# Efficacy and Safety of Low-Dose Transdermal Buprenorphine Patches (5, 10, and 20 μg/h) Versus Prolonged-Release Tramadol Tablets (75, 100, 150, and 200 mg) in Patients With Chronic Osteoarthritis Pain: A 12-Week, Randomized, Open-Label, Controlled, Parallel-Group Noninferiority Study

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## ABSTRACT

**Objective:** This study compared the efficacy and safety of low-dose 7-day buprenorphine patches and prolonged-release tramadol tablets in patients with chronic, moderate to severe osteoarthritis (OA) pain of the hip and/or knee.

**Methods:** Eligible patients were adults with a clinical and radiologic diagnosis of OA of the hip and/or knee and moderate to severe pain, as confirmed by a mean Box Scale 11 (BS-11) score ≥4 while using paracetamol 4000 mg/d for pain during the screening week. Patients were randomized in a 1:1 ratio to receive either low-dose 7-day buprenorphine patches (patch strengths of 5, 10, and 20 μg/h, with a maximum dosage of 20 μg/h) or twice-daily prolonged-release tramadol tablets (tablet strengths of 75, 100, 150, and 200 mg, with a maximum dosage of 400 mg/d) over a 12-week open-label treatment period. Supplementary paracetamol was available as rescue medication throughout the study. The primary end point was the difference in BS-11 scores from baseline to the completion of treatment. Noninferiority was assumed if the treatment difference on the BS-11 scale was −1.5 boxes, indicating a clinically meaningful result. Secondary efficacy variables were rescue medication use, sleep disturbance and quality of sleep, and patients' and investigators' global assessments of pain relief. In addition, patient preference was assessed at the completion visit by asking patients whether, given equal pain relief, they would prefer basic treatment for OA pain with a patch applied once weekly or a tablet taken twice daily. Exploratory variables included investigators' assessments of patients' pain, stiffness, and ability to perform daily activities (Western Ontario and McMaster Universities Osteoarthritis Index); patients' quality of life (EuroQol EQ-5D health states index and EuroQol visual analog scale); and abuse and diversion of study drug.

**Results:** One hundred thirty-four patients (69 receiving 7-day buprenorphine patches and 65 receiving tramadol tablets) were randomized and received ≥1 dose of study medication. A respective 98.6% and 100% of the 2 treatment groups were white, with mean (SD) ages of 64.4 (11.1) and 64.2 (9.3) years. Both treatments were associated with a clinically meaningful reduction in pain from baseline to study completion. The least squares mean change from baseline in BS-11 scores in the 7-day buprenorphine patch and tramadol tablet groups was −2.26 (95% CI, −2.76 to −1.76) and −2.09 (95% CI, −2.61 to −1.58). The efficacy of 7-day buprenorphine patches was noninferior to that of prolonged-release tramadol tablets. The incidence of adverse events (AEs) was comparable in the 2 treatment groups: 226 AEs were reported in 61 patients (88.4%) in the 7-day buprenorphine patch group, and 152 AEs were reported in 51 patients (78.5%) in the tramadol group. Ten patients (14.5%) in the 7-day buprenorphine patch group and 19 (29.2%) in the tramadol tablet group withdrew from the study due to AEs. The most common AEs in the 7-day buprenorphine patch group were nausea (30.4%), constipation (18.8%), and dizziness (15.9%); the most

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common AEs in the tramadol tablet group were nausea (24.6%), fatigue (18.5%), and pain (12.3%). Most patients (47/67 [70.1%] in the 7-day buprenorphine patch group and 43/61 [70.5%] in the tramadol tablet group) reported that they would prefer a 7-day patch to a twice-daily tablet for future pain treatment.

**Conclusions:** In these patients with chronic, moderate to severe OA pain of the hip and/or knee, 7-day low-dose buprenorphine patches were an effective and well-tolerated analgesic. The buprenorphine patches were noninferior to prolonged-release tramadol tablets. European Union Drug Regulating Authorities Clinical Trials number: 2006-003233-32. (*Clin Ther.* 2009;31:503–513) © 2009 Excerpta Medica Inc.

**Key words:** transdermal, buprenorphine, knee osteoarthritis, hip osteoarthritis, pain, tramadol.

## INTRODUCTION

Osteoarthritis (OA) is the most prevalent joint disease worldwide. Results of a 2004 telephone survey involving 4839 respondents indicated that just under 1 in 5 European adults had a chronic pain condition for at least 6 months, and that arthritis was the most frequent cause of pain.[1] No curative treatments are available for OA. Its main symptom is pain; therefore, effective analgesia plays a pivotal role in the medical treatment of OA. Swedish guidelines recommend paracetamol for the initial treatment of OA pain.[2] If paracetamol does not provide optimal treatment of pain, the guidelines recommend second-line treatment with a low-potency opioid analgesic (eg, codeine, dextropropoxyphene) or tramadol. The 7-day buprenorphine patches, which are available in low doses, fit the guideline recommendations in this respect.[3–5]

Buprenorphine is a synthetic opioid analgesic with partial μ-opioid–agonist and κ-opioid–antagonist properties.[6–8] It has been marketed in Scandinavia in parenteral (0.3 mg/mL) and sublingual (0.2 and 0.4 mg) forms since the early 1980s, primarily for the management of postoperative pain. Sublingual buprenorphine was approved in Scandinavia in 1999 for the treatment of addiction.[9] In 2005, 7-day buprenorphine patches* (5, 10, and 20 μg/h) were approved in Sweden for the treatment of severe opioid-responsive pain conditions that have not responded adequately to nonopioid analgesics.[10] The 7-day buprenorphine patches have also been approved in Australia, Denmark, Finland, Iceland, Ireland, Israel, New Zealand, Norway, South Korea, and the United Kingdom. They are not currently approved in the United States. Buprenorphine is classified as a narcotic drug in Sweden.[9]

The availability of 7-day buprenorphine patches in 3 low-dose strengths enables titration to achieve optimal pain control[10] and provide continuous delivery of buprenorphine over a 7-day period. Given that appropriate analgesic prescribing can be difficult in elderly patients with OA and that patients may be taking a number of concomitant medications, the buprenorphine patches offer an alternative to the use of oral medication. A patch that provides 7 days' background analgesia may improve patient compliance by reducing the pill burden. Adverse effects that have been reported with the use of 7-day buprenorphine patches are nausea, dizziness, and constipation, all well-known μ-opioid agonist–related effects, and application-site reactions.[10]

Tramadol† is a centrally acting μ-opioid receptor analgesic. It is a nonselective pure agonist at μ-, δ-, and κ-opioid receptors, with a higher affinity for the μ-opioid receptor.[11] The analgesic effect of tramadol is mediated mainly by its metabolite (+) M1 ([+]-o-desmethyltramadol), which has ~300-fold higher affinity for the μ-opioid receptor than does the parent compound.[12] This metabolite is produced by the action of the cytochrome P450 (CYP) 2D6 isozyme. A gene mutation occurring in ~7% to 10% of Northern Europeans renders them unable to metabolize tramadol to its active metabolite; as a result, they may receive little, if any, analgesia from its use.[13–15] CYP2D6 activation may also cause some drug interactions. Studies of tramadol have suggested that administration of the antiarrhythmic agent quinidine, a known CYP2D6 inhibitor, eliminates the analgesic effect of tramadol.[16] Tramadol also has an antidepressant effect due to stimulation of neuronal serotonin release and inhibition of presynaptic reuptake of noradrenalin and serotonin.[17] Tramadol is approved in Sweden for the treatment of chronic pain,[11] although there are few data on its long-term tolerability and efficacy. Reported adverse effects associated with tramadol are dizziness, nausea, sedation, dry mouth, and sweating.[18]

*Trademark: Norspan® (Mundipharma AB, Göteborg, Sweden).

†Trademark: Tiparol® Retard (AstraZeneca AB, Södertälje, Sweden).

Sleep disturbances have also been reported. Tramadol is reported to be associated with a lower prevalence of opioid adverse effects such as constipation.[19] This may be due to its weak affinity for opioid receptors.[20] It has also been reported to have little depressive effect on respiration.[21] However, tramadol has been associated with psychiatric drug reactions (hallucinations and confusion).[22] Since June 2008, tramadol has been classified as a narcotic drug in Sweden because of the risk for abuse and physical and psychological dependence.[23]

The present study was conducted to evaluate the efficacy and safety of low-dose 7-day buprenorphine patches (5, 10, and 20 μg/h) compared with prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic, moderate to severe OA pain of the hip and/or knee.

## PATIENTS AND METHODS

This randomized, open-label, controlled, parallel-group noninferiority study was conducted at 14 sites in Sweden. The study was performed in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and applicable regulatory requirements. The clinical study protocol, patient information sheet, and informed-consent form were approved by the appropriate independent ethics committee. All patients signed the informed-consent form at screening before any study-specific procedures were conducted.

Eligible patients were aged >18 years with a clinical diagnosis of OA of the hip and/or knee, based on American College of Rheumatology and radiographic criteria.[24,25] Analgesia in the primary osteoarthritic joint had to be suboptimal in the week before the baseline visit, as evidenced by a Box Scale 11 (BS-11) score ≥4. In addition, patients had to experience inadequate pain relief while taking immediate-release paracetamol 4000 mg/d during the screening week. Patients were excluded from the study if they had been treated for OA pain with high-potency opioid analgesics (eg, morphine, fentanyl, oxycodone, methadone, hydromorphone, ketobemidone, buprenorphine) or with a usual dose of tramadol, codeine, or dextropropoxyphene for >1 week in the past 3 months; if they required frequent analgesic therapy for other chronic conditions (eg, migraine, gout, rheumatoid arthritis); if they were scheduled for surgery during the screening or treatment phase of the study; if they were abusing controlled substances or alcohol or, in the opinion of the investigator, demonstrated behaviors suggestive of addiction or substance abuse; and if they received a diagnosis of cancer (except basal cell carcinoma) or had cancer in the past 5 years (except treated basal cell carcinoma).

The study consisted of a screening phase, a treatment phase, and a follow-up phase (**Figure 1**). The screening visit (visit 1) was conducted 1 week before the baseline visit. At visit 1, the patient discontinued current analgesic treatment and began taking sponsor-provided paracetamol tablets (4000 mg/d). Paracetamol tablets (≤2000 mg/d) were also available as rescue medication throughout the study. At the baseline visit (visit 2), a computer-generated randomization schedule was used to allocate patients to receive 7-day buprenorphine patches or twice-daily oral tramadol

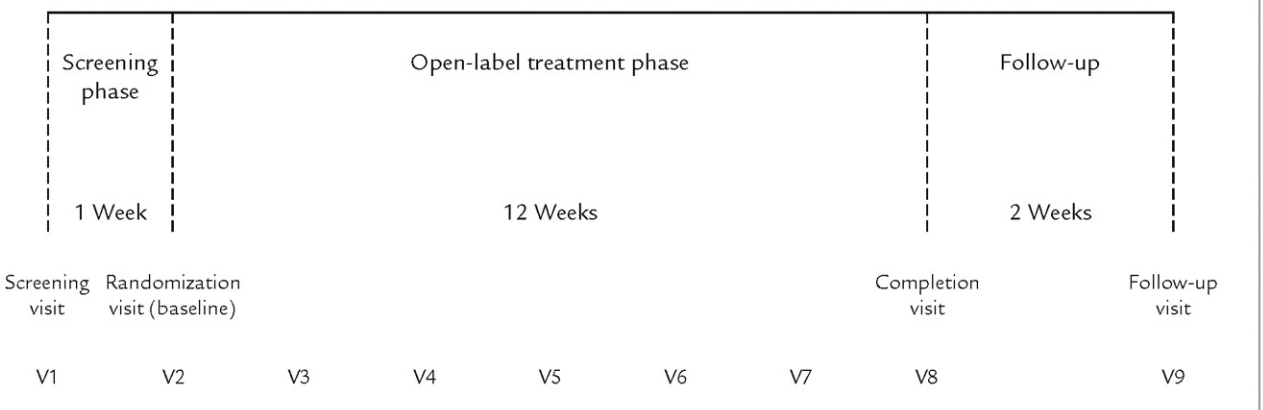


Figure 1. Study design. V = visit.

tablets. Randomization was performed in randomly permuted blocks of 10 patients. Patients were allocated to 7-day buprenorphine patches or oral twice-daily tramadol tablets in a 1:1 ratio balanced over all blocks, but not within each block to avoid bias. Sealed envelopes with the treatment codes were forwarded to the investigators at each site. Eligible patients were randomized to the lowest available patient number at their site.

The study involved a maximum of 9 visits; the follow-up visit (visit 9) could be conducted by telephone if all used (patches) and unused (tablets) study medication had been returned. The treatment phase lasted 12 weeks, during which doses of study medication could be titrated as needed to achieve stable pain control. The possible doses of the 7-day buprenorphine patches were 5, 10, 15, and 20 μg/h; up to 2 patches could be worn at the same time to achieve the required doses. The possible doses of tramadol tablets were 150, 200, 300, and 400 mg/d. The selection of doses was made according to recommendations in the summary of product characteristics for each drug[10,11] and based on general guidelines for the treatment of pain.[4] Investigators assessed whether patients had achieved stable pain control based on information entered on the case record form, including adverse events (AEs), and in patient diaries (pain score and number of paracetamol tablets taken). Antiemetics could be taken as needed.

After completion of or withdrawal from the study, patients stopped taking study medication. Because of their sustained-release formulations, no downward titration of either study drug was considered necessary. However, if downward titration was required, it was to be completed within 3 to 4 days, and the patient had to attend the follow-up visit (visit 9) in person.

### Study Assessments

The primary efficacy measure was the mean weekly BS-11 pain score, calculated from the scores recorded in the patient diaries every evening. Secondary efficacy measures included the patient-recorded number of paracetamol tablets (rescue medication) taken daily.

Sleep disturbance and quality of sleep were assessed by asking patients the following questions: "How many nights have you woken due to pain in the past 7 nights?" and "Please rate the quality of sleep over the past 7 nights" (response options: very poor, poor, fair, good, and very good). These questions were asked at screening, baseline, and all visits during the treatment phase (visits 3–8).

At the completion visit (visit 8), a global assessment of pain relief was obtained by asking patients and investigators to rate the study medication in terms of pain relief (very poor, poor, fair, good, or very good). Patient preference was assessed at the completion visit by asking subjects the following question: "Imagine equal pain relief—what would you prefer as a basic analgesic treatment for your OA pain in the future: a patch applied once a week or a tablet taken twice daily?"

To assess patient compliance, the site clinical research associate reviewed drug accountability during site visits and at the completion of the study.

### Exploratory Measures

At visits 1, 2, and 8, investigators assessed patients' pain, stiffness, and ability to perform daily activities using the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. They evaluated patients' quality of life using the EuroQol EQ-5D health states index and the EuroQol visual analog scale (EQ-VAS).

At visit 8, the investigators recorded any findings of abuse or diversion of the study drug on a specific page in the case record form. The following questions were used to capture these data: (1) "Was there any indication of abuse of alcohol or illicit drugs by this subject at any time during the study?" (2) "Was there any indication of abuse of the study drug by this subject at any time during the study?" and (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?"

### Safety Assessments

At each study visit, the investigator asked patients if they had experienced any AEs. All serious AEs (SAEs) were reported on a standard SAE form within 24 hours. At visits 2 and 8, a physical examination was performed, and systolic and diastolic blood pressure and heart rate were measured.

### Statistical Methods

It was estimated that 39 patients completing treatment in each group would provide 90% power at the 2.5% significance level to suggest that the 7-day buprenorphine patches were noninferior to the tramadol

tablets. The main study hypothesis was that the response to 7-day buprenorphine patches would be noninferior to the response to tramadol tablets; noninferiority was assumed if the treatment difference on the BS-11 scale was –1.5 boxes, indicating a clinically meaningful difference. For the primary efficacy measure, a 1-sided CI for the mean treatment difference was calculated with a 97.5% coverage probability. A 95% CI for the treatment difference was calculated in the same way for the secondary variables. No formal statistical inference was performed for the safety analysis. Variables for the 2 treatment groups are presented using descriptive statistics.

The full analysis set (FAS) included all patients who were randomized and received at least 1 dose of study medication. The per-protocol analysis set (PPAS) included patients who were in the FAS and had no major protocol violations.

## RESULTS

The numbers of patients completing each part of the study and the reasons for withdrawal are shown in Figure 2. The FAS included 69 patients in the 7-day buprenorphine patch group and 65 patients in the tramadol tablet group (66 patients were randomized to receive tramadol, but 1 patient in the tramadol

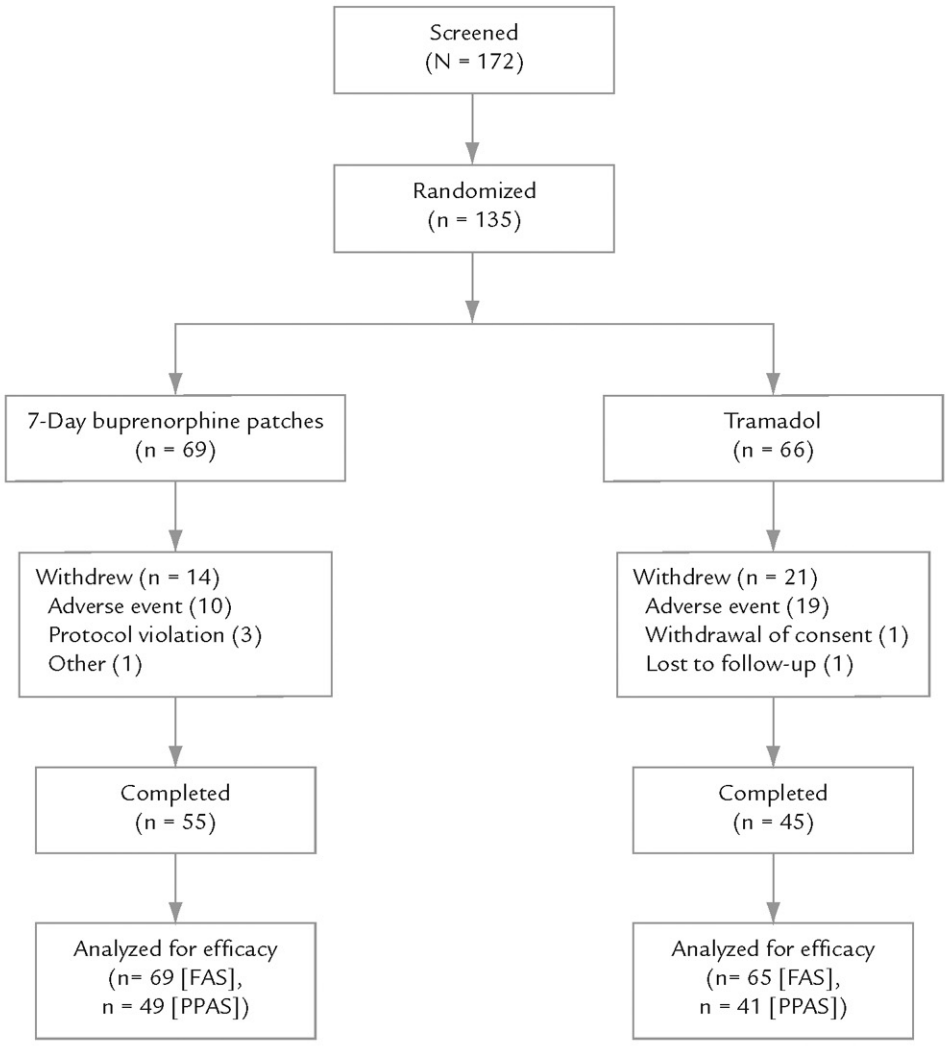


Figure 2. Flow of patients through the study. FAS = full analysis set; PPAS = per-protocol analysis set.

tablet group discontinued immediately after randomization). After removing patients in the FAS who had major protocol violations, the PPAS included 49 and 41 patients, respectively; the most common major protocol violations were lack of treatment for at least 79 days and occurrence of the visit-8 BS-11 assessment before day 78. The demographic characteristics of the treatment groups are summarized in **Table I.**

Table I. Demographic characteristics of the full analysis set.

| Characteristic | 7-Day Buprenorphine Patches (n = 69) | Tramadol Tablets (n = 65) |
|---|---|---|
| Age, y | | |
| Mean (SD) | 64.4 (11.1) | 64.2 (9.3) |
| Median (range) | 64.0 (36–87) | 63.0 (43–88) |
| Age group, no. (%) | | |
| >65 Years | 33 (47.8) | 25 (38.5) |
| >75 Years | 12 (17.4) | 9 (13.8) |
| Sex, no. (%) | | |
| Female | 41 (59.4) | 35 (53.8) |
| Male | 28 (40.6) | 30 (46.2) |
| Race, no. (%) | | |
| White | 68 (98.6) | 65 (100) |
| Asian | 1 (1.4) | 0 |

## Efficacy Assessments

**Table II** summarizes mean BS-11 pain scores at baseline and study completion, and the least squares mean change in scores from baseline to study completion. The upper confidence limit for the difference between the 7-day buprenorphine patch group and the tramadol tablet group was 0.54 in the FAS analysis and 0.59 in the PPAS analysis. Both values were below the prespecified noninferiority margin (treatment difference of –1.5 boxes).

In the FAS, the mean number of rescue paracetamol tablets used during the study was 206.4 in the 7-day buprenorphine patch group and 203.7 in the tramadol tablet group. In the PPAS, the corresponding values were 223.9 and 244.8 tablets. These differences between groups were not statistically significant.

The number of nights in the preceding 7 nights that patients reported waking because of pain decreased by 2 nights between baseline and study completion in both treatment groups (FAS). In the PPAS, the decrease was 2.5 nights in the 7-day buprenorphine patch group and 2.9 nights in the tramadol tablet group. The difference between treatments was not statistically significant in either analytic set.

The quality of sleep was reported as improved by at least 1 category from baseline to study completion by 59% of patients in the 7-day buprenorphine patch group and 48% of patients in the tramadol tablet group (FAS). In the PPAS, the corresponding values were 71% and 63%. The difference was not statistically significant between groups.

The global impression of pain relief derived from patients' (**Table III**) and investigators' (**Table IV**) ratings of the study medication compared with prestudy medication significantly favored the 7-day buprenorphine patches ($P = 0.039$ and $P = 0.020$, respectively). Numerically more patients in the 7-day buprenorphine patch group (FAS) reported that they achieved good or very good pain relief compared with the tramadol group (44 vs 33, respectively) (**Table III**). The results were similar in the PPAS group. On the patient preference question, 90 of the 128 patients (70.3%) who answered the question preferred a patch applied once a week (95% CI, 62–78) (FAS); in the PPAS, 57 of 89 patients (64.0%) answering the question preferred a once-weekly patch (95% CI, 54–74).

There were changes from baseline to study completion on all WOMAC Osteoarthritis Index subscale scores in both treatment groups, with no significant differences between treatment groups. As measured on the EQ-5D, mobility, self-care, usual activities, and pain/discomfort did not differ significantly between groups. There was an improvement in anxiety/depression in the tramadol group. There were also improvements on the EQ-VAS in both treatment groups but no difference between treatments. There was no indication of abuse or diversion in either treatment group.

## Safety Profile

There were no differences between groups in terms of the total number of AEs or total number of patients with at least 1 AE. Two hundred twenty-six AEs were

Table II. Box Scale 11 (BS-11) scores at baseline and study completion, and change from baseline to study completion.

| Variable | Full Analysis Set | | Per-Protocol Analysis Set | |
|---|---|---|---|---|
| | 7-Day Buprenorphine Patches (n = 69) | Tramadol Tablets (n = 65) | 7-Day Buprenorphine Patches (n = 49) | Tramadol Tablets (n = 41) |
| BS-11 score, mean (SD) | | | | |
| Baseline | 6.16 (1.35) | 6.21 (1.55) | 6.07 (1.31) | 6.39 (1.58) |
| Study completion | 3.92 (2.07) | 4.10 (2.15) | 3.50 (1.83) | 3.80 (2.20) |
| Point estimate for change from baseline, LSM (95% CI) | −2.26 (−2.76 to −1.76) | −2.09 (−2.61 to −1.58) | −2.69 (−3.27 to −2.12) | −2.43 (−3.06 to −1.80) |
| Point estimate for difference in change from baseline between 7-day buprenorphine patches and tramadol tablets, LSM (95% CI) | −0.17 (−0.89 to 0.54) | −0.26 (−1.11 to 0.59) | – | – |

LSM = least squares mean.

Table III. Patients' ratings of pain relief with study medication compared with their prestudy medication (full analysis set).* Data are no. (%) of patients.

| Rating | 7-Day Buprenorphine Patches (n = 68) | Tramadol Tablets (n = 62) |
|---|---|---|
| Very poor | 1 (1.5) | 6 (9.7) |
| Poor | 6 (8.8) | 15 (24.2) |
| Fair | 17 (25.0) | 8 (12.9) |
| Good | 28 (41.2) | 22 (35.5) |
| Very good | 16 (23.5) | 11 (17.7) |

*$P$ = 0.039 for 7-day buprenorphine patches versus tramadol tablets.

Table IV. Investigators' ratings of pain relief with study medication compared with patients' prestudy medication (full analysis set).* Data are no. (%) of patients.

| Rating | 7-Day Buprenorphine Patches (n = 68) | Tramadol Tablets (n = 63) |
|---|---|---|
| Very poor | 1 (1.5) | 4 (6.3) |
| Poor | 4 (5.9) | 16 (25.4) |
| Fair | 14 (20.6) | 9 (14.3) |
| Good | 38 (55.9) | 25 (39.7) |
| Very good | 11 (16.2) | 9 (14.3) |

*$P$ = 0.020 for the difference between 7-day buprenorphine patches and tramadol tablets.

reported in 61 patients (88.4%) in the 7-day buprenorphine patch group, and 152 AEs were reported in 51 patients (78.5%) in the tramadol group. There were too few events in the various Medical Dictionary for Regulatory Activities organ classes to draw any conclusions regarding differences between the treatments.

The most common AE in both groups was nausea, reported by 21 patients (30.4%) in the 7-day buprenorphine patch group and 16 patients (24.6%) in the tramadol tablet group (**Table V**). The next most common AEs in the 7-day buprenorphine patch group were constipation (18.8%) and dizziness (15.9%); in the tramadol tablet group, the next most common AEs were fatigue (18.5%) and pain (12.3%).

Fourteen patients (20.3%) in the 7-day buprenorphine patch group and 21 (32.3%) in the tramadol tablet group withdrew from the study. Ten (14.5%) and 19 (29.2%) of the respective withdrawals were due to AEs.

Three SAEs were reported during the study, all in the tramadol group. The SAEs of abdominal pain and chest pain were not considered related to treatment. The only SAE considered possibly related to study medication was a subendocardial myocardial infarction in a 66-year-old man for whom no medical history was available. At study entry, the patient began treatment with tramadol 150 mg/d, which was titrated to 200 mg/d after a week. The patient, who took only 1 tablet (75 mg) of his assigned dose of 150 mg/d, contacted the investigator 5 days later because of pain in the chest radiating into the neck. Electrocardiographic findings, blood pressure, and laboratory test results were normal. Five days later, the pain had worsened, and the patient was anxious and sweating. He was hospitalized and subsequently recovered. This patient was withdrawn from the study.

There were no clinically significant changes in blood pressure or heart rate from screening to the end of the study in either treatment group.

## DISCUSSION

The results of this noninferiority study of low-dose 7-day buprenorphine patches and prolonged-release tramadol tablets suggest that the buprenorphine patches were noninferior to the tramadol tablets, and that both products provided statistical and clinically significant reductions in pain. The validated BS-11 pain scale was used to measure pain reduction. How-

**Table V. Most commonly reported adverse events, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (safety population).**

| | 7-Day Buprenorphine Patches (n = 69) | | Tramadol Tablets (n = 65) | |
|---|---|---|---|---|
| MedDRA Preferred Term | No. (%) of Patients Reporting Event | No. of Events | No. (%) of Patients Reporting Event | No. of Events |
| Nausea | 21 (30.4) | 26 | 16 (24.6) | 19 |
| Constipation | 13 (18.8) | 15 | 5 (7.7) | 6 |
| Dizziness | 11 (15.9) | 11 | 3 (4.6) | 3 |
| Pain | 10 (14.5) | 13 | 8 (12.3) | 8 |
| Hyperhidrosis | 10 (14.5) | 10 | 4 (6.2) | 5 |
| Fatigue | 9 (13.0) | 10 | 12 (18.5) | 12 |
| Vertigo | 9 (13.0) | 13 | 1 (1.5) | 1 |
| Headache | 8 (11.6) | 13 | 7 (10.8) | 7 |
| Arthralgia | 4 (5.8) | 5 | 2 (3.1) | 2 |
| Application-site pruritus | 4 (5.8) | 4 | 0 | 0 |
| Edema, peripheral | 4 (5.8) | 4 | 0 | 0 |
| Nasopharyngitis | 4 (5.8) | 5 | 0 | 0 |
| Dry mouth | 2 (2.9) | 2 | 7 (10.8) | 8 |
| Pruritus | 2 (2.9) | 2 | 6 (9.2) | 7 |

ever, it is becoming increasingly clear that pain reduction cannot be measured in isolation and that a number of other factors should be taken into account, including the use of rescue analgesics, quality of sleep, functionality, AEs, and patients' overall impression of treatment. In the present study, these additional factors were analyzed through the secondary and exploratory end points, as well as in the safety assessment.

A noninferiority design was chosen as, at the time the study was planned, no other studies comparing the low-dose 7-day buprenorphine patch and a clinically relevant and commonly used treatment in Sweden had been conducted in patients with chronic, moderate to severe OA pain of the hip and/or knee. There was also limited clinical experience with use of the patch.

In Sweden, the most commonly prescribed formulation of tramadol is the short-acting one. It may therefore be argued that the prolonged-release formulation used in this trial does not reflect typical clinical practice in Sweden. The reason for selecting the prolonged-release formulation was to conduct a usual-care comparison between 2 long-acting preparations. The current Swedish treatment guidelines for chronic pain conditions recommend the use of long-acting preparations.[4]

The demographic characteristics of the study population, particularly with respect to sex and racial distribution, reflected the characteristics of the overall Swedish population. One weakness of the study may be the low proportion of patients aged >75 years. The mean age of the study population was 64 years, but a considerable number of patients with OA pain in the hip and/or knee are aged >75 years.

Most secondary and exploratory parameters suggested favorable changes or significant improvements from baseline to study completion with both treatments. The exceptions were patients' and investigators' ratings of pain relief with study medication compared with prestudy medication, which were significantly higher for the 7-day buprenorphine patches compared with tramadol tablets ($P = 0.039$ and $P = 0.020$, respectively), and the significantly lower incidence of anxiety/depression at study completion in the tramadol tablet group compared with the 7-day buprenorphine patch group (FAS: $P = 0.049$; PPAS: $P = 0.036$). The latter finding may have been a result of the antidepressant activity of tramadol. In addition, 70.3% of patients, regardless of treatment allocation, indicated that they would prefer treatment with a patch applied once weekly rather than a tablet taken twice daily. This preference with respect to the mode of drug delivery may lead to improved patient compliance, which is an important factor in successful pain management.

Based on previous studies and clinical experience, the AEs reported in the 2 treatment groups were as expected. Nausea was the most common AE in both treatment groups. Antiemetics could be taken if needed, but not as prophylactic treatment. Considering the findings of this study, a prophylactic approach may be advisable for both products.

Transdermal treatment can cause skin irritation at the application site, predominantly due to the adhesives used or to the drug itself. The general recommendation for avoiding skin irritation is to keep the skin in good condition, for example by using skin lotion regularly and avoiding skin dehydration. The patch application site should be changed weekly when the old patch is removed and a new patch is applied.[10]

One patient experienced a subendocardial myocardial infarction that was considered possibly related to tramadol. According to the summary of product characteristics for tramadol,[11] cardiovascular events are uncommon AEs for this product.

Even though the pattern of reported AEs was as expected in both treatment groups, premature discontinuation of study treatment due to AEs was approximately twice as high in the tramadol tablet group as in the 7-day buprenorphine patch group. The reason for this difference is unclear, although the explanation could be of clinical importance, as the results reflect a common clinical experience. The most common reason for withdrawal in both treatment groups was AEs, the most common of which was nausea.

An open-label design was chosen for 2 reasons. The primary consideration was to reflect usual clinical practice in a way that was relevant to the 2 treatment options studied, including slow titration, flexible dosing, and minimized use of concomitant and rescue analgesics.[26] Second, it was necessary to allow flexible dose titration in accordance with the prescribing information for the 2 products, treatment guidelines, and individual needs. Use of this design may have introduced bias, as patients and investigators may have had differing expectations with respect to the allocated treatments. When the study was designed, it was felt that the potential benefits of an open-label design outweighed those of a blinded design. The higher dropout rate in the tramadol group may also be as-

sociated with the open-label design, as it is well documented that patients enroll in clinical trials in hopes of receiving a newer treatment. Nevertheless, the total study dropout rate was lower than rates in other published chronic pain studies.

## CONCLUSIONS

In these patients with chronic, moderate to severe OA pain of the hip and/or knee, 7-day low-dose buprenorphine patches were effective in providing pain relief and were well tolerated. The 7-day buprenorphine patches were noninferior to prolonged-release tramadol tablets.

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