An open-label six-month extension study to investigate the safety and efficacy of an extract of *Artemisia annua* for managing pain, stiffness and functional limitation associated with osteoarthritis of the hip and knee

Sheena Hunt, Debra McNamara, Simon Stebbings

**ABSTRACT**

**AIMS:** This six-month single-centre open-label extension study, conducted at the University of Otago, Dunedin, follows from a previously published 12-week pilot double-blind randomised placebo-controlled study of dietary supplement, Arthrem® (ART) in patients with osteoarthritis (OA) of the hip or knee. The pilot double-blind study showed that treatment with ART 150 mg twice-daily was associated with clinically relevant pain reduction. The extension study aims were to assess longer-term safety and efficacy during six months’ treatment following the pilot trial.

**METHOD:** Patients who completed the pilot double-blind study had the option to continue on open-label treatment with ART for a further six months. Safety was assessed by adverse event monitoring and laboratory tests at three and six months. Efficacy was assessed at three and six months using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®).

**RESULTS:** Thirty-four patients entered the optional extension and 28 completed six months’ treatment. ART was well tolerated when taken for up to nine months. Improvements in WOMAC® efficacy parameters reported in the double-blind phase of the study were maintained over six months.

**CONCLUSION:** ART appears to be a safe and effective alternative for managing the symptoms of OA over an extended period.

A recent randomised controlled pilot trial was conducted to investigate the safety and efficacy of an extract of *Artemisia annua* as potential therapy for osteoarthritis (OA). The study investigated the dietary supplement, Arthrem® (ART) which contains 150mg of standardised supercritical extract of *Artemisia annua* per capsule. Supplementation with ART (at a dose equivalent to one capsule of the dietary supplement twice-daily [BD]) showed benefits in patients with hip or knee OA over the 12-week study. The primary efficacy endpoint was reduction in Western Ontario and McMaster Universities Arthritis Index (WOMAC®) 3.1 index. The published results of the study showed both statistically significant improvements from baseline in mean scores for the primary efficacy endpoint WOMAC® total, WOMAC® stiffness, WOMAC® physical function and VAS pain, and clinically relevant reductions in pain. There were no statistically significant changes from baseline in the placebo group for any parameter. After the 12-week double-blind phase of the study, there was an optional, open-label safety extension study for an additional six months. This report presents the results of the extension study.
Method

Study design
ARTH01 was a phase 2 randomised placebo-controlled double-blind study with an optional open-label six-month extension (Australia and New Zealand Clinical Trials Registry: ACTRN12614000259640). The study was conducted at a single center; the Dunedin School of Medicine, University of Otago, Dunedin, New Zealand, and investigated the efficacy and safety of supplementation with ART on pain, stiffness and functional limitations associated with hip and knee OA. The study was conducted according to the principals of Good Clinical Practice, which protects the rights, safety and well-being of trial subjects in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before any study-related procedures. The study received ethical approval from the Health and Disability Ethics Committee New Zealand (14/NTB/11).

At the conclusion of the previously reported double-blind phase of the randomised controlled 12-week study,1 patients who had completed the study were given the option to continue to take ART for an additional six months in an open-label extension study. All patients received one soft gelatin capsule of ART (containing 150 mg of standardised supercritical extract of *Artemisia annua* per capsule) twice-daily, regardless of the dose received during the double-blind phase of the study.

Efficacy and safety evaluation
Safety and efficacy in the open label extension study were assessed at baseline (conclusion of the double-blind phase of the trial) and at three months and six months afterwards. Safety outcomes included safety adverse events (AEs) (classified using the Medical Dictionary for Regulatory Activities [MedDRA] classification), laboratory data and vital signs measurements. Efficacy endpoints included WOMAC® total scores and individual WOMAC® components for pain, stiffness and physical function over the six-month extension study.

Statistical analysis
There was no formal statistical analysis of the open-label extension study and results are presented descriptively.

Results

Patients
The first patient was enrolled into the extension study on 28 August 2014 and the last patient completed on 18 September 2015. Of the 38 patients who completed the double-blind phase of the study,1 34 patients entered the optional extension study. Of these patients during the double-blind phase, 12 patients had taken ART 150 mg BD, nine had taken ART 300 mg BD and 13 had taken placebo. The extent of exposure was therefore between six and nine months. A total of 28 patients completed the extension study. Six patients withdrew: five patients due to AEs and one due to the patient's...
wishes. Mean age was 62 years (range 45 to 75 years). Mean body mass index was 30.2 kg/m$^2$ (range 20.9 to 39.6 kg/m$^2$). Eighteen of 34 patients (52.9%) were male.

**Safety**

AEs are summarised in Table 1. Overall, there were 16 treatment emergent AEs in 12 patients (35.3%). There were four AEs in three patients (8.8%) that were considered possibly related to treatment; all other AEs were considered unlikely related or unrelated to treatment. The AEs considered possibly related to treatment were stomach pain and flatulence (reported in the same patient), constipation and diarrhoea.

There was one serious AE (SAE) during the study (ovarian cancer), which was considered unrelated to treatment. There were AEs in five patients that lead to withdrawal during the study. Two of these AEs that led to withdrawal were ovarian cancer (considered unrelated to treatment) and elevated liver enzymes (considered unlikely related to treatment). Three patients withdrew due to AEs that were considered possibly related to treatment: stomach pain and flatulence (reported in the same patient), constipation and diarrhoea.

In general, clinical laboratory parameters were within normal limits with isolated results out of normal range. There were no laboratory changes that were considered clinically significant.

**Efficacy**

Table 2 summarises change in mean WOMAC$^\circledast$ total scores and the individual WOMAC$^\circledast$ components for pain, stiffness and physical function. During the six-month extension study, the reduction in WOMAC$^\circledast$ efficacy parameters observed in the double-blind phase of the study$^1$ appeared to be maintained with WOMAC$^\circledast$ total score and individual component mean scores remaining considerably below those of the baseline values of the double-blind study. Mean (standard deviation) WOMAC$^\circledast$ total score was 41.1 (15.8) at the double-blind baseline, 33.0 (18.4) at the extension study baseline, 33.8 (20.8) at 24 weeks, 31.1 (20.3) at 36 weeks (Figure 1).

**Figure 1:** Mean WOMAC$^\circledast$ total scores (± standard deviation) during extension study.

### Table 2: Changes in mean (SD) efficacy parameters.

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<tr>
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<th>Mean WOMAC$^\circledast$ parameter score</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Baseline double-blind study</td>
<td>41.1 (15.8)</td>
</tr>
<tr>
<td>Baseline extension study</td>
<td>33.0 (18.4)</td>
</tr>
<tr>
<td>Week 24</td>
<td>33.8 (20.8)</td>
</tr>
<tr>
<td>Week 36</td>
<td>31.1 (20.3)</td>
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N=34. SD, standard deviation; WOMAC$^\circledast$, Western Ontario and McMaster Universities Osteoarthritis Index.
Discussion

ART appeared to be safe and well tolerated by patients with OA continuing treatment over six months. Three of 34 patients (8.8%) reported AEs (all gastrointestinal) that were considered possibly related to treatment. One patient developed abnormal liver function tests. It was not possible to exclude this as being related to ART, but since none of the other participants in the study developed any liver test abnormalities it was considered unlikely to be ART related.

Supplementation with ART (one capsule of the dietary supplement twice-daily) showed benefits in patients with hip or knee OA over the six-month extension study. There was no formal statistical analysis conducted in this open-label extension phase of the study. There were, however, improvements from the double-blind baseline in mean scores for WOMAC® total and individual WOMAC® components, which appeared to persist throughout the six-month study.

Pain is often poorly managed in patients with OA and therefore there is an urgent need to identify new compounds with anti-inflammatory and analgesic properties, given that current conventional therapies are associated with significant adverse effects.3,4

Artemisia annua, known as qinghao, has been used in Chinese traditional medicine for more than 2,000 years, and traditional medicinal uses include treatment for malaria, fever, hemorrhoids and as an anti-inflammatory.5 Artemisia annua plants contain approximately 600 secondary metabolites including artemisinin, which is unique to this genus.5,6 Artemisinin-based therapy is one of the most effective agents for the prevention and treatment of malaria6–8 and has been used to treat millions of people worldwide.6,10 Other antimalarial drugs, especially quinine derivatives, are standard therapies for the treatment for rheumatoid arthritis where they appear to have both disease-modifying and anti-inflammatory effects.11

Several studies in animal models have demonstrated anti-inflammatory and immunosuppressive activity in extracts from Artemisia annua.12–14 It appears likely that the activity of Artemisia annua is not solely due to artemisinin and that other compounds within the plant may enhance bioavailability and/or bioactivity.15–17

Minimum clinically important differences (MCIDs) for the WOMAC questionnaire have been calculated and range from 0.67–0.75 for improvement (both total and subscale scores).18 In one study of over 1,800 patients, the Multicenter Osteoarthritis Study (MOST),19 several definitions of MCID were used to calculate the frequency of clinically important improvement based on the WOMAC physical function subscale. These included the MCID26% and MCID17% (26% and 17% improvement from baseline, respectively). It is important to remember that MCID values need to be interpreted with caution since a wide range of different methodologies have been used to calculate them (including use of subscale components as noted above) so any value should not be seen as an absolute threshold. In the current study, the WOMAC physical function subscale improved by 23% from the double-blind baseline to end point, which achieves MCID17% but not MCID26%. This demonstrates a clinically significant improvement in physical function over the course of the follow-up period.

In summary, ART appears to be a safe and effective therapy with a sustained efficacy and clinically relevant improvements in function over a six-month period. As such it shows promise as a potential alternative to current pharmacotherapies used to manage OA symptoms. The results of this extension study are encouraging, and further investigation is warranted to investigate ART as a treatment for OA and as an anti-inflammatory/analgesic.
Competing interests:
The study was funded by Promisia Ltd, the manufacturer of Arthrem®. Sheena Hunt is an employee of Promisia Ltd.

Sheena Hunt provided assistance in the design. The interpretation of data and writing of the manuscript was performed by Dr Stebbings. All authors had input into the final manuscript.

The final decision to publish lay solely with Dr Stebbings.

Simon Stebbings has no financial interests or other conflicts of interest in association with Promisia Ltd, including stock ownership, honoraria, paid expert testimony or personal relationships which may inappropriately influence the conduct of the trial.

There are no conflicts of interest for Debra McNamara.

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