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Original experimental

A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids

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ABSTRACT

Objective: Patients with osteoarthritis (OA) pain often have insufficient pain relief from non-opioid analgesics. The aim of this trial was to study efficacy and tolerability of a low dose 7-day buprenorphine transdermal delivery system, added to a NSAID or coxib regimen, in opioid-naïve patients with moderate to severe OA pain.
Methods: A 6 months randomised, double-blind, parallel-group study at 19 centres in Denmark, Finland, Norway, and Sweden, in which *OA patients (>40 years)* with at least moderate radiographic OA changes and at least moderate pain in a hip and/or knee while on a NSAID or a coxib were randomised to a 7-day buprenorphine patch ($n = 100$) or an identical placebo patch ($n = 99$). The initial patch delivered buprenorphine 5 μg/h. This was titrated to 10 or 20 μg/h, as needed. Rescue analgesic was paracetamol 0.5–4 g daily. Statistical analysis of outcome data was mainly with a general linear model, with treatment as factor, the primary joint of osteoarthritis, baseline scores, and season as covariates.
Results: Most patients had OA-radiographic grade II (moderate) or grade III (severe), only 8 in each group had very severe OA (grade IV). The median buprenorphine dose was 10 μg/h. 31 buprenorphine-treated patients and 2 placebo-treated patients withdrew because of side effects. Lack of effect caused 12 placebo-treated and 7 buprenorphine-treated patients to withdraw. The differences in effects between treatments: Daytime pain on movement, recorded every evening on a 0–10 numeric rating scale decreased significantly more ($P = 0.029$) in the buprenorphine group. Patients' Global Impression of Change at the end of the double blind period was significantly improved in the buprenorphine group ($P = 0.017$). The chosen primary effect outcome measure, the Western Ontario and McMaster Universities (WOMAC) OA Index for Pain ($P = 0.061$), and secondary outcome measures, the WOMAC OA score for functional abilities ($P = 0.055$), and the WOMAC total score ($P = 0.059$) indicated more effects from buprenorphine than placebo, but these differences were not statistically significant. In a post-hoc, subgroup analysis with the 16 patients with radiographic grad IV (very severe) excluded, WOMAC OA Index for Pain was significantly ($P = 0.039$) reduced by buprenorphine, compared with placebo. WOMAC OA score for stiffness and the amount of rescue medication taken did not differ. Sleep disturbance, quality of sleep, and quality of life improved in both groups. *Side effects*: Typical opioid side effects caused withdrawal at a median of 11 days before completing the 168 days double blind trial in 1/3 of the buprenorphine group. Mostly mild local skin reactions occurred equally often (1/3) in both groups.
Conclusions: Although the 24 hours WOMAC OsteoArthritis Index of pain was not statistically significantly superior to placebo, day-time movement-related pain and patients' global impression of improvement at the end of the 6-months double blind treatment period were significantly better in patients treated with buprenorphine compared with placebo. Opioid side effects caused 1/3 of the buprenorphine-patients to withdraw before the end of the 6-months double blind study period.
Implications: A low dose 7-days buprenorphine patch at 5–20 μg/h is a possible means of pain relief in about 2/3 of elderly osteoarthritis patients, in whom pain is opioid-sensitive, surgery is not possible, NSAIDs and coxibs are not recommended, and paracetamol in tolerable doses is not effective enough. Vigilant focus on and management of opioid side effects are essential.

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1. Introduction

The World Health Organisation (WHO) estimates that almost 10% of men and 20% of women over the age of 60 have symptomatic osteoarthritis (OA), 80% of those with osteoarthritis will have limitations in movement, and 25% cannot perform their activities of daily life [1]. OA is already one of the ten most disabling diseases in developed countries [1]. Pain is the most burdensome symptom, often difficult to relieve because it is aggravated by movements, especially of the weight bearing hip and knee joints. Paracetamol (acetaminophen), traditional Non-Steroidal-Anti-Inflammatory Drugs (NSAIDs), which are COX-1 and COX-2 inhibitors, and COX-2 specific inhibitors (coxibs) may relieve pain of moderate severity. Paracetamol has few adverse effects in therapeutic doses, but NSAIDs and coxibs have many potentially serious side effects, especially in elderly patients [2]. NSAIDs cause ulcers and bleeding in the gastrointestinal tract, kidney dysfunctions, increased blood pressure and adverse cardiovascular events [2]. Coxibs have less ulcerogenic effects, but they impede healing of gastric ulcers, elevate blood pressure, cause oedema, aggravate congestive heart failure, and decrease kidney functions [2]. In the 2008 updated European guidelines on primary care management of OA pain, NSAIDs and coxibs are only recommended for short term treatment of inflammatory flare-ups of joint pain [3]. The American Geriatric Society 2009 guidelines on management of pain in elderly patients state that "NSAIDs should be considered rarely, and with extreme caution, in highly selected individuals" [2]. This is in sharp contrast to their 2002 guidelines [2] and The American College of Rheumatology guidelines from 2000 [4]. The 2008 and 2009 guidelines now recommend weak opioids or low doses of strong opioids when paracetamol, with or without topical NSAIDs, does not relieve pain sufficiently [2,3]. However, whereas a number of short term randomized placebo-controlled studies have documented analgesic effects in musculoskeletal pain, adverse effects are common, and about 50% discontinue opioid treatment because of adverse effects and/or lack of long term analgesic effects [5,6]. Evaluation of long term effects and safety of opioids are based on weak evidence from open label, post market monitoring, and epidemiological data: Meta-analyses of available literature at the time this study was planned [5] had repeatedly demonstrated a lack of long-term controlled clinical studies, most studies being of short duration, some only 3 days and only one lasting 16 weeks [5]. Even the most recent 2010 Cochrane review [6] found only one placebo controlled RCT lasting 4 months [6,7]. They found no RCT lasting more than 4 months, although 26 reports on *uncontrolled* series lasting at least 6 months were found [6].

A low-dose 7-days buprenorphine patch was introduced in the Nordic countries about 5 years ago and appeared to be well suited for long term, low-dose potent opioid treatment of elderly patients with ongoing pain. At that time no long-term controlled evaluation of this patch had been done.

Therefore, the present 6 months, randomised, double-blind, placebo-controlled study was undertaken to evaluate long-term opioid treatment of patients with chronic OA pain, comparing efficacy and safety of the 7-day Buprenorphine Transdermal Delivery System (Norspan® in the Nordic countries and BuTrans® in the UK) with a placebo patch.

2. Patients and methods

This randomised, double-blind, placebo-controlled, parallel-group study was conducted at 19 investigator centres in Denmark, Finland, Norway, and Sweden (Fig. 1).

2.1. Study medication

Buprenorphine is a semi-synthetic opioid, a derivative of the opium alkaloid thebaine. Buprenorphine has been in regular clinical use for three decades, administered as sublingual tablets or as injections for acute or chronic pain. Pharmacodynamic and pharmacokinetic properties of buprenorphine have recently been thoroughly updated and documented in a review by Kress [8]. The longer half-life of buprenorphine and its high affinity to the μ-receptor, make it longer lasting and 25 to 100 times more efficacious (per mg) as an analgesic than morphine [8]. Buprenorphine

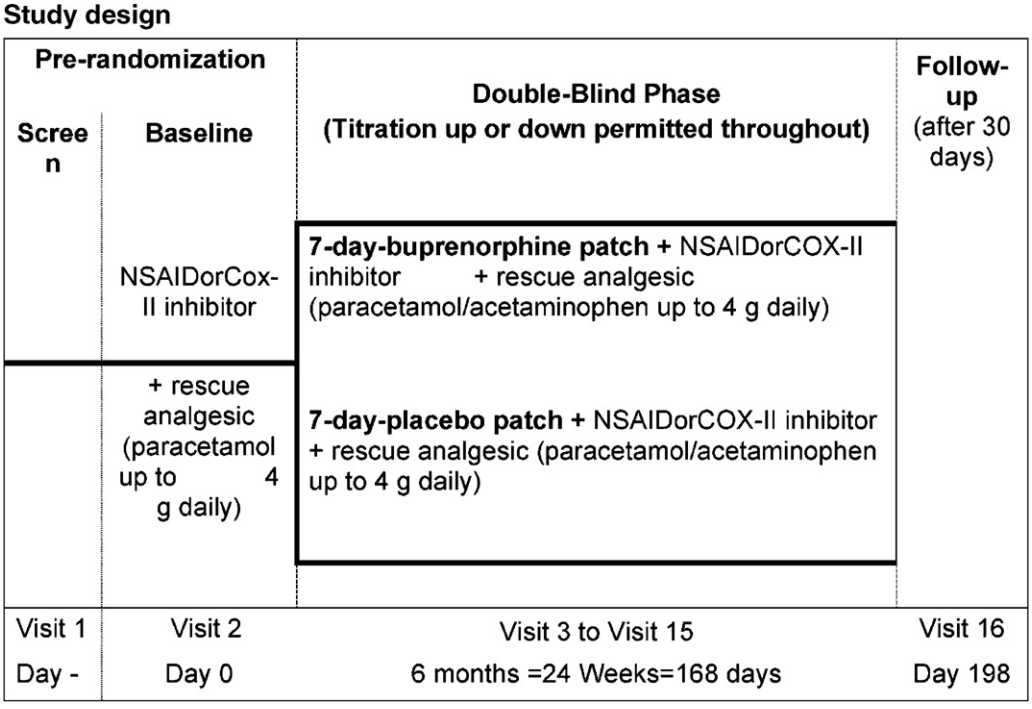


Fig. 1. Diagram of study design and time-line.

is an antagonist at the κ-opioid and the δ-opioid receptors and therefore lacks the psychotomimetic effects and dysphoria associated with agonists of these opioid receptors, especially the κ-opioid receptor agonists [8]. Noteworthy is that buprenorphine now is convincingly shown not to have an analgesic ceiling effect and it is not an antagonist to other μ-agonists, but rather has supra-additive analgesic effects when administered with pure μ-agonists, such as morphine or oxycodone [8]. There is a ceiling phenomenon on the respiratory effect of buprenorphine and it appears to cause less gastrointestinal dysfunction than morphine in equianalgesic doses [8].

Buprenorphine is highly lipophilic and therefore suitable for transdermal administration. The buprenorphine transdermal delivery system studied in this trial is designed for continuous 7 days wear at three strengths, giving a slow onset and slow offset with about 6 days of stable delivery of 5 μg, 10 μg, or 20 μg buprenorphine per hour. With the most recent morphine equivalent estimates of 25-100 [8], the 10 μg/h-patch delivers buprenorphine approximately equal to a morphine dose of 0.25-1.0 mg/h, or 6-24 mg per 24 hours.

Following removal of the patch, concentrations decrease to about one-half in 12 hours, and then decline more gradually with an apparent half-life of about 26 hours. These pharmacokinetics should minimise some of the adverse effects typical of fast onset, fast offset delivery of potent opioids. It allows a practical means of administering the drug to patients who may be unable to take medication orally and to elderly patients with cognitive dysfunction or impaired memory.

Purdue Pharma L.P. of USA has developed this buprenorphine transdermal system, registered as Norspan® in the Nordic countries and BuTrans® in the UK. Steady-state plasma concentrations are reached by day 3 of exposure to Norspan® / BuTrans®. No accumulation of buprenorphine plasma concentrations have been observed in subjects exposed to Norspan® / BuTrans® for over 60 days.

2.2. Patients: recruitment, inclusion and exclusion criteria

Patients with osteoarthritis pain were recruited to this randomised, double-blind, placebo-controlled, parallel-group, multicentre study at the 19 investigator centres in Denmark, Finland, Norway, and Sweden. Patients were recruited mostly from pain clinics and rheumatology clinics and by newspaper advertisements.

2.2.1. Inclusion criteria

Men and women over the age of 40 were included if

- they had a clinical diagnosis of osteoarthritis of the hip and/or knee
- fulfilled the American College of Rheumatology (ACR) Criteria for osteoarthritis [4],
- and had experienced pain from the relevant joint for at least one year prior to enrolment
- they had radiographic evidence of osteoarthritis of the hip and/or knee, as defined by Grades II to IV of the Kellgren and Lawrence scale (Table 1), evaluating the extent of narrowing of joint space, presence of osteophytes, and possible deformity of bone ends [9]
- were taking NSAIDs or coxibs for their osteoarthritis pain for at least one month prior to the Screening Visit (visit 1), at a stable frequency and dose, and at least half the maximum allowed daily dose which gives an anti-inflammatory effect (Table 2). *Note that* this study was planned before the American Geriatric Society's 2009 [2] and European 2008 updated guidelines on OA treatment [3], in which NSAIDs and coxibs are now to be used only rarely for short periods to treat flare-ups of pain. The AGS's 2002 guidelines in fact recommended NSAIDs as the basic pharmacological treatment of OA-pain [2].

Table 1
Osteoarthritis Radiographic Grading Scale (after Kellgren & Lawrence (9)).

Knee joint (Gades 0-IV in radiogram taken in standing position)	
0	Normal
I	Doubtful narrowing of joint space and possible osteophytic lipping.
II	Definite osteophytes and possible narrowing of joint space.
III	Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.
IV	Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.
Hip joint (Grades 0-IV in radiogram taken in supine position):	
0	Normal
I	Possible narrowing of joint space medially and possible osteophytes around femoral head.
II	Definite narrowing of joint space inferiorly, definite osteophytes and slight sclerosis.
III	Marked narrowing of joint space, slight osteophytes, some sclerosis and cyst formation and deformity of femoral head and acetabulum.
IV	Gross loss of joint space with sclerosis and cysts, marked deformity of femoral head and acetabulum and large osteophytes.

For inclusion in the trial, patients were required to have radiographic evidence of Grade II - IV osteoarthritis of the hip or knee.

- they continued to experience at least moderate pain when walking on a flat surface, in spite of treatment with NSAIDs or coxibs,
- they were willing to continue their treatment with NSAID or coxib, at a stable frequency and dose, until the end of the double-blind phase,
- those who had been using *intermittently* low-potent opioids (e.g. tramadol, low dose codeine) were willing to discontinue this regimen from the screening visit until the completion or discontinuation visit and take paracetamol tablets provided by the Sponsor as intermittent analgesic rescue.
- those who were receiving transcutaneous nerve stimulation (TENS) or biofeedback prior to study entry were willing to discontinue this therapy for the duration of the study.

2.2.2. Exclusion criteria

Patients were excluded if

- they had been treated with strong opioid analgesics (e.g. morphine, oxycodone, methadone, fentanyl-patch),

Table 2
Examples of daily regimens of NSAID or coxibs required for inclusion into the trial.

Ibuprofen:	1 200 mg per day
Naproxen:	500 mg per day
Diclofenac:	75 mg per day
Piroxicam:	10 mg per day
Ketoprofen:	100 mg per day
Etodolac:	400 mg per day
Meloxicam:	7.5 mg per day
Celecoxib:	200 mg per day
Etoricoxib:	60 mg per day
Valdecoxib:	10 mg per day

These are half the maximum daily allowed doses (which give anti-inflammatory effects).

- were treated regularly with weak opioid analgesics such as tramadol, or codeine, for longer than three weeks prior to the screening visit
- if any intermittent, short-term, treatment with weak opioids could not be discontinued for the duration of the study
- if they had a history of other chronic condition(s) for which they required frequent analgesic therapy (e.g., headaches, migraine, gout)
- were scheduled for any major surgery that would fall within the screening phase or the double-blind phase of the study
- if transcutaneous nerve stimulation (TENS) or biofeedback prior to enrolment could not be discontinued for the duration of the study
- if the investigator deemed that the patient had any contraindication to treatment with opioid medication, such as history of alcohol or substance abuse
- if the patient had any other clinically significant disease or any reduced organ function
- if the patient was using antidepressants, antiepileptic drugs, steroids, hypnotics (that may increase respiratory depression of buprenorphine)
- if the patient, or any close relatives, had long QT-syndrome, were on anti-arrhythmic medication (Class IA or Class III), or had any unstable or symptomatic cardiac abnormality.

2.3. Study design

This was a 6 months (24 weeks; 168 days), randomised, double-blind, placebo-controlled, parallel-group, multicentre study of the effects on osteoarthritis pain, functions, quality of sleep, and aspects of health-related quality of life with low doses transdermal buprenorphine patch or placebo patch, that was added to the patients' NSAID or coxib regimen (Table 2; Fig. 1).

The trial consisted of two phases: the screening phase and the double-blind phase (Fig. 1). The study comprised up to 16 visits, where six visits could be carried out by telephone. The screening visit (visit 1) was conducted 5 to 9 days prior to the baseline visit (visit 2). In the double-blind phase, subjects were randomly allocated to either the buprenorphine or the placebo patch group in a 1:1 ratio. This phase of the study lasted 168 days during which the assessment visits were conducted at weekly intervals for the first 2 weeks (visits 3 and 4) and thereafter at biweekly visits, or by telephone contacts until visit 15. The safety follow up contact (visit 16), in the form of a telephone interview, took place 30 days following either discontinuation of the patient's participation in the trial, or following completion of the study.

The enrolled patients began the study on the lowest dose of the buprenorphine, 5 μg/h, or placebo patch, whilst maintaining their NSAID or coxib analgesic regimen at a stable frequency and dose. Titration of dose of the study medication by the investigator was permitted for the entire duration of the double-blind phase, taking place in a stepwise fashion. Up-titration up to a maximum dose of 20 μg /h could be carried out only after a minimum of three days treatment of any given dose of buprenorphine patch or placebo patch.

Rescue analgesic was provided as paracetamol (acetaminophen) tablets 0.5 g for breakthrough osteoarthritis pain until the end of the double-blind phase, up to 4 g allowed daily. Every evening they recorded their *use of rescue analgesic drug*, i.e. number of paracetamol tablets used during that day in the patient's diary. At the same time they recorded their *pain on movement during that day* in patient's diary, using a numeric rating scale (NRS-11- see below).

2.3.1. Ethics

The study was conducted in compliance with the Declaration of Helsinki and its amendments [10], the International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) guidelines [11], and the legal regulations in Denmark, Finland, Norway, and Sweden. The protocol, amendment(s), and written patient information and consent forms were submitted to the appropriate ethics committees in Denmark, Finland, Norway, and Sweden for independent review and approval.

2.4. Screening phase

In the screening phase, the osteoarthritis pain of the patient was characterised, and compliance and tolerance of their current analgesic regimen were confirmed. The screening phase consisted of the screening and baseline visits, taking place approximately one week apart. The criteria for inclusion or exclusion, medical history, concomitant medication, vital signs, demography, and laboratory tests were checked for each patient. Informed consent was obtained, and all subjects agreed to discontinue all intermittent weak opioid and/or non-opioid analgesic therapy other than their NSAID or coxib regimen, and aspirin taken for cardiovascular indications.

2.5. Randomisation

Enrolled patients were randomised to one of the two treatment groups. Randomisation was performed using a validated computer system that automates the random assignment of subjects to randomisation numbers. Treatment allocation was in balanced, randomly permuted blocks, block size was unknown to investigators. The randomisation scheme was reviewed by the Biostatistics and Statistical Programming Department at the Sponsor's site, and locked after approval. All patients, investigators, and study centre and Sponsor personnel were blinded to the medication codes. The randomisation schedule was filed in a secure location in a manner such that blinding was properly maintained throughout the study.

2.6. Double-blind phase

The buprenorphine and placebo transdermal patches were administered in 5, 10, and 20 μg/h doses. They were identical in appearance, packed in a labelled foil pouch, containing coded treatment group identification. The medication codes were not available until the completion of the study and clinical database lock, except in case of emergency. Blinding was not broken during the study.

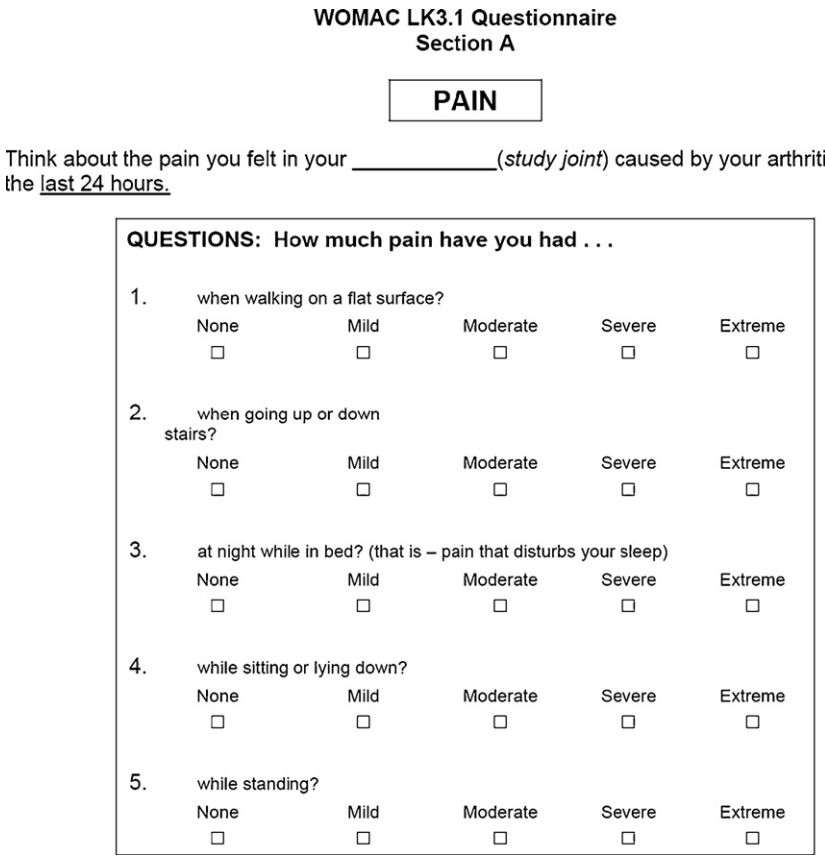
Patients started with buprenorphine 5 μg/h or identically appearing placebo patch, titrating up to the 10 μg/h and 20 μg/h as needed. Reduction of dose was also allowed if adverse effects and analgesic effect indicated this.

2.7. Rescue medication

The rescue medication supplied was paracetamol (acetaminophen) 0.5 g tablets taken every 4-6 hours as needed; with a daily maximum recommended dose of 4 g. Subjects had to abstain from taking paracetamol rescue for at least 24 hours prior to each study visit.

2.8. Assessments of efficacy outcomes

The study focused on one OA pain site, either the hip or the knee, defined as the primary osteoarthritis site, the joint most affected by OA pain, for each participant.



WOMAC LK3.1 Questionnaire
Section A

PAIN

Think about the pain you felt in your _____(*study joint*) caused by your arthritis during the last 24 hours.

QUESTIONS: How much pain have you had . . .

		None	Mild	Moderate	Severe	Extreme
1.	when walking on a flat surface?	☐	☐	☐	☐	☐
2.	when going up or down stairs?	☐	☐	☐	☐	☐
3.	at night while in bed? (that is – pain that disturbs your sleep)	☐	☐	☐	☐	☐
4.	while sitting or lying down?	☐	☐	☐	☐	☐
5.	while standing?	☐	☐	☐	☐	☐

Fig. 2. The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index for pain.

2.8.1. Primary outcome variable

The primary efficacy variable chosen was the change in the pain subscale (Fig. 2) of the WOMAC Osteoarthritis (OA) Index [12,13,14] from baseline (visit 2) to the end of the 6-months double-blind period, or until the patient withdrew from the trial, because of lack of analgesic effect or intolerable side effects. The WOMAC OA Index for Pain is the sum of pain evaluated in five different situations (walking on flat surface, when going up and down stairs, pain that disturbs sleep, sitting or lying down, standing) in five verbal rating (VRS) intensity categories (none, mild, moderate, sever, extreme) (Fig. 2). This WOMAC OA Index for pain was recorded at the baseline screening visit and throughout the double blind phase including visit 15 (Fig. 1).

The patient scored the pain in the morning, thinking back on how the pain had been during the last 24 hours.

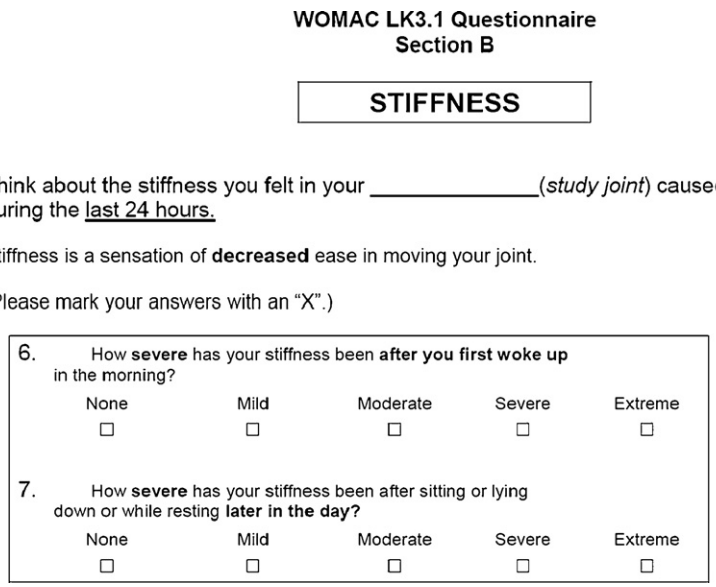
2.8.2. Secondary outcome variables

The secondary efficacy variables were

- the changes from baseline to the end of the double-blind period in
  - ○ the WOMAC Osteoarthritis Index subscale score for Stiffness (Fig. 3),
  - ○ the WOMAC Osteoarthritis Index subscale score for Functional ability (Fig. 4a, b, c),
  - ○ and the WOMAC Osteoarthritis Index Total score, i.e. the sum of the scores for pain, stiffness, and functional abilities.
- The score for pain intensity on movement during the day, recorded every evening from the evening before the randomisation visit (visit 2 = baseline value – Fig. 1) and throughout the double blind treatment phase. A numeric rating scale for pain-intensity (NRS-11) was used, where 0 = "no pain" and 10 = "pain is as bad as you can imagine". Every evening before going to bed, starting during the screening phase, the patients recorded in their diary the NRS-11-answer to the following question: *"Overall, what has your pain on movement been like today?"*
- The daily rescue medication used (number of paracetamol 0.5 g tablets) was recorded in the diary every evening.
- The number of nights woken because of pain (sleep disturbance) and quality of sleep (*very poor, poor, fair, good, or very good*) during the last 7 nights, recorded at each visit.
- *Patient's Global Impression of Change* (PGIC) in their overall status at the end of the 6 months double blind phase, or when the patient withdrew from the study. The PGIC was scored from 1 = 'very much improved" to 7 = 'very much worse', i.e. the lower the scores, the better the patient felt by the end of the study period (Table 3).
- The time that the patients remained in the study, i.e. from randomisation – till completing the double blind phase after 168 days, or when the patient withdrew from the treatment due to lack of effect, intolerable side effects, or any cause, which the patient did not need to explain.

Table 3
Patient's Global Impression of Change.

Since the start of the study, my overall status is (check only one choice):	
1.	very much improved
2.	much improved
3.	minimally improved
4.	no change
5.	minimally worse
6.	much worse
7.	very much worse



WOMAC LK3.1 Questionnaire
Section B

STIFFNESS

Think about the stiffness you felt in your _____(*study joint*) caused by your arthritis during the last 24 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an "X".)

6. How **severe** has your stiffness been **after you first woke up** in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

7. How **severe** has your stiffness been after sitting or lying down or while resting **later in the day?**

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Fig. 3. The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index for stiffness.

2.8.3. Explorative outcome measures

The exploratory efficacy variables were

- European Quality of Life Health Questionnaire (EuroQoL EQ-5D) [15] consisting of five questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, completed at the baseline visit and throughout the double blind phase till the end of the double blind treatment phase, or at a discontinuation visit before day 168 (Fig. 5).
- A general health state Visual Analogue Scale (VAS) from 0 (worst imaginable health state) to 100 (best imaginable health state) was scored at baseline and at the end of the study period (Fig. 6).
- Investigator answered the Abuse/Diversion questions for each patient at the end of the study period (Fig. 7).

2.8.4. Scoring and questionnaires

The patients filled in the WOMAC OA Index for pain, stiffness, functional abilities (with index variables accounting for the previous 24 hours), EuroQoL (describing patient health-related quality of life today), and sleep questionnaires (for the previous 7 days) at baseline and at visits 3, 4, 5, 7, 9, 11, 13, and 15. The NRS-11 score for pain on movement during the day, and the number of sponsor provided rescue paracetamol analgesic tablets (0.5 g) were recorded by the patient every evening before going to bed. At the final visit (completion or discontinuation visit), the PGIC questionnaire was completed and the Investigator answered the Abuse/Diversion questions.

The VAS-scale for the patient's general health state was scored at baseline and at the final visit.

2.9. Safety assessments

For the purposes of safety reporting, the study period was defined as the interval between the time of randomisation and the end of the follow-up period. Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, blood and urine β-hCG pregnancy testing for women of child bearing potential, vital signs, and physical examinations. Blood samples for haematology and blood chemistry were taken at screening and at the final visit, and the investigators reported all abnormal values as adverse events if they were evaluated to be clinically significant. Adverse events were recorded when occurring immediately following study drug administration, up to 7 days after the outcome visit, or up to 30 days after for serious adverse events. All efficacy and safety assessments used are considered standard and were in compliance with both national and international regulatory guidelines.

2.10. Statistical analyses

The *intention to-treat (ITT) population* comprised all subjects enrolled into the study. The *full analysis population* was defined as all subjects who received at least one dose of the study drug and for whom at least one post-dose observation was recorded for the primary efficacy outcome measure. The *safety population* was defined as all subjects who had received at least one dose of treatment and had at least one safety assessment. The *per-protocol (PP) population* was a subset of the full analysis population and consisted of subjects who complied with the protocol, also those who, for any reason, chose to discontinue before the completion of the 168 days double blind phase. This was primarily to be able to assess tolerability in the start up phase of buprenorphine patch treatment, although including those who discontinued already after one or two weeks hardly would give a correct picture of the efficacy of optimally applied transdermal buprenorphine for chronic pain.

The null hypothesis was that there would be no difference between the buprenorphine patch and the placebo patch treatments in the mean change in the WOMAC OA Index for pain score from baseline to the end of the double blind assessment period.

Both the primary and secondary efficacy variables were evaluated using a General Linear Model (GLM) with treatment as a factor and the following as covariates: the primary site of osteoarthritis pain (hip or knee), the season (which month) in which each patient entered the study, the baseline values of the four WOMAC scores and NRS-11 scores for movement-related daytime pain, and these values at the 19 investigator centres.

The primary efficacy variable was analysed in both the ITT and PP populations. All other efficacy variables were analysed in the full ITT analysis population only.

The average daily rescue medication used during the last month of the study was summarised by treatment group for patients in the ITT population.

WOMAC LK3.1 Questionnaire
Section C

(a)

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____(*study joint*) during the last 24 hours. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an "X".)

QUESTION: How much difficulty have you had	None	Mild	Moderate	Severe	Extreme
8. when going down the stairs?	☐	☐	☐	☐	☐
9. when going up the stairs?	☐	☐	☐	☐	☐
10. when getting up from a sitting position?	☐	☐	☐	☐	☐
11. while standing?	☐	☐	☐	☐	☐
12. when bending to the floor?	☐	☐	☐	☐	☐
13. while walking on a flat surface?	☐	☐	☐	☐	☐

WOMAC LK3.1 Questionnaire
Section C (continued)

(b)

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____(*study joint*) during the last 24 hours. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an "X".)

QUESTION: How much difficulty have you had	None	Mild	Moderate	Severe	Extreme
14. getting in or out of a car, or getting on or off a bus?	☐	☐	☐	☐	☐
15. while going shopping?	☐	☐	☐	☐	☐
16. when putting on your socks or panty hose or stockings?	☐	☐	☐	☐	☐
17. when getting out of bed?	☐	☐	☐	☐	☐
18. when taking off your socks or panty hose or stockings?	☐	☐	☐	☐	☐
19. while lying in bed?	☐	☐	☐	☐	☐

Fig. 4. a, b, c The Western Ontario and McMaster Universities (WOMAC) osteoarthritis index for functional abilities.

WOMAC LK3.1 Questionnaire
Section C (continued)

(c) **DIFFICULTY PERFORMING DAILY ACTIVITIES**

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____(*study joint*) during the last 24 hours. By this we mean **your ability to move around and take care of yourself.**

(Please mark your answers with an "X".)

QUESTION: How much difficulty have you had . . . .

		None	Mild	Moderate	Severe	Extreme
20.	when getting in or out of the bathtub?	☐	☐	☐	☐	☐
21.	when sitting?	☐	☐	☐	☐	☐
22.	when getting on or off the toilet?	☐	☐	☐	☐	☐
23.	while doing heavy household chores?	☐	☐	☐	☐	☐
24.	while doing light household chores?	☐	☐	☐	☐	☐

Fig. 4. (*Continued*).

European Quality of Life Health Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care
I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

Fig. 5. European Health-related Quality of Life questionnaire.

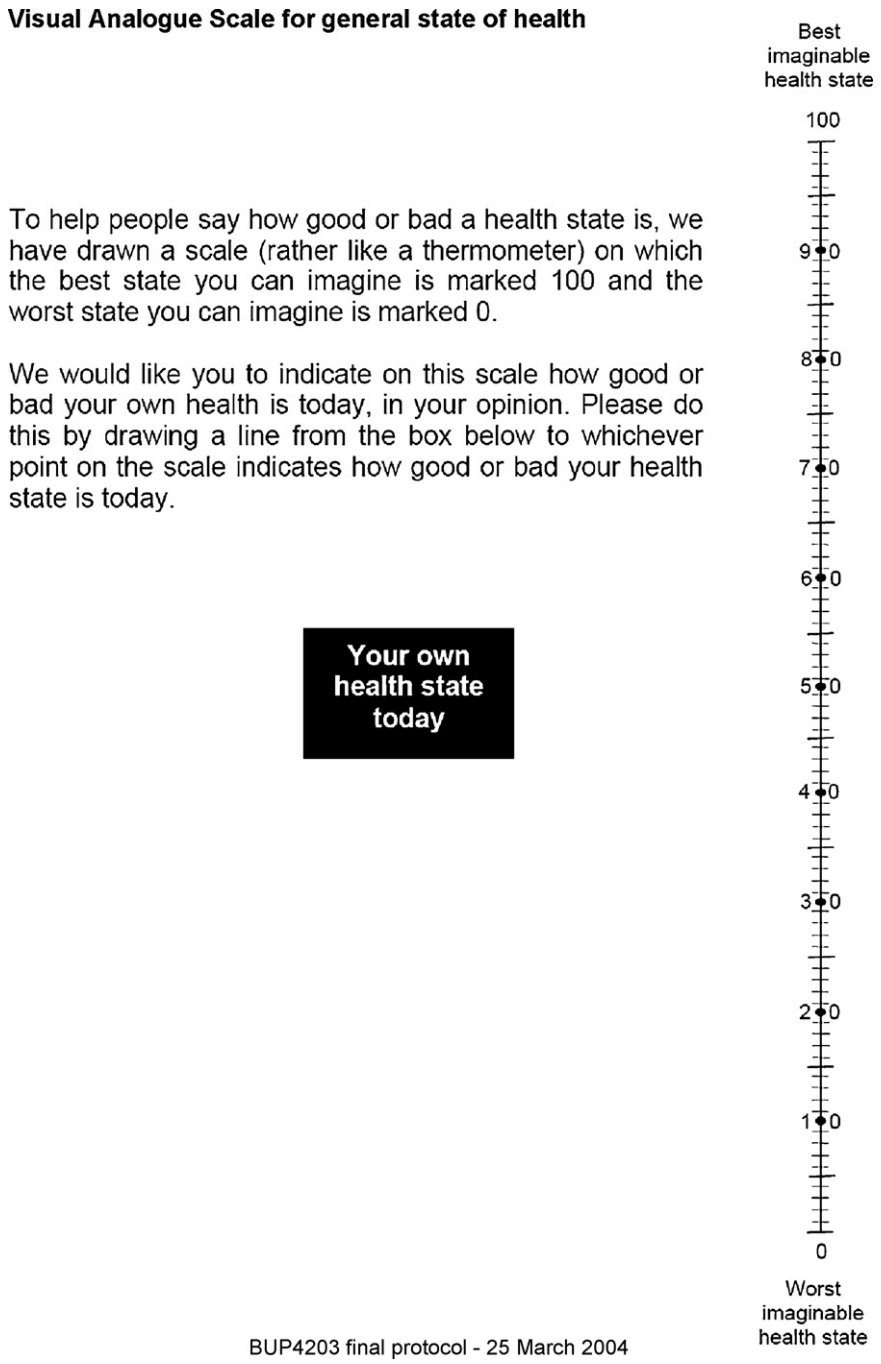


Fig. 6. Visual Analogue Scale for general state of health.

The number of nights woken because of pain and the quality of sleep recorded for the 7-day period prior to each visit, as well as the patient's global impression of change in their (health) state (PGIC) at study completion were summarised as ordered categorical data and analysed using the Wilcoxon two-sample test.

The duration of test drug treatment (168 days or time to withdrawal if the 6 months double blind treatment period was not completed) was analysed using proportional hazards modelling, with treatment, primary site of osteoarthritis pain, gender, adverse effects, and season as factors.

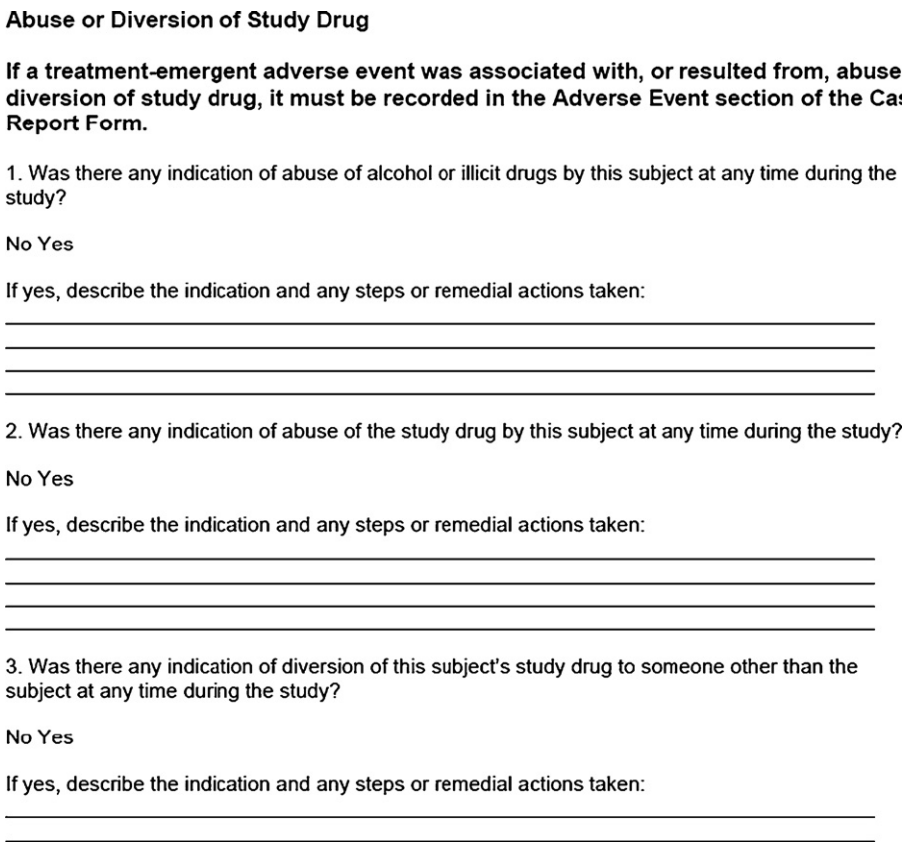
In the exploratory efficacy analysis, each question in the EuroQoL EQ-5-D questionnaire was summarised as categorical data.

The sample size was based on the primary endpoint: with a sample size of 160 subjects, 80 could be allocated to each treatment group, giving the study an 80% power at the 5% significance level in order to detect a 1.0 difference between treatment groups in the WOMAC OA Index of Pain, with a common SD = 2.25, based on a previously conducted trial (BUP.CLIN0001- data with the Sponsor). Assuming an approximate 30% drop out rate, then 224 eligible subjects were required for randomisation with 112 patients assigned to each treatment group. The effect size was estimated to be approximately 0.44 (=1/2.25).

3. Results

3.1. Patient recruitment and characteristics

Patients were recruited mainly from pain clinics and rheumatology clinics at the 19 investigator centres, as well as through newspaper advertising. After the protocol of this study had been



Abuse or Diversion of Study Drug

If a treatment-emergent adverse event was associated with, or resulted from, abuse diversion of study drug, it must be recorded in the Adverse Event section of the Ca Report Form.

1. Was there any indication of abuse of alcohol or illicit drugs by this subject at any time during the study?

No Yes

If yes, describe the indication and any steps or remedial actions taken:

2. Was there any indication of abuse of the study drug by this subject at any time during the study?

No Yes

If yes, describe the indication and any steps or remedial actions taken:

3. Was there any indication of diversion of this subject's study drug to someone other than the subject at any time during the study?

No Yes

If yes, describe the indication and any steps or remedial actions taken:

Fig. 7. Investigators' evaluation of possible drug abuse or drug diversion.

finalized and approved by all appropriate ethical and regulatory authorities, early in 2004, there was an increasing awareness of the adverse effects of NSAIDs and COX-2-specific inhibitors in elderly patients, which eventually resulted in updated guidelines for pharmacological treatment of pain in elderly patients in 2008-2009 [2,3]. These guidelines now advice against prolonged use of NSAIDs; they recommend that NSAIDs should be used only for severe flare-ups of pain, and for brief periods only [2,3]. This created increasing difficulties in recruiting patients who were taking NSAIDs in high enough and stable doses for 6 months, as required by the inclusion criteria of this trial. The original estimates of sample size of 224 were therefore adjusted to 200 (in an Amendment to the protocol), with some loss of statistical power of the study. In the end, the drop out rate was 44%, higher than the estimated dropout rate of 30% used in estimating sample size. This also decreased the power of the trial to avoid Type I errors, i.e. concluding that there is no difference between groups, when in reality there is a difference in effects between the buprenorphine and the placebo patch.

Of recruited and screened patients, 199 patients were included into the double-blind phase of the study from August 2004 to September 2005. Of these, 100 patients were randomised to receive the buprenorphine transdermal patch and 99 the placebo transdermal patch (Fig. 8). There were more female patients in the buprenorphine group (72%) than in the placebo group (65%) (Table 4). There were no differences between the active and placebo groups in age or weight (Table 4), in joints primarily affected by OA, and in radiographic severity grade of the OA-joints (Table 5). The primary site of osteoarthritis pain was in a hip in 73 (36.7%) and in a knee in 126 (63.3%) patients, the majority having radiographic OA severity grade II (moderate) and grade III (severe), only 8 patients in each group had grade IV (very severe) OA (Table 5).

At baseline there were no differences between the overall mean values in the buprenorphine and the placebo groups in WOMAC-OA scores for pain (Fig. 9), for abilities to perform activities of daily functions (Fig. 10), for total score (Fig. 11), and baseline NRS-11 intensity score for daytime pain on movement scored each evening for the preceding daytime (Fig. 12), WOMAC OA-score for stiffness, quality of sleep, quality of life, VAS of state of health, heart rate, and blood pressure (data for the last six variables are not shown).

The number of patients recruited varied from 6 to 15 (mean 11) at each of 18 investigator centres, but one investigator centre recruited only 1 patient. There were statistically highly significant differences between the 19 investigator centres in the patients recruited, as shown by the differences in baseline values of the main outcome variables:

Table 4
Demographic details of participating osteoarthritis patients.

	Treatment	
	7-day buprenorphine patch	Placebo patch
Analysis set		
ITT-intention to treat	100 (50.25%)	99 (49.75%)
Gender		
Male	28 (28.00%)	35 (35.35%)
Female	72 (72.00%)	64 (64.65%)
Ethnic Origin		
Caucasian	100 (100.00%)	99 (100.00%)
Age (years)		
Mean (Std)	62.9 (9.9)	62.9 (9.0)
Median	63.0	63.0
[Min;Max]	[41.0;84.0]	[43.0;82.0]
Weight (Kg)		
Mean (Std)	83.62 (14.19)	85.21 (17.60)
Median	83.15	83.35
[Min;Max]	[54.00;133.00]	[53.00;136.00]

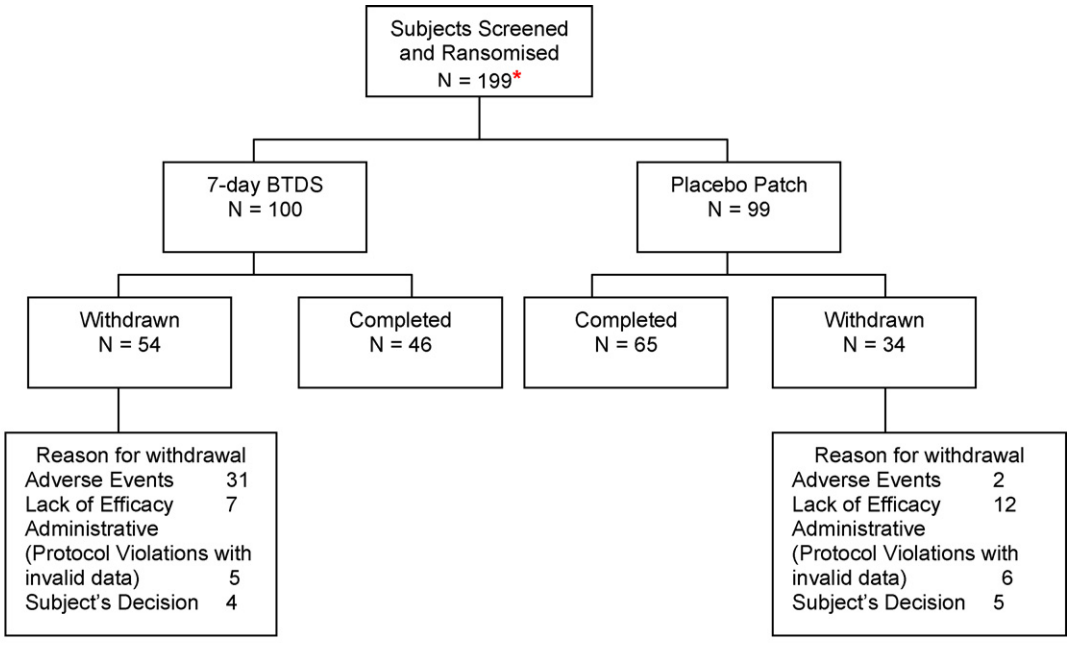


Fig. 8. Patients screened and included, randomised, completers, withdrawals and reasons for early discontinuations.

Table 5
Primary site of pain and radiographic grading of osteoarthritis (OA) at baseline, according to Kellgren and Lawrence, see Table 1 (7).

	Treatment	
	7-day buprenorphine patch	Placebo patch
Analysis set		
ITT population	100 (50.25%)	99 (49.75%)
Site of Pain: Hip		
Radiographic grade II	24 (60.00%)	19 (57.58%)
Radiographic grade III	13 (32.50%)	12 (36.36%)
Radiographic grade IV	3 (7.50%)	2 (6.06%)
Site of Pain: Knee		
Radiographic grade II	29 (48.33%)	31 (46.97%)
Radiographic grade III	26 (43.33%)	29 (43.94%)
Radiographic grade IV	5 (8.33%)	6 (9.09%)

Radiographic grade I = moderate OA; Radiographic grade II = severe OA; Radiographic grade IV = very severe OA.

- WOMAC OA score for pain (mean centre score for pain varied from 8.1 to 14.3; P = 0.0035),
- WOMAC OA score for functional abilities (mean scores from 30.3 to 50.5; P = 0.0003),
- and WOMAC OA total score (centre mean from 41.9 to 69.5; P = 0.0028).

However, the NRS-11scores for movement-related pain during daytime at baseline did not differ significantly between centres (daytime movement-related pain intensity, centre means varied from 3.7 to 6.1 (P = 0.089)).

3.1.1. The intention to treat (ITT) and safety evaluation populations

All of the enrolled patients received at least one dose of study medication, had at least one post-dose observation recorded for the primary outcome measure, and at least one safety assessment. This ITT-population and the evaluation of safety population were identical and consisted of all 199 patients (Table 6).

3.1.2. The per protocol population (PP) and sensitivity population

The PP analysis comprised 175 patients: 85 from the buprenorphine patch and 90 from the placebo patch group (Table 6). A sensitivity population was also included in the analyses for the primary outcome measure, comprising 186 patients from the ITT population, because there were 13 patients (7% of all participants) randomised and given first dose of study drug who should have been excluded at screening because they violated at least one of the inclusion or exclusion criteria. This sensitivity analysis demonstrated that the results were the same for the ITT-analyses with or without these 13 patients (data not shown).

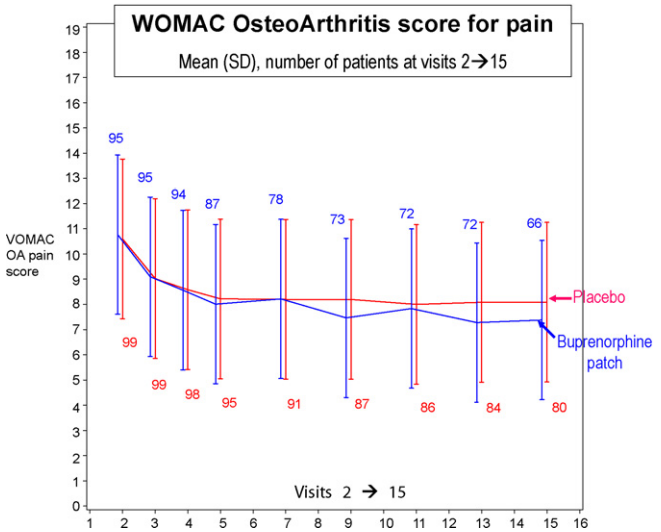


Fig. 9. WOMAC Osteoarthritis Index score for pain from baseline (visit 2) to end of treatment (EOT) at 6 months (visit 15) or earlier withdrawal.

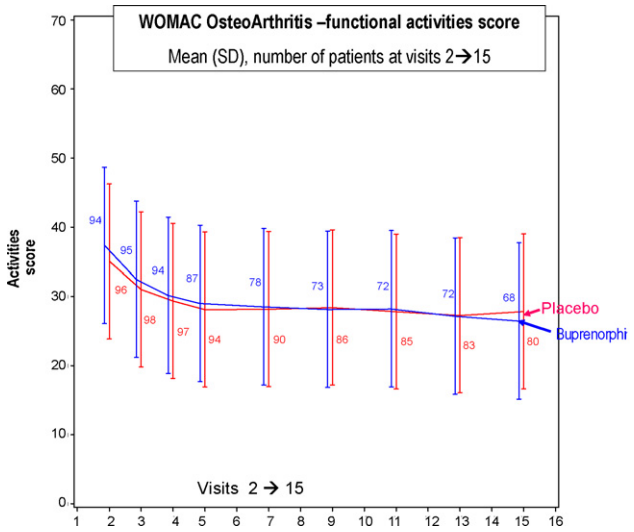


Fig. 10. WOMAC Osteoarthritis Index for abilities to perform activities of daily living from baseline (visit 2) to end of treatment (EOT) at 6 months (visit 15) or earlier withdrawal.

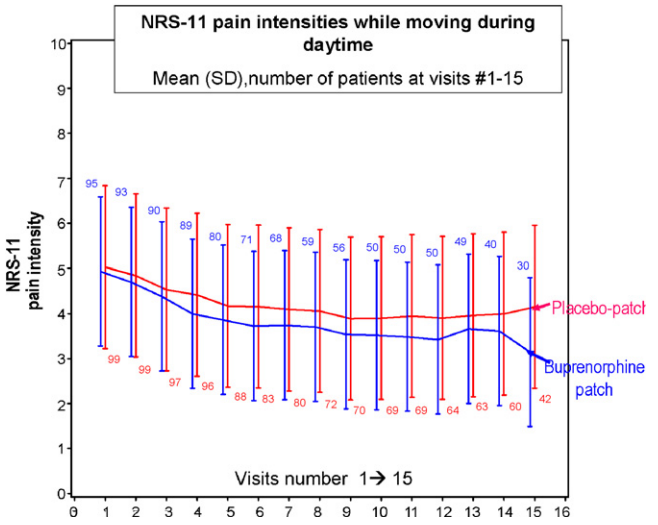


Fig. 12. Movement-related daytime pain score every evening on a NRS-11 pain intensity scale from baseline (visit 2) to end of treatment (EOT) at 6 months (visit 15) or earlier withdrawal.

Table 6
Patients randomized, withdrawals, completers, intention to treat (ITT), per-protocol (PP), and safety analysis set.

	Treatment N (%)		All
	7-day buprenorphine patch	Placebo patch	
Randomized subjects	100 (50.3)	99 (49.7)	199 (100.0)
Exposed subjects	100 (50.3)	99 (49.7)	199 (100.0)
Safety analysis set	100 (50.3)	99 (49.7)	199 (100.0)
Withdrawals	54 (61.4)	34 (38.6)	88 (100.0)
Completers	46 (41.4)	65 (58.6)	111 (100.0)
ITT population	100 (50.3)	99 (49.7)	199 (100.0)
PP population	85 (48.6)	90 (51.4)	175 (100.0)
Screened subjects	100 (50.3)	99 (49.7)	199 (100.0)

3.1.3. Withdrawals before completion of the 6 months double blind treatment phase

As many as 88 patients (Fig. 8; Table 6) discontinued prematurely; adverse events caused 31 to withdraw in the buprenorphine group, 2 in the placebo group. Lack of efficacy caused 7 patients to withdraw in the buprenorphine group, 12 in the placebo group.

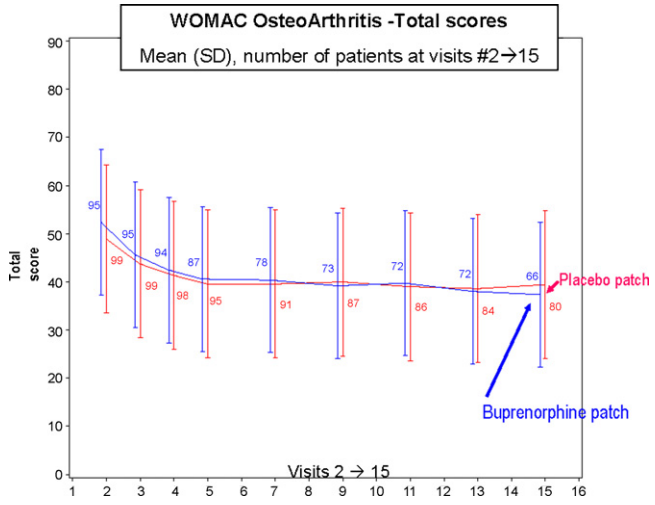


Fig. 11. WOMAC Osteoarthritis Index total score (for pain, activities and stiffness) from baseline (visit 2) to end of treatment (EOT) at 6 months (visit 15) or earlier withdrawal.

Four patients in the buprenorphine group and 5 in the placebo group withdrew without giving a reason. Protocol violations with invalid data occurred in 5 patients in the buprenorphine group and in 6 patients in the placebo group. The Kaplan-Meier survival plot shows similar dropout curves for the two groups (Fig. 13); a slightly higher risk of early withdrawal in the buprenorphine patch group than in the placebo group was not statistically significant. The risk of withdrawal was not significantly associated with gender, adverse events, or baseline WOMAC OA index for pain (data not shown).

Thus, only 46 patients in the buprenorphine group and 65 patients in the placebo group (total 111, 56% of all included patients) completed the entire 168 days double-blind treatment phase of the study.

The duration of patch treatment, i.e. how long the patients remained in the double-blind phase until withdrawing, was an important safety and tolerability outcome measure. Therefore, their premature withdrawal was not by itself a protocol violation, and those with valid data are included in the analyses of the PP-population (Fig. 8; Table 6), although it may give a biased, negative picture of efficacy of the buprenorphine patch when the very early quitters are included (see above).

3.1.4. Titration and dosing

There were no significant differences in mean doses of buprenorphine-active (11.0 (SD 5.7) μg/h) and buprenorphine-placebo (13.6 (SD 6.4) μg /h) or number of dose-titrations per month between the two treatment groups (Table 7).

Table 7
Transdermal dose of buprenorphine (μg per hour) for double-blind period.

	Treatment	
	7-day buprenorphine patch	Placebo Patch
Analysis set		
ITT population	100 (50.25%)	99 (49.75%)
Dose (μg/h)		
Mean (Std)	11.0 (5.7)	13.6 (6.4)
Median	10.0	10.0
[Min;Max]	[5.0; 20.0]	[5.0; 20.0]
Mean number of titrations per month		
Mean (Std)	1.6 (1.4)	1.1 (1.0)
Median	1.1	0.7
[Min;Max]	[0.3; 7.5]	[0.3; 4.6]

Table 8
WOMAC OA Index of Pain: Baseline and end of treatment (EOT), intention to treat population (ITT).

	Treatment		All
Mean (SD)	Active	Placebo	
Hip pain			
N	37	33	70
Baseline	11.0 (2.3)	10.5 (3.2)	10.8 (2.8)
Change	-3.4 (3.7)	-1.7 (4.0)	-2.6 (3.9)
EOT	7.6 (3.9)	8.9 (3.6)	8.2 (3.7)
Knee pain			
N	58	66	124
Baseline	10.6 (2.8)	10.6 (2.6)	10.6 (2.6)
Change	-3.1 (3.9)	-2.6 (3.6)	-2.9 (3.7)
EOT	7.5 (3.5)	8.0 (3.4)	7.8 (3.4)
All			
N	95	99	194
Baseline	10.8 (2.6)	10.6 (2.8)	10.7 (2.7)
Change	-3.2 (3.8)	-2.3 (3.7)	-2.7 (3.8)
EOT	7.5 (3.6)	8.3 (3.5)	7.9 (3.6)
Difference between means of buprenorphine and placebo (EOT)	-0.86	95%CI [-1.76; 0.05]	**P = 0.0608**
Difference between knee and hip(EOT)	-0.09	95%CI [-1.12; 0.94]	P = 0.8652

3.2. Efficacy

The primary efficacy variable was normally distributed both in the ITT-population and the PP-population (data not shown).

3.2.1. Primary efficacy variable

The primary outcome measure, the change in the WOMAC OA score for pain, i.e. the 5-verbal categories of pain-intensities at five different situations (pain while walking on flat surface, pain when walking up or down stairs, pain that disturbs sleep, pain while sitting or lying down, pain while standing (Fig. 2)) from baseline to the end of the 6 months double-blind treatment phase in the ITT population showed a clear tendency for greater reduction in pain in the buprenorphine group (from 10.8 to 7.5 = - 3.2) compared with the placebo group (10.6 to 8.3 = - 2.3) (Fig. 9; Table 8). In the PP population, that comprised completers and withdrawers, 25 of whom withdrew early (Fig. 9), before optimal up-titration of dose, the changes were from baseline 11.0 to EOT 7.5 in the buprenorphine group and from 10.7 to 8.3 in the placebo group. (Table 9). The differences at the end of treatment, however, did not quite reach statistical significance in the ITT-population (treatment difference: -0.86; 95% CI [−1.76; 0.04]; **P = 0.061**), or in the PP population (treatment difference: -0.96; 95% CI [-1.95; 0.03]; **P = 0.058**).

The effects on hip- and knee-pain were similar (Tables 8 and 9).

There was no significant effect of the seasons (month) in which patients entered the study (data not shown).

3.2.2 *Subgroup analysis of primary outcome in patients with moderate and severe radiographic osteoarthritis (OA grade II and III), excluding 16 patients with very severe osteoarthritis (OA grade IV)*

The rational for this subgroup analysis is that those with the most severe osteoarthritis, with OA grade IV – very severe radiographic osteoarthritis, cannot be expected to have much effect of this relatively low dose buprenorphine, equivalent to approx-

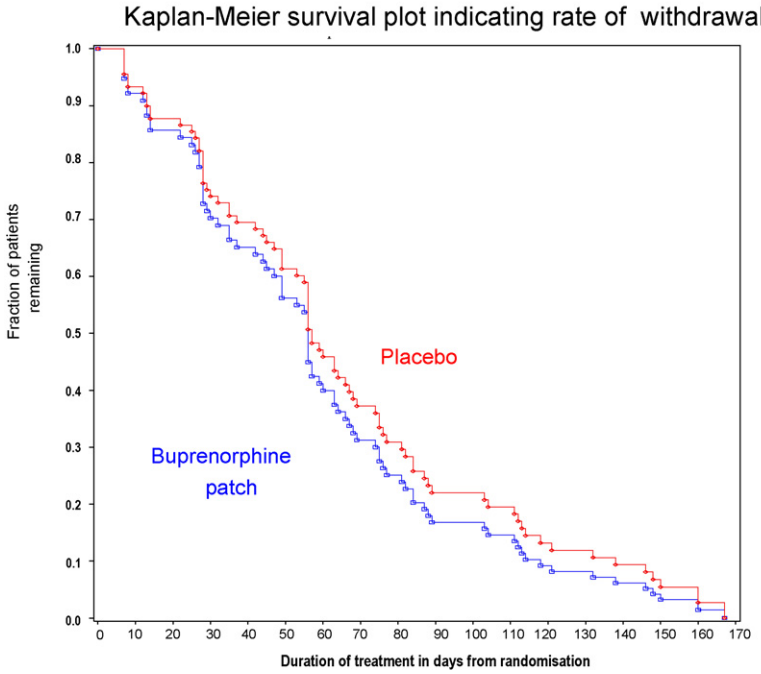


Fig. 13. Kaplan-Meier plot of fraction of patients remaining until 168 days, illustrating withdrawal of 54 patients in the buprenorphine patch group and 34 patients in the placebo patch group before end of double blind treatment phase. Completers are not included in this Kaplan-Meier plot.

Table 9
WOMAC OA Index of Pain, per protocol(PP)-analysis.

Mean (SD)	Treatment		All
	Active	Placebo	
Analysis set			
PP -population	85 (48.57%)	90 (51.43%)	175 (100.00%)
Hip pain			
N	35	31	66
Baseline	11.0 (2.3)	10.6 (3.3)	10.8 (2.8)
Change	-3.3 (3.8)	-1.8 (4.1)	-2.6 (4.0)
EOT	7.7 (3.9)	8.9 (3.6)	8.3 (3.8)
Knee pain			
N	50	59	109
Baseline	10.9 (2.6)	10.7 (2.7)	10.8 (2.7)
Change	-3.5 (4.0)	-2.7 (3.7)	-3.1 (3.8)
EOT	7.4 (3.4)	8.0 (3.6)	7.7 (3.5)
All			
N	85	90	175
Baseline	11.0 (2.5)	10.7 (2.9)	10.8 (2.7)
Change	-3.4 (3.9)	-2.4 (3.9)	-2.9 (3.9)
EOT	7.5 (3.6)	8.3 (3.6)	7.9 (3.6)
Difference between means of buprenorphine and placebo	-0.96	95%CI [-1.95; 0.03]	**P = 0.0582**
Difference between means of knee and hip	0.09	95%CI [-1.05; 1.22]	P = 0.8797

Table 10
Subgroup analysis of WOMAC OA Index of Pain of patients from ITT population of Table 8 with radiographic grad II (moderate) and grade III (severe).

	EOT pain	SD	95%CI	P-value
Active buprenorphine patch (N = 85-8 = 77)	7.21	0.40		
Placebo patch (N = 90-8 = **82**)	8.21	0.38		
Difference between means of buprenorphine and placebo	-1.00		[-1.94; -0.05]	**0.0385**

In each treatment group, 8 patients with grade IV (very severe) osteoarthritis were excluded in this subgroup analysis. Study treatments were assumed to be insufficient for patients with very severe OA.

imately 0.2-1 mg of morphine per hour administered parenterally [8].

Analysis of the primary outcome measure for patients with grade II or grade III osteoarthritis severity (Tables 5 and 10) did show a statistically significant difference between the buprenorphine and the placebo patches (treatment difference: -1.00; 95% CI [-1.94; −0.05]; **P = 0.039**).

3.2.2. Secondary efficacy variables

3.2.2.1. WOMAC OA Index scores for stiffness, functional ability, and the total score. The ITT population analysis, the WOMAC OA Index scores for stiffness (Table 11), functional ability (Table 12; Fig. 10), and the total WOMAC OA Index scores (Table 13; Fig. 11) showed no statistically significant difference between the buprenorphine patch and the placebo patch, or between primary hip or primary knee osteoarthritis, although, except for stiffness, they all tended toward better score-values in the buprenorphine-patch group compared with the placebo-patch group. Thus, the difference in treatments for the WOMAC Index scores for stiffness was -0.18, 95% CI [-0.56; 0.19], *P* = 0.331; for functional abilities -2.90, 95% CI [-5.86; 0.06], **P = 0.055**, and for the WOMAC total scores the difference between treatments by the end of the study period was -3.95 in favour of the buprenorphine patch, with 95% CI = [-8.06; 0.16], **P = 0.0592**. There were no differences in these WOMAC Index scores between the knee and the hip joints.

Table 11
WOMAC OA Index for Stiffness, ITT population.

Mean (SD)	Treatment		All
	Active	Placebo	
Hip pain			
N	37	33	70
Baseline	4.7 (1.1)	4.4 (1.1)	4.6 (1.1)
Change	-1.0 (1.7)	-0.7 (1.4)	-0.9 (1.5)
EOT	3.6 (1.5)	3.7 (1.4)	3.6 (1.4)
Knee pain			
N	58	66	124
Baseline	4.5 (1.5)	4.3 (1.5)	4.4 (1.5)
Change	-1.0 (1.7)	-0.8 (1.6)	-1.0 (1.7)
EOT	3.4 (1.6)	3.4 (1.6)	3.4 (1.6)
All			
N	95	99	194
Baseline	4.6 (1.3)	4.3 (1.4)	4.5 (1.4)
Change	-1.0 (1.7)	-0.8 (1.5)	-0.9 (1.6)
EOT	3.5 (1.5)	3.5 (1.5)	3.5 (1.5)

No statistically significant differences.

3.2.2.2. Movement-related daytime pain, scored every evening on a numeric rating scale for pain intensity (NRS-11). When recording the WOMAC Index scores, the patient need to remember the last 24 hours, trying to decide on a mean value for the preceding 24 hours period. In contrast, the daytime pain on movement was scored every evening on a NRS-11 pain intensity scale. At baseline this pain was 4.8 in the buprenorphine group and 4.9 in the placebo group. The difference between means at EOT was -0.5; 95% CI: [-0.95; -0.05] and statistically significant **P = 0.0292** (Table 14; Fig. 12). This pain on movement was not different for patients with primary osteoarthritis at the hip compared with the knee.

3.2.2.3. Duration of double blind treatment until patients withdrew from the study. Of the 88 patients (44%) who discontinued the study prematurely, 7 (7%) discontinued from the buprenorphine-patch group and 12 (12%) discontinued from the placebo patch group due

Table 12
WOMAC OA Index for Functional Ability, ITT populaiton.

Mean (SD)	Treatment		All
	Active	Placebo	
Site of Pain: Hip			
N	36	31	67
Baseline	38.6 (8.3)	35.6 (10.9)	37.2 (9.7)
Change	-9.9 (12.1)	-4.2 (11.2)	-7.3 (11.9)
EOT	28.9 (13.3)	31.4 (11.3)	30.1 (12.4)
Site of Pain: Knee			
N	58	65	123
Baseline	36.6 (9.3)	34.8 (9.3)	35.7 (9.3)
Change	-10. 0 (11.6)	-7.6 (11.4)	-8.8 (11.5)
EOT	26.5 (11.8)	27.2 (11.6)	26.9 (11.7)
All			
N	94	96	190
Baseline	37.4 (9.0)	35.1 (9.8)	36.2 (9.4)
Change	-10. 0 (11.7)	-6.5 (11.4)	-8.2 (11.7)
EOT	27.5 (12.4)	28.6 (11.7)	28.1 (12.0)
Difference between means of buprenorphine and placebo at EOT	-2.90	95%CI [-5.86; 0.06]	**P = 0.0552**

Table 13
WOMAC OA Total score, ITT population.

Mean (SD)	Treatment		All
	Active	Placebo	
Hip pain			
N	37	33	70
Baseline	53.2 (12.2)	48.4 (16.4)	51.0 (14.4)
Change	-1.0 3 (18.6)	-4.4 (18.1)	-9.0 (18.8)
EOT	40.1 (17.8)	44.0 (15.6)	42.0 (16.8)
Knee pain			
N	58	66	124
Baseline	51.8 (12.3)	49.2 (12.9)	50.4 (12.6)
Change	-1.0 4 (16.1)	-1.0 1 (16.4)	-1.0 2 (16.3)
EOT	37.5 (15.9)	38.7 (16.0)	38.1 (15.9)
All			
N	95	99	194
Baseline	52.4 (12.2)	48.9 (14.1)	50.6 (13.3)
Change	-1.0 4 (17.0)	-8.5 (17.2)	-1.0 1 (17.3)
EOT	38.5 (16.7)	40.4 (16.0)	39.5 (16.3)
Difference between means of buprenorphine and placebo at EOT	-3.95	95%CI [-8.06; 0.16]	**P = 0.0592**

to lack of efficacy. Only 2 patients (2%) in the placebo group, but 31 patients (31%) in the buprenorphine group withdrew because of adverse effects (Fig. 8).

The median duration of treatment was 157 days for the buprenorphine patch group (164 days for subjects primarily suffering with hip pain, 143 days for patients with knee pain) and 167 for the placebo patch group (almost identical for hip pain and knee pain) (Fig. 13). None of the following variables analysed had a significant effect on the treatment duration: primary site of pain, i.e. knee or hip (P = 0.3617); adverse events (*P* = 0.2618); seasons (P = 0.9872); patient gender (P = 0.1207), or the WOMAC score for pain at baseline (P = 0.3928).

Table 14
Movement-related day-time pain recorded every evening (NRS-11). Baseline vs. end of treatment (EOT). ITT-population.

Mean (SD)	Treatment		All
	Active	Placebo	
Hip pain			
N	33	31	64
Baseline	5.0 (1.5)	4.9 (1.7)	5.0 (1.6)
Change	0.6 (1.5)	0.2 (1.3)	0.5 (1.4)
EOT	4.4 (1.9)	4.7 (1.9)	4.5 (1.9)
Knee pain			
N	53	60	113
Baseline	4.7 (1.5)	4.9 (1.4)	4.8 (1.5)
Change	1.1 (2.0)	0.6 (1.6)	0.8 (1.8)
EOT	3.6 (1.7)	4.3 (2.0)	4.0 (1.9)
All			
N	86	91	177
Baseline	4.8 (1.5)	4.9 (1.5)	4.9 (1.5)
Change	0.9 (1.8)	0.5 (1.5)	0.7 (1.7)
EOT	3.9 (1.8)	4.4 (2.0)	4.2 (1.9)
Difference between means of buprenorphine and placebo at EOT	-0.50	95%CI [-0.95; -0.05]	**P = 0.0292**
Difference knee - hip)	0.13	95%CI [-0.39; 0.65]	P = 0.6182

Table 15
Number of nights awoken due to pain during week preceding end of treatment (EOT).

	Mean number nights awoken by pain	P-value
Hip pain		
Buprenorphine patch	2.0270	
Placebo patch	3.0909	0.0949
Knee pain		
Buprenorphine patch	2.1207	
Placebo patch	1.8788	0.3457
All		
Buprenorphine patch	2.0842	
Placebo patch	2.2828	0.8542

3.2.2.4. Average daily rescue medication. There was no difference between the two groups in patients' records of rescue analgesic use: The mean for all patients were 2 tablets of paracetamol 0.5 g per day with a range from 0 to 7 tablets.

3.2.2.5. Sleep disturbance.

3.2.2.5.1. Number of nights awoken due to pain during the previous week. At the end of treatment, for patients in the buprenorphine group with pain located primarily at the hip, the mean number of nights disrupted by pain was 2.0; for those receiving the placebo patch for hip pain 3.1 nights were disrupted by pain in the preceding week (P = 0.09; Table 15). Sleep had been interrupted by knee pain in 2 of 7 nights in both groups.

3.2.2.5.2. Quality of Sleep. There was an overall improvement in quality of sleep for both groups by the end of the study period, but there were no significant differences between the treatment groups (data not shown).

3.2.2.6. Patients' Global Impression of Change (PGIC) in their overall status. Overall, patients felt significantly better with the buprenorphine patches compared with the placebo patches by the end of the double blind treatment period. The mean PGIC score was better (2.9: between minimally improved and much improved) for the buprenorphine than for the placebo group (3.4:between no change and minimally improved) (Tables 3 and 16; Fig. 14), the difference between the two treatments was statistically significant (***P* = 0.0171**).

3.2.3. Exploratory endpoint

3.2.3.1. The EQ-5-D quality of life questionnaire (Fig. 5). This variable showed an overall improvement in all areas at the end of the study in both treatment groups. Collectively, there was an increase in the number of patients reporting no problems, and a decrease in patients who at the end of the trial answered either 'some' or 'severe' problems for the individual questions. A tendency for more improvement was seen in the buprenorphine group compared with the placebo group for the subscale of mobility, but no difference was seen between the groups in the subscales for self care, usual activities, pain and discomfort, anxiety and depression (data not shown).

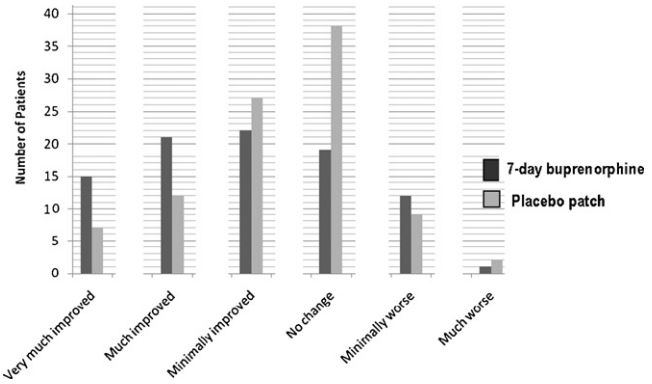


Fig. 14. Patient's Global Impression of Change (PGIC) in overall status at end of treatment.

3.2.3.2. The mean Visual Analogue Scale (VAS) for state of health. At baseline, at the end of the double-blind phase, and the change during the study period, this variable, although improving somewhat with time, did not showed any significant differences between the two groups (data not shown).

3.3. Safety and tolerability

3.3.1. Tolerability

In the buprenorphine group 31 patients withdrew from the study because they could not tolerate the adverse events, 2 patients withdrew from the placebo patch group because of adverse events (Fig. 8).

3.3.2. Adverse events

3.3.2.1. Overall adverse events. Application site reactions occurred in 35 patients in the buprenorphine patch group and 30 patients in the placebo patch group. The majority of the local side reactions were mild to moderate (Table 17).

There were more adverse events in the buprenorphine patch group, especially nausea, vomiting, constipation, dizziness and somnolence (Table 17). There were also more severe adverse events in the buprenorphine patch group than in the placebo patch group (Table 18).

The frequency of nausea and vomiting reported for the time intervals in days from start of double blind treatment are shown in Fig. 15. Clearly, these were more frequent in the beginning of treatment and higher in the buprenorphine group than in the placebo patch group.

Women less than 63 years generally tolerated the buprenorphine patch better than both older women and men irrespective of age (data not shown).

3.3.2.2. Serious adverse events. There were 10 serious adverse events reported: four from the placebo, five from the active treatment group, and one for a patient during screening who withdrew from the study prior to randomisation and start of treatment.

Table 16
Patients general impression of change of status at end of double blind observation period. ITT population.

N (%)	Very much impoved	Much improved	Minimally improved	No change	Minimally worse	Much worse
All						
Placebo	7 (7.4%)	12 (12.6%)	27 (28.4%)	38 (40.0%)	9 (9.5%)	2 (2.1%)
Active	15 (16.7%)	21 (23.3%)	22 (24.4%)	19 (21.1%)	12 (13.3%)	1 (1.1%)
All	22 (11.9%)	33 (17.8%)	49 (26.5%)	57 (30.8%)	21 (11.4%)	3 (1.6%)
Buprenorphine patch mean score					2.9444	
Placebo patch mean score					3.3789	**P = 0.0171**

Table 17
Most common adverse effects (AE).

	Treatment					
	7-day buprenorphine patch			Placebo Patch		
	N	%	E*	N	%	E*
ITT-population	100	100.0		99	100.0	
All repoting AE	92	92.0%	589	73	73.7	258
Gastro-Intestinal disorders	57	57.0	162	25	25.3	38
Abdominal discomfort	1	1.0	1	0	0	0
Constipation	24	24.0	35	5	5.1	5
Nausea	37	37.0	69	10	10.1	11
Vomiting	16	16.0	19	2	2.0	2
General disorders and administration site conditions	61	61.0	177	40	40.4	69
Application site dermatitis	10	10.0	14	5	5.1	8
Application site eczema	9	9.0	16	5	5.1	8
Application site erythema	3	3.0	7	4	4.0	7
Application site irritation	2	2.0	2	1	1.0	1
Application site pruritis	11	11.0	34	15	15.2	17
Nervous System Disorders	45	45.0	97	18	18.2	33
Dizziness	25	25.0	45	9	9.1	11
Headache	7	7.0	9	6	6.1	14
Somnolence	4	4.0	7	0	0	0

* E= Total Number of Adverse Events (AEs).

One serious adverse event was considered possibly drug related, involving a patient reporting vomiting and dehydration during buprenorphine patch treatment.

Another serious adverse event during buprenorphine patch treatment deemed probably related to the study drug, involved abdominal pain, nausea, migraine, and constipation. This subject continued with the study. All 10 patients made complete recovery.

3.3.2.3. Probably significant adverse events. Two clinically significant abnormalities in the buprenorphine group occurred in one patient who had increased levels of blood alkaline phosphatase, deemed possibly drug related; another patient had elevated blood alanine-aminotransferase levels, deemed by the investigator as probably drug related.

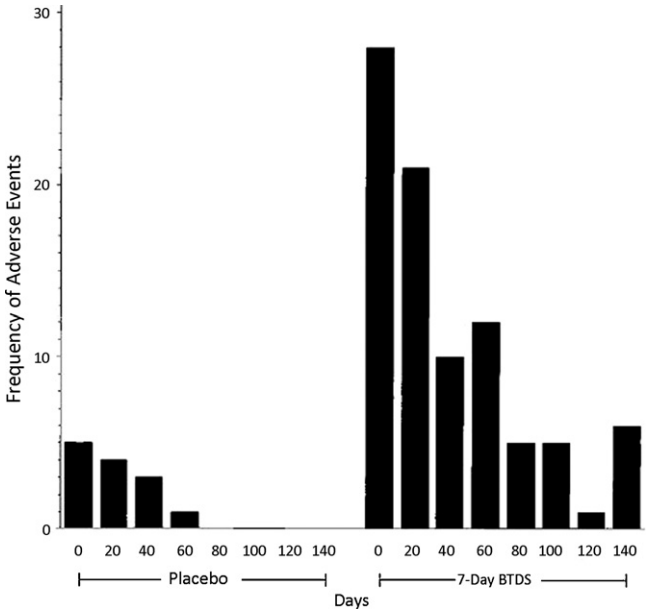


Fig. 15. Frequency of nausea and vomiting reported by patients from start of double blind treatment in the time intervals shown: Days 0-20; 21-40; 41-60; 61-80; 81-100; 101-120; 121-140; 141-168 (end of double blind period).

Table 18
Adverse events by severity. ITT-population.

	Treatment			
	Buprenorphine		Placebo	
	N (%)	E*	N (%)	E*
Reported AEs	172 (100.0%)		111 (100.0%)	
Adverse Events				
Severe	29 (16.9%)	25	11 (9.9%)	17
Moderate	70 (40.7%)	74	42 (37.8%)	37
Mild	73 (42.4%)	69	58 (52.3%)	41

* E = Total Number of Adverse Events (AEs).

3.3.3. Drug abuse and drug diversion (Fig. 7)

The investigators considered that there were no signs or symptoms of drug abuse or drug diversion in any of the patients.

4. Discussion

This is an unusually long double blind randomised trial comparing a potent opioid with placebo for chronic pain. According to the latest Cochrane review of this topic, there is no published placebo-controlled study of opioids for chronic noncancer pain lasting more than a few days to a few weeks [6], and the only up to 4 months placebo controlled study was a study with the very weak opioid tramadol (plus paracetamol) for low back pain [7]. Difficulties maintaining double-blinding for prolonged periods is one reason for the lack of long term RCTs with potent opioids.

In the present study blinding was possible throughout the 6 months because a relatively low dose of buprenorphine (or placebo) was added to an ongoing treatment with NSAIDs or coxibs for moderate to severe pain due to osteoarthritis. The transdermal administration of buprenorphine causes a stable tissue concentration of the opioid for 6-7 days, avoiding effects and adverse effects related to administration of more fast onset and fast offset opioid administrations.

4.1. Prolonged analgesic effect was documented for low dose transdermal buprenorphine added to NSAID or coxib treatment in opioid-naïve osteoarthritis patients

Although the chosen primary outcome variable, the WOMAC OA Index of Pain did not quite reach statistical significance ($P < 0.06$), in a subgroup analysis excluding the 8 patients in each group

who had very severe radiographic OA, the buprenorphine patch was significantly superior to the placebo patch (P < 0.04). The trial confirmed that, in spite of a 30% withdrawal rate before 6 months, the buprenorphine patch at a median dose of 10 μg per hour effectively relieves daytime movement-related pain (P < 0.03). Even more importantly, the patients' overall impression of change in their overall status at the end of the 6 months double blind treatment period, was significantly better in the buprenorphine treated patients than in the patients treated with the placebo-patch (P < 0.02).

The patients were allowed paracetamol *ad libitum* up to 4 g a day. The median consumption of paracetamol as rescue analgesic was 1 g per day and not different between the two groups. Paracetamol has a potent additive analgesic effect with NSAIDs for acute pain [16,17]. Thus, the paracetamol rescue medication may have reduced the difference between a NSAID regimen with buprenorphine patch and placebo patch.

4.2. Effects on functional abilities, quality of sleep, and quality of life: Patient's Global Impression of Change

With better pain relief, it would be reasonable to expect that the osteoarthritis patients would be able to function better in every day life, sleep better and enjoy improved state of health and health related quality of life. With the WOMAC OA index of Functional abilities, evaluating abilities to perform 17 different activities of everyday life, an effect was indicated by the buprenorphine patch (P < 0.06). The patients with primarily hip OA pain were awakened less frequently, although not statistically significantly so (P = 0.09), in the buprenorphine group. Although, less pain may lead to more activity, more pain may be provoked by using weight-bearing OA joints, which again may mean less ability to function for a period. Such variations may become less obvious in the 24 hours-mean scores required by the patients when answering the WOMAC questionnaires (Fig. 4a-c). The movement-related daytime pain evaluated by the patient every evening clearly demonstrated better pain relief from the buprenorphine patch during movement compared with the placebo patch (P < 0.03 – Table 14, Fig. 12).

The subgroup analysis of the ITT-population without the 16 patients who had very severe radiographic OA, also documented a significantly better pain relief (P < 0.04; Tables 5 and 10) with the buprenorphine patch compared with the placebo patch. The rational for doing this subgroup analysis was that patients with very severe OA, if they did have pain relief at all, and then were more active, for sure would have a rebound of their pain intensity, both at rest and during movement.

The measures of quality of sleep and quality of life, as well as general health state improved somewhat in both groups, especially during the first few weeks of the double blind observation period. During almost 7.5 months we had close contact with our trial patients; this is bound to have a significant context sensitive therapeutic effect, an observation that has been made repeatedly in pain trials [18]. This underscores the importance of having a watertight double blind study design [18,19].

Still, the patients' evaluation of their *Global Impression of Change* at the end of the double blind treatment period significantly (P < 0.02) documented that the buprenorphine patch resulted in an improved overall situation for the osteoarthritis patients with pain (between "*minimally improved*" and "*much improved*") compared with the placebo treated patients (mostly between "*no change*" and "*minimally improved*") (Table 16; Fig. 14).

4.3. Safety of the 7- day buprenorphine patch

There were equal numbers patients with serious adverse events in the two treatment groups, 10 in all. In the buprenorphine group two patients suffered serious gastrointestinal adverse events, deemed probably drug related, with nausea, vomiting, dehydration, abdominal pain. One patient continued while one discontinued the trial. Two had possibly significant elevation of liver enzymes, deemed probably related to study drug, however, paracetamol as rescue analgesic (varied from 0 to 3.5 g per day) is a more likely explanation than the buprenorphine [20].

Except for the two clearly opioid-induced gastrointestinal side effects, none of the other serious adverse events seem relevant for the safety of buprenorphine. Buprenorphine has been in clinical use for more than 3 decades without liver damage as a recognized side effect.

4.4. Tolerability of the 7 day buprenorphine patch

Skin reactions to the patch were similar in the two patch groups with about 30% of patients experiencing local irritation-type reactions, mostly of mild severity.

The tolerability of the buprenorphine patch was otherwise good, although more patients discontinued the buprenorphine patch due to side effects before the end of the 6 months double blind period than patients having the placebo-patch. These adverse effects were mostly typical opioid side effects in opioid-naïve patients, such as nausea, vomiting and constipation, less common were dizziness and sedation (Table 17). Such opioid side effects can be reduced by a more gradual increase in buprenorphine dose than was mandated by the study protocol in the present trial.

4.5. Balance between benefits and side effects

Our present study thus confirms a solid clinical observation, that not all patients are satisfied with even low dose opioid treatment of their chronic pain. This is sometimes due to lack of perceived effect on the burden of the pain condition, but more often it is due to bothersome side effects [5]. The gastrointestinal dysfunctions that are almost obligatory for opioid receptor agonists [21], clearly also occur with buprenorphine. While attention to diet and prescription of appropriate laxative medication can mitigate constipation, the upper gastrointestinal side effects (nausea, vomiting, gastro-oesophageal reflux, dyspepsia, abdominal bloating) can be reduced only by reducing the dose or discontinuing the opioid.

An alternative which is now becoming available is to administer a μ-opioid antagonist that has only peripheral effects, such as methylnaltrexone or alvimopan. These antagonists do not cross the blood-brain-barrier [21]. Naloxone, in oral controlled release depot tablets containing oxycodone, will act on the opioid receptors of the intestinal autonomic nervous system, before being transported to the liver where naloxone is almost completely transformed to inactive metabolites, so that only a very small amount of unmetabolized naloxone reaches the systemic circulation and the CNS [21].

4.6. Limitations of the trial

This study confirmed that a multicentre study risks wide variation in characteristics of the included patients, thereby decreasing sensitivity of the trial: There was a significant variation in the baseline values of most of the outcome variables between the 19 investigator centres. Pain-trial-sensitivity is always better if pain-variables, such as pain intensity and reduced function and pain-related quality of life, are appropriately severe and uniform at baseline. This is logical and intuitively obvious: The more pain and pain problems there are to relieve, the better will the trial be able to distinguish between a more potent and a less potent analgesic therapy [18,19]. When pain is only mild or moderate, or baseline pain varies a lot between patients, even morphine will appear to be no more effective than a very weak analgesic, e.g. tramadol [18].

In the present study patients were included if they had at least moderate pain in spite of their ongoing NSAID or coxib regimen. Thus patients in one investigator centres where mean (of 10 patients) baseline pain was only 3.7 on a NRS-11 scale, clearly had patients with pain at randomisation which was low enough to reduce the trial sensitivity of this study [18,19].

This study also confirms the important observation that a straight forward numeric rating scale for pain intensity during movement [22], recorded every evening by the patients, is more sensitive in measuring differences between an active analgesic and placebo than a more elaborate outcome measure, especially when the patient has to remember what a number of variables were like during 24 hours, and in his mind, estimate the mean values for this time period [23]. The various WOMAC OA subscales dependent on the patient's memory and ability to create a 24 hour average of several aspects of their pain condition. Thus, the defined primary outcome in this study, the WOMAC OA Index of pain, where the patient has to remember what the pain was like in 5 different situations during the last 24 hours, was clearly less sensitive than the secondary outcome measure, the daytime-movement-related pain-intensity on a 11-point numeric rating scale from 0 = no pain to 10 = worst pain imaginable. The patients scored their day-time movement related pain every evening, when they were likely to remember well what the day was like.

An aspect of our trial design, which now can be criticized, was the choice of elderly OA-patients taking continuously relatively high doses of NSAIDs or coxibs as a major inclusion criterion. This would not be ethically acceptable only a few years after the study was planned and approved by the appropriate ethical and regulatory control authorities. NSAIDs and coxibes are now not recommended for continuous use in elderly patients in general, and for OA-patients only for very brief periods of episodic flare-up OA-pain [2,3].

It should not be clinical practice to initiate long term opioid treatment for chronic noncancer pain, unless the patient is documented to have a pain condition that responds to opioid analgesics. This was not performed in the present trial, and can be criticised. However, osteoarthritis pain has been considered to be mainly nociceptive type pain, which normally responds to opioid analgesics. We now know that even in osteoarthritis, much of the pain is due to neuropathic type mechanisms [24]. Neuropathic pain does not always respond to even potent opioids [25].

The post-hoc analysis where the patients with very sever OA were excluded, indicated that their pain condition was too severe for the low dose buprenorphine patch to be helpful. Thus, we probably included patients with too little baseline pain and patients with much too severe baseline pain for the analgesic drug we tested to be appropriate analgesic treatment (see paragraph 4.8).

Finally, our study can be criticised for not documenting well enough who and how many of the included patients had, intermittently, been using analgesic tablets containing codeine or tramadol before the study. Thus, an unknown number of our patients may not have been truly opioid-naïve patients. Buprenorphine, especially in the low doses used in the present study, would be expected to have less analgesic effect if the patients in fact had been using codeine or tramadol, even if only intermittently, for prolonged periods before entering the study. The so-called "weak" opioids, codeine and tramadol are well documented to cause development of opioid tolerance. Patients who have been treated with fast onset, codeine-containing analgesics, when prescribed the low-dose buprenorphine patch, mostly continued using their codeine containing tablets alongside the new treatment with buprenorphine patch [26].

A recent review of the properties of buprenorphine emphasizes that this potent, full μ-opioid agonist has additive or supra-additive analgesic effects with other μ-agonists, that buprenorphine differs from other opioids in common use in having a pronounced antihyperalgesic effect, favourable safety profile in elderly patients and those with renal impairment, and its lack of effect on sex hormones and the immune system [27].

4.7. Strong aspects of this study

To the best of our knowledge, and according to the 2010 Cochrane review [6], this 6-months double blind, placebo controlled study is the only one published study lasting as long as half-a-year. It is therefore unique in documenting that the opioid analgesic effect is maintained for at least 6 months. It clearly also documents, that in spite of the low doses of buprenorphine, a third of the patients do not tolerate the gastrointestinal adverse effects, and therefore discontinue the treatment after a few months. A more careful, slow escalation to an effective buprenorphine dose may increase tolerability.

We selected patients carefully for any indication in their history of increased risk of problematic opioid use, and we examined the patients carefully for signs or symptoms of drug abuse or drug diversion after the 6 months study period. None were observed in any of the 100 patients randomized to prolonged buprenorphine treatment.

4.8. What would be an ideal design for a follow-up study of buprenorphine patch 5-35 μg/h for OA-pain

Too low pain intensity causes loss of assay sensitivity. Too high pain intensity causes early withdrawal. Therefore, select patients who, without analgesic treatment, have movement-related pain intensity about 6-8 on a NRS-11scale and most days have 5 or higher pain intensity at rest

- Include only truly opioid-naïve patients (also codeine and tramadol induce opioid tolerance).
- Include only patients who have opioid-sensitive pain, pain that responds to buprenorphine in the dose range to be tested. This will cause an enriched sample, but will give a true picture of efficacy and tolerability of the drug.
- Start with a low dose, and escalate slowly to analgesic effect, or to intolerable side effects occur.
- Prevent, or treat promptly side effect: Laxatives for constipation. Antiemetics for nausea.
- Offer paracetamol **1 g** as rescue analgesic, up to 4 g per day. And monitor liver enzymes.
- Offer an effective treatment for occasional break-through-pain: a fast onset-potent NSAID, if tolerated (e.g. ketorolac).

5. Conclusions

Although the chosen primary outcome variable, the 24 hours WOMAC OsteoArthritis Index of pain did not reach statistical significance, day-time movement-related pain was significantly better relieved by buprenorphine 10 μg per hour, than placebo, as add-on to a continuous high-dose NSAID- or coxib-regimen and paracetamol. The patients' global impression of improvement at the end of the 6-months double blind treatment period was significantly better in patients treated with buprenorphine (between minimally and much improved) than in the patients treated with placebo (between no change and minimally improved). Almost 1/3 of the patients withdrew (median 11 days) before the end of the 6-months double blind period, mostly because of typical opioid side effects.

It is possible that without the ongoing NSAID- or coxib-regimen and paracetamol liberally taken as rescue analgesic, the

buprenorphine pain relieving effect would have been more clearly demonstrated.

6. Implications

A low-dose 7-days buprenorphine patch at about 10 μg/h, approximately equivalent to 6-24 mg morphine per 24 hours, is a practical means of relieving moderate to severe pain in elderly osteoarthritis patients with continuous pain, in whom pain is opioid sensitive, surgery is not possible, NSAIDs and coxibs are not recommended, and paracetamol in tolerable doses is not effective enough. A robust regime for monitoring and managing opioid side effects is mandatory.

Conflict of interest

The authors received no personal remuneration from the sponsors.

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