation, radiographic eligibility was centrally appraised by an independent observer (EM) who verified the above mentioned conditions and the quality of radiographs, according to predefined quality criteria (below). In addition, patients had to provide written informed consent to enter the study.

The main exclusion criteria were: secondary hip OA (as defined by Schumacher[45]) such as post-traumatic OA, congenital subluxation, acetabular dysplasia, avascular femoral head necrosis, inflammatory arthritis, metabolic arthritis, chondrocalcinosis (calcium deposition on the hip cartilage), Paget's disease or haemophilic arthritis; a high level of pain and few radiographic damages; posterior hip OA (posterior/inferoposterior JSN on Lequesne's oblique view)[46]; patients likely to undergo a total joint replacement within the next 6 months; homolateral symptomatic knee OA; oral or parenteral corticosteroids during the previous month; intra-articular injection during the previous 3 months (except radiocontrast); and any serious concomitant medical illness.

### Study design
This was a prospective, multicentre, randomised, double blind, placebo controlled, parallel group trial of 3 years' duration. The study protocol was approved by the ethics review board of the Pitié-Salpêtrière Hospital (Paris, France).

### Drug administration and concomitant therapies
After confirmation that they fulfilled the selection criteria and written informed consent had been obtained, patients were randomly assigned to either the 300 mg capsule of ASU-E group (Piascledine 300; Laboratoires Expanscience) or to the placebo capsule group, daily, for 3 years.

The randomisation list was previously established by an independent company (Creapharm, Le Haillan, France) by blocks of two for each stratum defined by baseline JSW: <2.5 mm and ≥2.5 mm (according to a previous trial[21]). Treatment units were prepared by the same company in boxes of 3 months of treatment.

Treatment allocation was done following the central check of radiological selection criteria determining the stratum by the investigator following a numerical order. Treatment units were delivered by the investigator.

### Concomitant medications
The use of analgesics and non steroidal anti-inflammatory drugs (NSAIDs) for OA symptoms was allowed after entry but had to be as low as possible and recorded. The amount taken was recorded by the patient using a self-report weekly diary. The investigator recorded the intake for each given period since the previous visit. Corticosteroid injections (periarticular around the target hip or intra-articular) were not allowed during the trial. Steroid injections in another articular site were allowed, if judged necessary by the investigator. Other symptom modifying drugs for OA were prohibited during the study period, as was indomethacin.[47]

### Treatment observance
Treatment units given to the patient had to be returned at each visit to count and report study drug intake.

### Radiological and clinical outcomes
The primary outcome was the change in JSW on the AP target hip view (or on the pelvic view if not available)[48] at year 3 (or at the end of the study if not available). Three views were taken at selection and then yearly (12 views per patient): a pelvic front AP view (beam centred on the pubis), a target hip AP view and a target hip oblique view ('false profile'[46]). AP target hip and pelvic views were performed according to a standardised protocol: (1) in the standing position[49 50]; (2) with standard distance from patient to radiography source of 1 m; (3) with an internal feet rotation of 15°±5° for front views; and (4) either plain or digitalised radiographs, provided they were made at the real size (1/1 or between 97% and 105% of the standard size if digitalised).

### Radiographic selection of patients
The three views performed at selection were sent to the central reader who verified the patient's eligibility, and measured JSW to determine in which stratum the patient should be randomised. Then, the central reader sent his assessment to the investigator and the radiographs to the CRO which stored the x-rays for the final reading of the primary outcome.

### Central radiographic measurement of joint space width
Before unblinding the patient's data, it was planned to assess the performance (intra-/interobserver reliabilities and sensitivity to change) of the 'manual' chondrometry (as described by Lequesne)[50] and a computer assisted measurement. The methods and results of these assessments have been described elsewhere[48 51] and, as a consequence, the 'manual' radiochondrometry with the best reader (CC) was therefore selected to perform the radiographic measurements. In addition, the performance of the three pelvic views was assessed. All baseline pelvic radiographs were also scored according to the Kellgren–Lawrence grading system.[52]

### Radiographic reading procedure
Radiographs were anonymised for the time sequence by a random attribution of a letter for each visit at which radiographs

Figure 1 Patient disposition in the trial (number of patients without any assessment of the primary outcome and number of protocol deviations were well balanced between the treatment groups). ASU-E, avocado–soybean unsaponifiable—Expanscience.
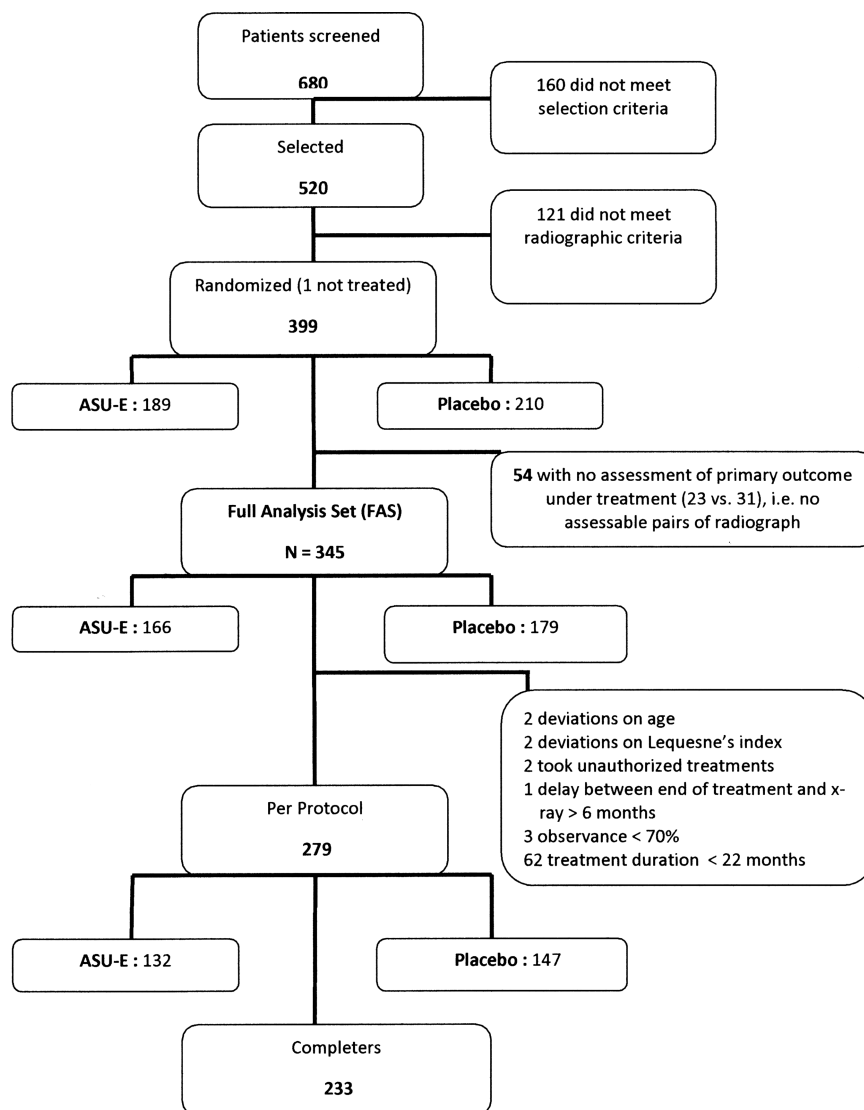


were performed. An envelope gathering all available views was labelled with the patient's trial number. The reader measured the minimal JSW on all radiographs of a given patient during the same session on a horizontal screen.

### Clinical assessments

Clinical assessments for efficacy and safety parameters were recorded at months 1, 3 and every 3 months until month 36, including: Lequesne's Index (0–24)[43] normalised on a 0–100 basis; the Western and Ontario MacMaster University (WOMAC) visual analogue scale (VAS)[53]; global hip pain level during the past 48 h on a 0–100 mm VAS[54]; global handicap rated by the patient on a 0–100 mm VAS and an 11 point numerical scale[55]; patient's global assessment of disease severity on a 0–100 mm VAS; percentages of patients having taken at least one NSAID and/or analgesic); and overall efficacy assessment by the patient and investigator. THR of the target hip occurring during the study was also assessed on all randomised patients having received the treatment. Safety was evaluated by the incidence of adverse events (AE) in each group, their description, rate of withdrawals for AEs and overall patient and physician assessments. Adherence was assessed by an open question and by counting the number of returned capsules.

### Statistical methods
#### Sample size

Sample size determination was based on the primary endpoint, the change in JSW between baseline and year 3, using previous data.[20][21] Expecting a difference of 0.25 mm versus placebo in mean JSW change at year 3 and a common SD of 0.75 mm,

**Table 1** Reasons for premature discontinuation of the trial

| Patient status | Placebo (n (%)) | ASU-E (n (%)) | Total (n (%)) |
|---|---|---|---|
| Randomised patients | 210 (100) | 189 (100) | 399 (100) |
| Completers | 127 (60.5) | 106 (56.1) | 233 (58.4) |
| Premature withdrawals | 83 (39.5) | 83 (43.9) | 166 (41.6) |
| Inefficacy with total joint replacement | 36 (17.1) | 38 (20.1) | 74 (18.5) |
| Inefficacy without total joint replacement | 9 (4.3) | 8 (4.2) | 17 (4.3) |
| Adverse events | 11 (5.2) | 10 (5.3) | 21 (5.3) |
| Consent withdrawal | 11 (5.2) | 17 (9.0) | 28 (7.0) |
| Lost to follow-up | 8 (3.8) | 3 (1.6) | 11 (2.8) |
| Other | 7 (3.3) | 6 (3.2) | 13 (3.3) |
| Deaths | 1 (0.5) | 1 (0.5) | 2 (0.5) |

ASU-E, avocado–soybean unsaponifiable—Expanscience.

**Table 2**  Patient demographic and baseline characteristics in the full analysis set

| Characteristic | Placebo (n=179) | ASU-E (n=166) | Total (n=345) |
|---|---|---|---|
| Gender (% women) | 56 | 51 | 54 |
| Age (years) (mean (SD)) | 62.7 (8.0) | 61.6 (7.9) | 62.2 (7.9) |
| BMI (kg/m$^2$) (mean (SD)) | 26.8 (4.4) | 27.0 (4.1) | 26.9 (4.2) |
| Delay since 1st symptoms (years) (mean (SD)) | 4.3 (4.6) | 4.4 (5.6) | 4.3 (5.1) |
| Delay since regular symptoms (years) (mean (SD)) | 1.6 (2.0) | 1.6 (1.8) | 1.6 (1.9) |
| Other osteoarthritic sites (% yes) | 56 | 50 | 53 |
| Concomitant medications (% yes) | 82 | 80 | 81 |
| Kellgren–Lawrence grade (n (%)) | | | |
| I | 12 (6.7) | 19 (11.4) | 31 (9) |
| II | 99 (55.3) | 88 (53.0) | 187 (54.2) |
| III | 66 (36.9) | 59 (35.5) | 125 (36.2) |
| IV | 2 (1.1) | 0 | 2 (0.6%) |
| Location of JSN at narrowest site (n (%)) | | | |
| Superolateral | 99 (55.3) | 80 (48.2) | 179 (51.9) |
| Superomedial | 42 (23.5) | 40 (24.1) | 82 (23.8) |
| Superior global | 38 (21.2) | 46 (27.7) | 84 (24.3) |
| JSW at narrowest site of target hip (mm) (mean (SD)) | 2.76 (0.9) | 2.85 (0.9) | 2.81 (0.9) |
| Lequesne Index (normalised 0–100) (mean (SD)) | 30.4 (10.0) | 30.0 (8.4) | 30.2 (9.3) |
| WOMAC pain score (0–100 mm) (mean (SD)) | 32.7 (20.6) | 31.6 (18.6) | 32.2 (19.7) |
| WOMAC stiffness score (0–100 mm) (mean (SD)) | 36.2 (25.3) | 35.4 (23.5) | 35.8 (24.4) |
| WOMAC function score (0–100 mm) (mean (SD)) | 31.9 (21.5) | 31.4 (20.5) | 31.7 (21.0) |
| Global hip pain (0–100 mm) (mean (SD)) | 36.6 (23.9) | 37.4 (23.1) | 37.0 (23.5) |
| Global handicap, numerical scale (0–10) (mean (SD)) | 4.4 (1.9) | 4.4 (1.8) | 4.4 (1.9) |
| Patient's global assessment (0–100 mm) (mean (SD)) | 40.3 (27.9) | 40.4 (25.3) | 40.3 (26.6) |

ASU-E, avocado–soybean unsaponifiable—Expanscience; BMI, body mass index; JSN, joint space narrowing; JSW, joint space width; WOMAC, Western and Ontario MacMaster University.

380 patients (190 per treatment group) were required to achieve 90% power considering a two sided nominal significance level of 0.05. With this sample size, an analysis performed in the subgroup of severe patients whose size was expected to be half the targeted sample size (ie, 180 patients) could still achieve 75% power to show a difference of 0.35 mm versus placebo.

### Analysis sets
Different sets were defined. (1) Safety set: all patients taking at least one treatment dose. (2) Randomised set based on the intention to treat principle. (3) Full analysis set (FAS)[56]: all randomised patients taking at least one study treatment dose and with at least one baseline and one post baseline x-ray to assess JSN on either the target hip AP or the pelvic view. (4) Completer set: all FAS patients with both baseline and month 36 x-rays. (5) Per protocol (PP) set: all FAS patients without any major deviation and with a treatment duration of at least 24±2 months.

FAS was considered as the primary efficacy analysis set. Sensitivity analyses were performed in other sets (intention to treat and PP sets) to investigate the results of robustness.[56]

### Statistical analyses
Descriptive statistics (mean, median, SD, quartiles for continuous and frequencies for categorical variables) were used to assess baseline characteristics in both groups. No statistical tests were performed between groups according to CPMP recommendations.[57] Statistical hypotheses were tested by two sided tests at the 5% nominal level of significance; 95% CI were considered. All analyses were performed with SAS V.9.2 software.

#### Primary efficacy analyses
The primary efficacy endpoint was the change in JSW from baseline to year 3, which was assumed to be normally distributed. The primary model was a Mixed Model for Repeated Measurements (MMRM), assuming an unstructured correlation matrix and adjusting for baseline JSW, visit (year 1, 2 and 3), treatment, treatment by visit and baseline by visit interactions. Differences in adjusted JSW means between treatment groups with 95% CI were estimated at year 3 using this mixed model. A sensitivity analysis using the Last Observation Carried Forward method for handling of missing data was also performed.

Several years after the study started, international consensus[23–25] recommended not choosing JSN as the primary endpoint as the distribution of the latter was found to be particularly asymmetric and not easily tractable with usual statistical methods. Consequently, an amendment to the study protocol was issued before unblinding, defining a secondary efficacy analysis of the primary endpoint—that is, analysis of a binary endpoint (progression vs non-progression at 3 years) derived from the continuous JSN. A patient was defined as a progressor when JSW loss was ≥0.5 mm at 3 years. This 0.5 mm cut-off was selected before unblinding, based on the available literature at the time of finalisation of the statistical analysis plan, including a recent consensus recommending defining the cut-off based on the smallest detectable difference in JSN assessment of the reader.[25] Also, another definition of a progressor was proposed: either a year 3 JSN≥0.5 mm or a THR. Progressors rates were compared between treatment groups using a

**Table 3**  Results of analyses on the primary outcome: joint space width change measured on anteroposterior pelvis or target hip views using manual radiochondrometry, and rate of progressors, at 3 years, in the full analysis set, according to the MAR-MMRM analysis model
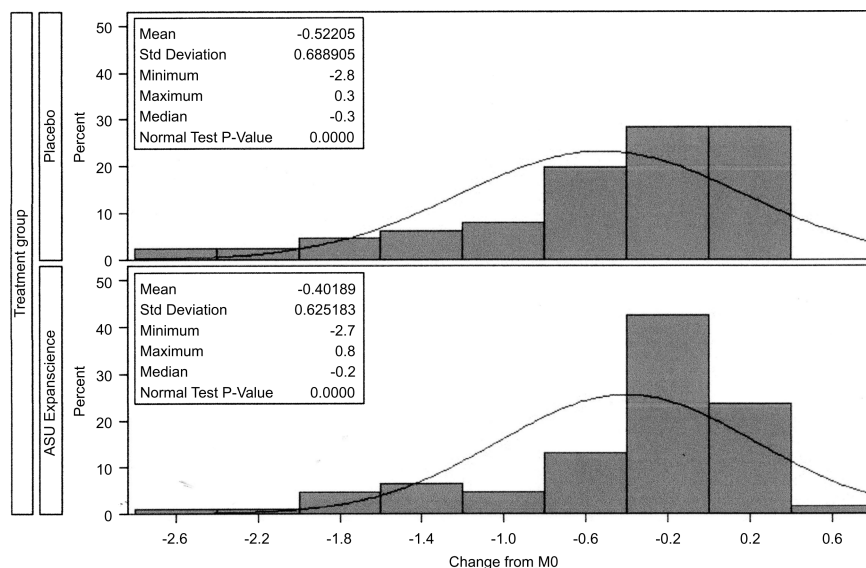
| | Placebo (n=179) | ASU-E (n=166) | p Value | OR/Diff | 95% CI |
|---|---|---|---|---|---|
| Change in JSW at the narrowest point (mm) (mean (SEM)) | −0.672 (0.066) | −0.638 (0.070) | 0.723* | 0.034 (0.096) | −0.156 to 0.224 |
| Progressors (progressor=JS loss≥0.5 mm at 3 years) (%) | 50.3 | 40.4 | 0.040† | 1.613 | 1.023 to 2.543 |

*ANOVA treatment effect.
†Cochran–Mantel–Haenzel test adjusted on stratum.
ASU-E, avocado–soybean unsaponifiable—Expanscience; JSW, joint space width; MAR-MMRM, Missing at Random–Mixed Model for Repeated Measurements; OR, odds ratio ASU-E versus placebo.

**Figure 2** Distribution of joint space narrowing in both groups of treatment. ASU-E, avocado–soybean unsaponifiable—Expanscience.
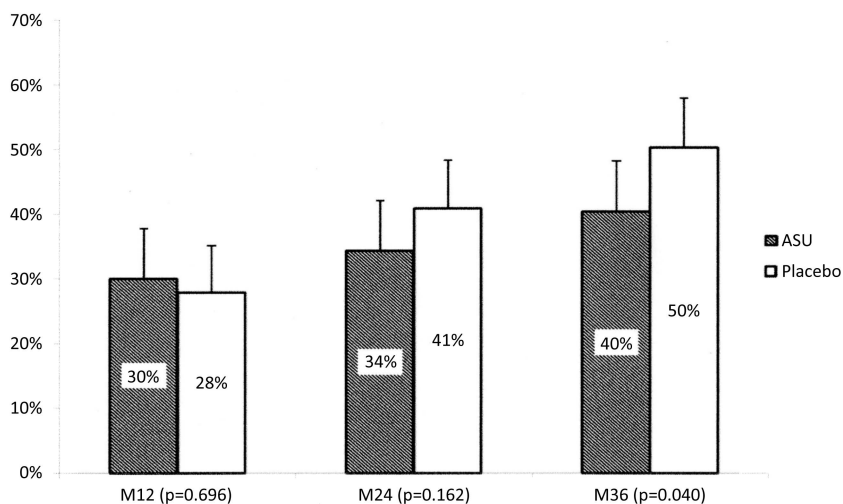
| | Placebo | |
|---|---|---|
| Mean | | -0.52205 |
| Std Deviation | | 0.688905 |
| Minimum | | -2.8 |
| Maximum | | 0.3 |
| Median | | -0.3 |
| Normal Test P-Value | | 0.0000 |

| | ASU Expanscience | |
|---|---|---|
| Mean | | -0.40189 |
| Std Deviation | | 0.625183 |
| Minimum | | -2.7 |
| Maximum | | 0.8 |
| Median | | -0.2 |
| Normal Test P-Value | | 0.0000 |

Cochran–Mantel–Haenszel test adjusted for severity stratum. A sensitivity logistic regression model adjusting for continuous baseline JSW was also fitted to compare the groups.[56] Missing data were handled assuming Missing at Random (MAR).[58] The MMRM which yields unbiased estimates of the treatment effect under this missing data mechanism was primarily favoured.[58 59] The Last Observation Carried Forward method was also applied to check the sensitivity result to missing data.[56] For the progressors analysis, year 3 missing values were predicted using both approaches.

**Figure 3** Mean joint space narrowing (joint space width (JSW) change) and rates of progressors (JSN≥0.5 mm vs baseline) at each time point, between baseline and year 3 in the full analysis set. ASU-E, avocado–soybean unsaponifiable—Expanscience.
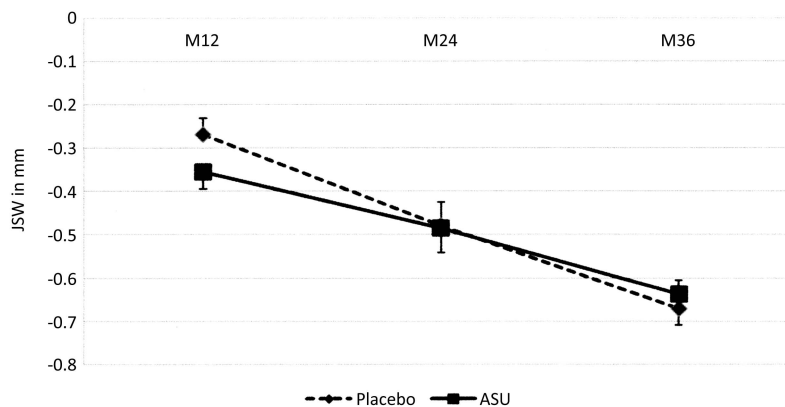
**Joint Space Width change from baseline**

Rates of progressors in the two groups at each year (JSN≥0.5 mm vs baseline).

**Table 4**  Clinical secondary outcomes between months 0 and 36 in the full analysis set (MAR-MMRM model)

| Clinical outcomes changes between months 0 and 36 | Placebo (n=179) | ASU-E (n=166) | p Value* | Difference | 95% CI |
|---|---|---|---|---|---|
| Lequesne Index (normalised 0–100) | −0.14 (1.69) | 1.50 (1.78) | 0.506 | −1.63 (2.45) | −6.45 to 3.19 |
| WOMAC pain (0–100 mm) | −0.98 (2.17) | −0.25 (2.33) | 0.818 | −0.73 (3.18) | −7.00 to 5.54 |
| WOMAC stiffness (0–100 mm) | −2.29 (2.23) | −1.80 (2.43) | 0.881 | −0.49 (3.30) | −6.99 to 6.01 |
| WOMAC function (0–100 mm) | 2.10 (2.13) | 1.48 (2.30) | 0.843 | 0.62 (3.13) | −5.55 to 6.79 |
| Global hip pain on VAS (0–100 mm) | −3.60 (2.35) | −4.26 (2.51) | 0.849 | 0.66 (3.43) | −6.10 to 7.42 |
| Global handicap on 0–10 scale | −0.21 (0.22) | −0.53 (0.24) | 0.326 | 0.32 (0.32) | −0.32 to 0.96 |
| Patient's global assessment (0–100) | −4.25 (2.64) | −4.42 (2.84) | 0.963 | 0.18 (3.87) | −7.45 to 7.81 |

Values are mean (SEM).
*ANOVA treatment effect.
ASU-E, avocado–soybean unsaponifiable—Expanscience; MAR-MMRM, Missing at Random–Mixed Model for Repeated Measurements; VAS, visual analogue scale; WOMAC, Western and Ontario MacMaster University.

## Secondary efficacy outcome analyses

Secondary clinical efficacy continuous endpoints were analysed at 6 months and at year 3 using the MMRM model. THR rates were compared using a Cochran–Mantel–Haenszel test stratified by severity and a Fisher exact test. Time to hip replacement (from baseline up to 6 months after trial cessation) was estimated by the Kaplan–Meier method and compared with the log rank test. Rates of patients taking NSAIDs and/or analgesics were compared using a $\chi^2$ test.

## Safety analyses

AE were coded in the MedDRA dictionary (by organ class and preferred term). Comparison of AE rates between groups was performed by a Fisher exact test.

## RESULTS

Disposition of patients in the study is described in figure 1. Of the 399 patients randomised, 189 belonged to the ASU-E and 210 to the placebo group; 345 (86.5%) patients made up the FAS as there was no assessment of the primary outcome under treatment available for 54 patients. Reasons for premature withdrawals are listed in table 1. The safety population included 398 patients as one randomised patient did not receive any study treatment while randomised.

Table 2 shows the demographic and baseline characteristics of the FAS.

## Primary endpoint

On the FAS population using the MMRM missing replacement method, adjusted mean JSN at year 3 at the site of maximal narrowing was −0.67 mm in the placebo group and −0.64 mm in the ASU-E group, the difference of 0.034 mm (95% CI −0.156 to 0.225) not being statistically significant (p=0.72) (table 3).

**Table 5**  Non-steroidal anti-inflammatory drug and analgesic intake between months 0 and 36 in the full analysis set

| Clinical outcome changes between months 0 and 36 | Placebo (n=179) | ASU-E (n=166) | p Value |
|---|---|---|---|
| NSAID/analgesic intake (n (%) of patients who had at least one intake of an NSAID or analgesic during the trial) | 157 (87.7) | 145 (87.3) | 0.919 |
| NSAID intake (n (%) of patients who had at least 1 intake during the trial) | 115 (64.2) | 109 (65.7) | 0.783 |

ASU-E, avocado–soybean unsaponifiable—Expanscience; NSAID, non-steroidal anti-inflammatory drug.

As shown in figure 2, the distribution of JSN inside the groups was not statistically normal, but shifted to the right, indicating a high rate of patients with no JS deterioration and justifying the dichotomisation of JSN change into progressors/non-progressors.

The secondary efficacy analysis of the primary endpoint based on progressors at year 3 is given in table 3: 40.4% of patients were classified as progressors in the ASU-E group versus 50.3% in the placebo group, with a statistically significant difference of approximately 10% (p=0.040). The relative risk reduction to be a progressor was 20% with ASU-E. Figure 3 indicates JSN and the rates of progressors at each time point.

The number needed to treat to obtain a non-progressor was 11.

Indicative results of sensitivity analyses for both outcomes (JSN and progressors rates) are provided in an online supplementary file (S1). PP analyses yielded similar results: no statistical difference in JSN and a statistically significant difference between progressors rates favouring ASU-E, using the MAR-MMRM approach (see online supplementary file (S2)). The same results were observed with JSN measured by the computer assisted method (see online supplementary file (S3)).

Analysis of progressors rate using the secondary definition (JSN≥0.5 mm or THR) gave 51.4% of progressors in the placebo group versus 42.2% in ASU-E group (p=0.054).

## Secondary endpoint analysis

Regardless of the statistical method used to handle missing data, there was no between group difference on clinical outcomes: Lequesne Index, WOMAC (pain, stiffness, function), global pain, global handicap, patient's overall assessment (table 4) or analgesic/NSAID intake (table 5).

In the safety population, 83 patients (20.9%) underwent a THR between months 0 and 42, with no between group difference (table 6). A higher percentage of THR was observed in the more severe patient stratum (JSW<2.5 mm): 37.5% vs 11.6%, with no intergroup difference. Mean compliance with treatment was 97% in both groups.

## Safety analysis

Mean exposure to treatment was 904 days in the placebo group and 880 in the ASU-E group (p=0.348). Results of the safety analysis are presented in table 7. Nearly 87% of patients reported at least one AE during the study and 32 patients reported at least one treatment related AE; the most frequent AEs were musculoskeletal/connective tissue and infections/infestations. Sixty-three patients withdrew from the study for safety reason (no between group difference).

**Table 6** Number and percentages of patients who underwent a total hip replacement in the safety population (n=398)

| Patients who underwent THR | Placebo (209) | ASU-E (189) | Total (398) | p (Fisher) |
|---|---|---|---|---|
| Between baseline and month 42 (n (%)) | 39/209* (18.7) | 44/189* (23.3) | 83/398 (20.9) | 0.269 |
| Baseline JSW<2.5 mm (n (%)) | 27/77 (35.1) | 27/67 (40.3) | 54/144 (37.5) | 0.605 |
| Baseline JSW≥2.5 mm (n (%)) | 12/130 (9.2) | 17/121 (14.0) | 29/251 (11.6) | 0.244 |
| Within 6 months after the end of the trial at patient level (n (%)) | 35/209* (16.7) | 38/189* (20.1) | 73/398 (18.3) | 0.437 |
| Baseline JSW<2.5 mm (n (%)) | 23/77 (29.9) | 24/67 (35.8) | 47/144 (32.6) | 0.480 |
| Baseline JSW≥2.5 mm (n (%)) | 12/130 (9.2) | 14/121 (11.6) | 26/251 (10.4) | 0.679 |

*Three patients had no target hip radiographs at baseline (two in the placebo group and one in the ASU-E group).
ASU-E, avocado–soybean unsaponifiable—Expanscience; JSW, joint space width; THR, total hip replacement.

Safety was judged very good/good or moderate by 84.2% of patients in the placebo group and in 85.8% of patients in the ASU-E group.

## DISCUSSION

Our main finding in this 3 year randomised controlled trial was that we observed no difference between the groups regarding JSW change, the continuous variable, at 3 years, but identified that ASU-E significantly decreased the rate of progressors to 40% compared with 50% in the placebo group, which represents a reduction by 20%. Also, there was no between group difference in clinical parameters.

The main strength of our trial lies in the high level methodology used to evaluate the structural effect of ASU-E in hip OA. Indeed, it is now well known that assessing OA progression on radiographs by measuring JSW and JSN, although the current gold standard for Agencies and Scientific Societies,[23–26] is problematic. For example: (1) reproducibility of the patient's positioning for taking radiographs; (2) reading method and selection of the reader(s); (3) definition of the primary outcome; (4) method of handling missing data, bearing in mind the 35–47% withdrawal rate in long term trials in symptomatic hip and knee OA usually reported,[20 41 60–64] in order to optimise the primary criterion analysis; and (5) definition of populations for the statistical analysis, particularly the intention to treat population. All of these issues were addressed as well as possibly using the highest standards of methodology and consensus working group discussions[23–25] prior to breaking the code. As more scientific information arose during the trial, it became obvious that JSN in OA is not a quantitative linear normally distributed parameter. Indeed, many patients do not vary at all, even over a 3 year period (figure 2). We therefore planned a secondary major analysis of the primary endpoint taking into account this new knowledge while keeping our original primary outcome. A protocol amendment was instigated to analyse our primary outcome using the recommended binary approach: the progressors rates.[25] This led to two analyses of the primary criterion, as reported. Only the latter analysis showed that ASU-E reduced the rate of progression in hip OA, compared with placebo. We defined our primary population (FAS) as patients having at least two measurements under treatment, on the same radiographic incidence, pelvis or target hip front view. Furthermore, we used the MMRM-MAR model, currently thought to be more accurate and clinically relevant for the purpose of trials than the Last Observation Carried Forward method using or not using the maximal bias,[58 59] to estimate and analyse missing data. This allowed us to keep 112 premature dropouts in our primary analysis, giving 345 patients in the FAS (compared with 233 completers), and limited to 54 the number of patients lost for the primary analysis. This is the first 3 year structure modification trial in OA with such a low number of patients lost for the main analysis.

Our study has limitations. The first relates to the analysis of the primary criterion, since the analysis of the continuous

**Table 7** Safety analyses in the ERADIAS trial

| No (%) of patients having: | Placebo (n=209) | ASU-E (n=189) | Total (n=398) |
|---|---|---|---|
| At least one AE (p=0.30) | 178 (85.2) | 168 (88.9) | 346 (86.9) |
| At least one AE of | | | |
| 'Moderate to severe' intensity and unknown intensity | 160 (76.6) | 146 (77.3) | 306 (76.9) |
| 'Mild' intensity | 119 (56.9) | 110 (58.2) | 229 (57.5) |
| No of patients with at least one treatment related* AE | 13 (6.2) | 19 (10.1) | 32 (8.0) |
| No of treatment related* AE | 20 (2.1) | 28 (3.4) | 48 (2.7) |
| At least one AE leading to treatment cessation | 31 (14.8)† | 32 (16.9)† | 63 (15.8)† |
| At least one serious AE (P=0.14) | 68 (32.5)‡ | 75 (39.7)‡ | 143 (35.9)‡ |
| At least one serious treatment related AE | 2 (1.0) 1 hip replacement 1 wrist fracture | 4 (2.1) 3 hip replacements 1 post surgery haematoma | 6 (1.5) |
| Deceased during the trial for treatment unrelated reasons | 1 glioblastoma 1 heart attack (ventricular tachycardia) | 1 myocardial infarction with operated interventricular communication | 3 |

*Related=missing, doubtful, probable, possible, highly possible.
†18 patients in the placebo group and 16 patients in the ASU-E group withdrew from the trial for hip arthroplasty after treatment discontinuation.
‡33 patients in the placebo group and 29 patients in the ASU-E group had a hip arthroplasty after treatment discontinuation.
AE, adverse event; ASU-E, avocado–soybean unsaponifiable—Expanscience.

parameter (3 year JSN) did not show any between group difference, in contrast with the responder analysis which showed a significant relative reduction by 20% of progressors rate in the ASU-E group. A second point to consider is the absence of a symptomatic effect of ASU-E in this trial conversely to previous shorter symptom modification randomised controlled trials of ASU-E. There might be three reasons for this: (1) this trial was not designed for symptom modification but for structure modification; (2) enrolled patients had few symptoms at baseline in order to keep them in the trial and avoid too many premature dropouts for THR: 50% were at the patient acceptable symptom state[65] for pain (<35 mm on pain VAS) and/or function. Mean pain level was 37.0 mm and the mean normalised Lequesne Index score was 30.2 (7.2 in the 0–24 usual scoring); and (3) surprisingly, there was no placebo effect on pain or function, which is unusual in hip OA, as recently reviewed.[66] It might be related to the fact that Zhang mostly identified the placebo effect in symptom modifying OA trials which included more symptomatic patients. However, it must be noticed that there was also no clinical effect observed in the structure modifying trials assessing diacerein[20] or glucosamine[22] in hip OA.

In this study, we did not evaluate the clinical relevance of the reduction in the numbers of progressors. A follow-up of patients is currently being performed with THR as the main outcome.

In summary, this is the first trial fulfilling the highest recommended methodological standards regarding the primary outcome measurement (JS loss) and its statistical analysis. It showed that 3 years of treatment with ASU-E did not reduce the average JS loss but reduced the percentage of JSW deteriorating patients compared with placebo, possibly indicating a potential structure modifying effect in hip OA. The clinical relevance of this requires further assessment.

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