The peak-and-trough effects of opioids are a major reason for their attractiveness for "social" use. Consequently, the plasma concentration curve associated with transdermal administration makes the drug less likely to be abused.

Conclusion
Buprenorphine has been shown to be an excellent candidate for transdermal drug delivery. It has ideal physico-chemical properties for administration as a patch in clinical practice. This non-oral formulation also overcomes high first-pass metabolism. In patients in whom breakthrough pain episodes occur, sublingual formulations can be used. Because of increased compliance associated with the patch, the quality of life of patients in pain will improve. Thus, this new buprenorphine delivery system meets the needs of both patients and their physicians.

References

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Buprenorphine TDS: The clinical development — rationale and results

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SUMMARY Buprenorphine, a powerful opioid, is mainly available for delivery in a transdermal formulation. As the transdermal system's matrix patch provides rate-controlled administration of the drug, three double-blind, placebo-controlled trials were conducted to evaluate efficacy and tolerability of the buprenorphine transdermal system (buprenorphine TDS, Transderm-Bup.). A total of 445 patients were enrolled in the studies. All suffered from moderate to severe pain and very severe pain, both cancer- and non-cancer-related. The percentage of responders increased as the rate of buprenorphine delivered by the transdermal system rose, ranging from a 26% (placebo) and 36% (opioid-naive responder rate associated with the lowest dose (39 pg), to 40% (cancer) and 45% (non-cancer) with the highest dose (70 µg). Patients receiving buprenorphine TDS slept longer, were interrupted by pain, than patients from the placebo group. Systemic adverse effects reported in the drug cohorts included nausea, vomiting and dizziness, and were typical of those reported in other studies of opioids; local adverse events, most commonly erythema and pruritus, were transient and mild to moderate. In an open-label, follow-up trial, in which 120 patients from the original clinical studies participated, 30% of patients reported that their analgesia was satisfactory or even better over a mean duration of 4.7 months; nearly 95% of patients found the patch to be user-friendly. This new transdermally delivered TDS appears to be an important new modality for managing pain in patients with non-acute pain.

KEYWORDS: Analgesics; Buprenorphine; Morphin; Matrix patch; Opioids; Transdermal

Introduction
Buprenorphine is a potent, widely used analgesic drug in humans. Its effects have been shown in both cancer and non-cancer pain of moderate to severe intensity.1,2 Although buprenorphine has been available for many years as a sublingual tablet and as a solution for intravenous injection, a new transdermal formulation of buprenorphine in a matrix patch (Transderm-Bup)3 has recently been developed.2 This transdermal delivery system (TDS) provides rate-controlled delivery of the opioid drug. Three patch sizes are available, with release rates of 35, 52.5 and 70 µg/h over a 72-hour period, which correspond to daily doses of 0.8 mg, 1.2 mg and 1.6 mg buprenorphine, respectively.

As part of the buprenorphine TDS clinical development programme, three multicenter, double-blind, parallel-group, placebo-controlled studies, as well as one open-label follow-up trial, were conducted (Figure 1). The studies were designed to evaluate the analgesic efficacy and tolerability of buprenorphine TDS.

Study protocols
The protocols of the three comparative trials were similar. In all of these placebo-controlled studies, patients had moderate to severe and very severe pain of a non-acute nature; the pain was either cancer- or non-cancer-related. All patients had been pretreated with other analgesics, including high doses of week
Figure 1: Overview of the clinical development programme for buprenorphine TDS

445 patients (249 tumour, 196 non-tumour)

322 patients receiving buprenorphine TDS
Study 1: 114, Study 2: 119, Study 3: 90

123 placebo patients:
Study 1: 37, Study 2: 38, Study 3: 47

Follow-up: 236 patients receiving buprenorphine TDS

* Taking additionally buprenorphine sublingual tablets as needed

Figure 2: Diagnosis of patients receiving buprenorphine TDS or placebo TDS (multiple indications possible)

opioids, low-dose morphine or sublingual buprenorphine.

In the three trials, a total of 445 patients with chronic pain were enrolled. The majority of patients were randomly allocated to receive the buprenorphine TDS (35, 52.5 and 70 μg/h) compared to placebo TDS in 151 patients who had been pretreated with sublingual buprenorphine (0.8-1.2 mg/day) in a five-day run-in phase. Patients who reported at least satisfactory pain relief in the run-in period were randomised to the double-blind phase, receiving two consecutive patches of one of the three strengths of buprenorphine TDS or placebo TDS.

Study 1 evaluated the analgesic efficacy and tolerability of three dosages of buprenorphine TDS (35, 52.5 and 70 μg/h) compared to placebo TDS in 151 patients who had been pretreated with sublingual buprenorphine (0.8-1.2 mg/day) in a five-day run-in phase. Patients who reported at least satisfactory pain relief during the run-in phase were randomised to the double-blind phase, receiving two consecutive patches of one of the three strengths of buprenorphine TDS or placebo TDS.

Study 1 compared the analgesic efficacy and safety of buprenorphine TDS (35, 52.5 and 70 μg/h) in 151 patients over a period of 15 days; some of these patients were opiate naive with severe chronic pain, while others had been inadequately treated with weak opioids. There was no run-in phase; patients were directly switched to the study medication and received five consecutive transdermal patches.

Study 2 compared the analgesic efficacy of only the 35 μg/h buprenorphine patch versus sublingual buprenorphine over a period of nine days in 137 patients. Patients had already participated in an open, five-day, run-in phase of treatment with sublingual buprenorphine (0.8-1.0 mg/day) before being switched to the double-blind phase, where patients were randomly assigned to receive three consecutive patches of buprenorphine TDS or placebo.

Study results

The endpoints for assessment of the transdermal system's efficacy included pain intensity (evaluated with a five-point verbal rating scale, or VRS); pain relief (four-step VRS); duration of sleep undisturbed by pain as an indicator of improved quality of life; and the number of sublingual tablets required to rescue medication. Patients were considered to be responders if they recorded at least satisfactory pain relief with buprenorphine TDS, and if they needed no more than one sublingual tablet per day.

In the three clinical trials, the percentage of responders increased with higher dosages (Figure 3). Forty-six per cent of the non-cancer patients receiving the 70 μg/h patch were responders, compared to 41% and 45% of those receiving the 52.5 and 35 μg/h patch, respectively. Among the cancer patients, 49% of those with the 70 μg/h patch and 42% and 38% of those with the 52.5 and 35 μg/h patch were responders. In the placebo cohort, 23% (non-cancer) and 25% (cancer) of the patients were responders. The placebo response rate, although relatively high, is not unexpected, based on other double-blind randomised trials of analgesics, including opioids.

Patients treated with buprenorphine TDS had longer sleep periods uninterrupted by pain, compared to placebo. The tolerability of the buprenorphine patch was also found to be very good, with a favourable side-effect profile that was generally benign. In patients treated with the active drug, 42% reported systemic adverse effects, primarily nausea, vomiting, and dizziness; these adverse events were already recognised as being associated with opioid drugs. Consistently, frequently seen with other opioids, was reported only for 5.3% of patients receiving the active drug in the three trials. The most frequent local adverse events were erythema and pruritus, both of which occurred in up to one-quarter of the drug group; in most cases, however, these local effects were mild and transient, lasting for up to 10 days after the patch was removed. Several side effects were rare, and only a few patients had to be switched to another opioid.

In addition, a decline in the need for rescue medication (sublingual tablets) was seen at all dosage levels of buprenorphine TDS. In study 2, for example, the use of sublingual buprenorphine tablets as rescue medication decreased to less than 50% (mean 43.3%) of the previously required sublingual doses.
Buprenorphine TDS: Use in daily practice, benefits for patients

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SUMMARY In Germany and many other countries, buprenorphine has been used for a long time for the management of pain in both cancer and non-cancer patients. Although a transdermal delivery system for buprenorphine (Transing) has recently been introduced, the clinical experience in daily practice with this drug, delivered in a matrix patch, is only now being evaluated. In preliminary data from a survey of 3,255 patients with chronic pain, 28% had cancer pain, while the most common diagnosis of the other respondents included back pain (33%), osteoarthritis (25%), osteoporosis (17%), and neuropathic pain (10%). A multiple analysis calculated that the Transing treatment led to a significant improvement in the number of patients that had been treated with World Health Organization (WHO) Step II opioids (43%) or WHO Step III opioids (10%) including tramadol (35% of patients) and a trihainibaine combination (10%), 9% had not been prescribed any opioids in advance of receiving transdermal buprenorphine. Most patients (77%) in the survey had been started on the lowest dose of the buprenorphine patch (35 μg), and nearly hal (45%) were placed on adequate analgesia, including tramadol or disodium stamine. Pain relief was rated as good or very good by 81% of the respondents. Adverse effects were similar to those seen in other opioids, although their intensity was milder in most cases. Local side effects, including erythema (4% of cases) and pruritus (1%), were transient. Based on the survey results, transdermal buprenorphine is considered an autotrophic opioid treatment for patients with stable cancer and non-cancer pain and may prove particularly useful in patients who have experienced side effects taking oral analgesic preparations, as well as in anesthesiologists who are taking preventive co-medications.

KEYWORDS: Analgesic; Buprenorphine; Naloxone; Opioids; Tolerability; Transing; Transdermal, World Health Organization (WHO).