SYNOPSIS

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Company: ALZA Corporation **Investigational Product:** D-TRANS® fentanyl with naltrexone HCl system **Active ingredient:** fentanyl		

Title: Safety Evaluation of D-TRANS® Fentanyl with Naltrexone HCl in Opioid Tolerant Patients	
Investigator(s)/Study Center: Multicenter	
Publication (reference): none	
Study period: First patient treated: 3 February 2003 Last patient completed: 18 July 2003	**Phase of Development:** 2* *Development of this system design has been discontinued.
Objective: To evaluate the safety of D-TRANS® fentanyl with naltrexone HCl in opioid tolerant patients.	
Methodology: This was a multicenter, randomized, double-blind, double dummy safety study in adult patients ≥18 years old who required continuous opioid treatment for chronic pain. Patients had to be on a stable dose of Duragesic® for 21 days prior to the start of the study treatment period and have completed a screening period of at least 14 days to enter this study. Eligible patients were randomized in a 2:1 fashion to receive the equivalent strength of D-TRANS® fentanyl with naltrexone HCl (and placebo Duragesic®) or the same dose of Duragesic® (and placebo D-TRANS® fentanyl with naltrexone HCl [D-TRANS® fentanyl with NTX]) for a 15-day treatment period. If necessary, patients could be titrated to higher or lower doses during the 15-day treatment period. Each system was worn for 72 hours then replaced by a new system until the end of the 15-day treatment period. Patients were telephoned 3 times a day during the first 3 days of the study and then once daily for the remainder of the study to determine if there were any signs of opiate overdose or withdrawal. The patient was to be followed as medically indicated based on the responses to the questions.	
Number of subjects (planned and analyzed): Planned n=500; Treated n=560; Evaluable n=559 (372 D-TRANS® fentanyl with NTX, 187 Duragesic®); Completed n=483 (316 D-TRANS® fentanyl with NTX, 167 Duragesic®).	
Diagnosis and main criteria for inclusion: Patients ≥18 years old with a diagnosis of chronic pain requiring continuous opioid analgesia who had been on a stable dose of Duragesic® for 21 days before the start of the study treatment period.	
Test product, dose and mode of administration, batch number: D-TRANS® fentanyl with naltrexone HCl systems delivering fentanyl transdermally at doses of 25 µg/h, 50 µg/h, 75 µg/h, or 100 µg/h, and an identical placebo system for each dose. Active and placebo lots used in this study are listed in Appendix 12.1.6 of this report.	
Duration of trial: 6-7 months	
Duration of individual participation: 30 days	
Reference therapy: Duragesic® (fentanyl transdermal system) delivering fentanyl transdermally at doses of 25 µg/h, 50 µg/h, 75 µg/h, or 100 µg/h, and an identical placebo system for each dose. Active and placebo lots used in this study are listed in Appendix 12.1.6 of this report.	

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Criteria for evaluation:

Primary: Adverse events including opioid overdose symptoms.

Additional: Opioid withdrawal symptoms, supplemental opioid use, dose increases or decreases, patient global assessment, investigator global assessment, pain intensity, brief pain inventory.

Topical AEs (spontaneously reported application site reactions [ASRs] and scheduled post-system removal assessments of presence of erythema, edema, papules, pustules, and itching), clinical laboratory tests (hematology, clinical chemistry, urinalysis), vital signs (diastolic and systolic blood pressure, heart rate, respiratory rate, temperature), and system functionality (adherence, cosmetic appearance, ease of removal, and extent of residue) were also evaluated.

Blood samples were also collected for analysis of naltrexone and fentanyl concentrations at scheduled times during the study. Blood samples were also to be collected for analysis of naltrexone and fentanyl prior to any dose change and if a patient experienced a serious adverse event possibly or probably related to study drug.

Statistical methods:

No hypotheses testing of the primary objective was planned.

The one-way analysis of variance (ANOVA) was used to make treatment group comparisons of the global assessment mean scores. The Chi-square test was utilized to compare the global assessments categorically. The Chi-square test was also used to compare supplemental opioid use. These tests were performed at the α=0.05 significance level. The statistical tests used for the analysis of baseline data were performed at the α=0.10 significance level. All tests were two-sided and no adjustment for multiple tests was made.

Efficacy Results Summary:

Efficacy results collected in this study demonstrated that mean pain intensity levels did not change when patients were converted from Duragesic® to D-TRANS® fentanyl with NTX and that mean pain intensity levels were similar between the two treatments at all assessments. The severity of pain, the impact of pain on daily function, and the amount of pain relief in the previous 24 hours or previous week were comparable for D-TRANS® fentanyl with NTX and Duragesic® treatments, based on patient responses to the short form of the Brief Pain Inventory. For the patient and investigator global assessments, D-TRANS® fentanyl with NTX and Duragesic® were rated equally as "good or excellent" for pain control, by 64.1% and 64.3% of patients, respectively and by 70.4% and 70.0% of investigators, respectively. Supplemental opioid use (proportion of patients, quantity, and duration) was also comparable between the two treatments.

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Efficacy Results Summary (continued):

The results of assessments of the study systems themselves, at 24 hours and 72 hours after selected applications, for adherence, cosmetic appearance, ease of removal, and extent of residue left at the application site were similar for D-TRANS® fentanyl with NTX and Duragesic® systems. Although most systems of either treatment left no residue behind, Duragesic® systems did appear to leave more minimal to moderate residue at the application site than D-TRANS® fentanyl with NTX systems.

Pharmacokinetic Results Summary:

Serum Fentanyl Concentrations

Blood samples were collected at baseline (before any study system application), 72 hours after the Day 1 application, 24 hours after the Day 7 application, and at 72 hours following the Day 13 application for analysis of serum fentanyl concentrations. In both treatment groups at all dose levels, baseline concentrations (before any study system application) were similar to the concentrations observed during the study. At all of these time points, mean serum fentanyl concentration values were similar for patients who converted from Duragesic® to D-TRANS® fentanyl with NTX and for patients who continued treatment with Duragesic®. Additionally, for both D-TRANS® fentanyl with NTX and Duragesic® treatments, the mean serum fentanyl concentration values appeared to be proportional to dose.

Serum Naltrexone Concentrations

Of the 2094 samples analyzed in this study, ninety-eight percent of patients showed no quantifiable naltrexone concentrations. Seven samples from 7 patients in the D-TRANS® fentanyl with NTX group (Nos. 3605, 4306, 4310, 5210, 5213, 5715, and 7017) had quantifiable serum naltrexone concentrations (LLOQ = 10 pg/mL) at isolated time points. One of the 7 patients (No. 7017) had an additional sample that had no quantifiable naltrexone, but its metabolite, 6-β-naltrexol, was detected. With the exception of one sample, which had a value of 723 pg/mL (No. 5715), the observed values ranged from 10pg/mL to 46 pg/mL.

Clinical efficacy, safety and withdrawal parameters in the 7 patients with isolated serum naltrexone values were not different from the evaluable patient population. No serious adverse events or discontinuations due to adverse events occurred in the 7 patients and there were no reports of opioid withdrawal syndrome.

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Safety Results Summary:

All safety results were similar for patients with chronic pain who converted from Duragesic® to D-TRANS® fentanyl with NTX or continued with Duragesic® treatment. Adverse events reported by patients in both treatment groups were those known to be associated with fentanyl, fentanyl transdermal delivery, or the underlying disease of patients requiring continuous opioid analgesia.

- One death as a result of coronary artery occlusion, judged as not related to treatment, occurred 11 days after the patient completed study treatment with D-TRANS® fentanyl with NTX.
- Of the 15 patients that experienced a serious adverse event, 10 (2.7%) in the D-TRANS® fentanyl with NTX group and 5 (2.7%) in the Duragesic® group, 14 had serious adverse events that were not attributed to study treatment. Hematemesis and diarrhea, requiring hospitalization, were assessed as possibly related to treatment in one elderly patient using Duragesic®.
- Twenty-seven patients (7.3%) in the D-TRANS® fentanyl with NTX group and 9 (4.8%) in the Duragesic® group discontinued from the study due to an AE.
- AEs reported by ≥3% of patients from either treatment group in this study were similar to those listed in the Duragesic® Package Insert, and, in this study, generally occurred at a similar or lower incidence in patients using D-TRANS® fentanyl with NTX or Duragesic®.
- Over 90% of the patients in each of the two treatment groups reported no ASRs after any of the active system applications. When reported, ASRs were all of mild or moderate severity, with one exception (severe ASR-other in 1 patient in the Duragesic® group).
- When observed, topical AEs (erythema, edema, papules, pustules and itching) were typically mild and occurred at a similar frequency in both treatment arms.
- No treatment differences were observed in results from the two withdrawal scales administered (COWS and ARSW). Most patients using D-TRANS® fentanyl with NTX or Duragesic® had no evidence of withdrawal (total score <5) on COWS at any time on study (87.4% and 89.8%, respectively). In both treatment groups, none to mild symptoms of withdrawal (score of 0 to 3) was the mean score for all but one of the ARSW assessments during the study treatment period. In both treatment groups, a moderate rating was given for two baseline assessments.

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Safety Results Summary (continued):

- Safety results for the 7 patients with isolated serum naltrexone values were not different from the evaluable patient population. No serious adverse events and no discontinuations due to adverse events occurred in these 7 patients. Adverse events reported were nausea, dizziness, paresthesia, and somnolence, all of mild or moderate severity. Four of the 7 patients had no AEs reported. COWS Withdrawal scores were all between 0 and 2, indicating no opioid withdrawal syndrome.

Conclusions:

The safety and efficacy of D-TRANS® fentanyl with NTX is comparable to Duragesic® in patients requiring management of chronic pain with continuous opioid analgesia. Sporadic serum naltrexone levels observed in a few patients in the D-TRANS® fentanyl with NTX group did not impact the safety and efficacy of D-TRANS® fentanyl with NTX.

Date of the report: March 2005

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