CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-338

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-338	Submission Date(s): 09/23/2003
Brand Name	E-TRANS® fentanyl HCl system
Generic Name	Fentanyl HCl transdermal patch
Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Reviewer	He Sun, Ph.D.
Pharmacometrics Reviewer	Meiyu Shen, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
OND division	Division of Anesthetics Critical Care and Addiction Drug Products
Sponsor	Alza Corporation, Mountain View, CA, USA
Relevant IND(s)	41,574
Submission Type; Code	Original NDA- 505b(1); 3 S
Formulation; Strength(s)	Transdermal; 40 µg/dose
Indication	[redacted]
Proposed Dosing Regimen	40 µg/dose up to 80 doses or up to 24 hours for patient controlled analgesia

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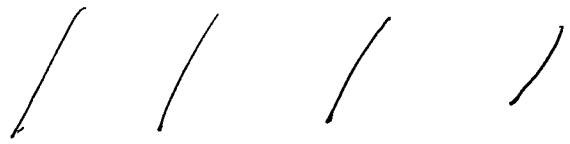
1 Executive Summary

E-TRANS® fentanyl HCl 40 µg/dose system is the subject of NDA 21-338 submitted by Alza Corporation. E-TRANS® fentanyl HCl system is designed to deliver 40 µg of fentanyl by transdermal route for the management of postoperative pain in adults. The sponsor adequately evaluated the pharmacokinetics of fentanyl following different sequences of E-TRANS® system application for one to three days. Effects of site of application and demographic factors on the pharmacokinetics of fentanyl from E-TRANS® system have been adequately evaluated. The , designed for determining fentanyl delivery from E-TRANS® systems, *in vitro*, is adequately validated. The proposed IVIVC analysis for scale up and postapproval changes of E-TRANS® fentanyl HCl system is acceptable.

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective the submitted data is acceptable provided that a mutually acceptable agreement can be reached between the Agency and Alza Corporation regarding the text in the package insert and *in vitro* release method specifications. The release specifications should be modified as follows;



1.2 Phase 4 Commitments

None

1.3 Summary of Important Clinical Pharmacology Biopharmaceutics Findings

Alza Corporation developed an electrotransport device (E-TRANS® system) for transdermal delivery of fentanyl, a potent opioid, for the management of postoperative pain in adults. The E-TRANS® (fentanyl HCl) System provides a nominal 40 µg dose of fentanyl (base equivalent) per activation, which is delivered over a 10-minute period. A maximum of six 40 µg doses per hour can be administered by the E-TRANS® (fentanyl HCl) System. Each system operates for 24 hours, or until 80 doses have been administered, whichever occurs first. The system becomes inoperable after this period.

Several clinical pharmacokinetic studies were conducted to compare absolute bioavailability of fentanyl following application of different E-TRANS® systems capable of delivering 100 – 230 µA of direct current (Studies C-96-009, C-97-001, C-94-068, C-2001-009, C-2002-027). Upon comparison with the pharmacokinetics of fentanyl following intravenous bolus administration, the sponsor determined that E-TRANS® systems employing 100, 140, 170, 200 and 230 µA deliver a transdermal fentanyl dose of 24.8, 35.1, 39.5, 49.5 and 53.9 µg, respectively. The dose of fentanyl delivered *in vivo* was found to correlate with the amount of direct current employed by the E-TRANS® system. E-TRANS® 170 µA fentanyl HCl system, capable of delivering 40 µg of fentanyl was developed as the commercial formulation. In addition, E-TRANS® 140 µA fentanyl HCl system capable of delivering 25

µg of fentanyl was also used in some clinical studies and also the exposure response relationship in the management of postoperative pain.

Study FEN-INT-006 evaluated the safety and efficacy of IV infusion (over 10 minutes) of fentanyl 20, 40 and 60 µg delivered by Patient Controlled Analgesia (PCA) to 150 patients with moderate to severe pain after major abdominal surgery. It was observed that patients receiving 40 µg of fentanyl IV infusion of 10 minutes had satisfactory analgesia in comparison with the subjects receiving lower dose of 20 µg. In addition, the number of adverse events was lower in this treatment group in comparison with the subjects receiving fentanyl 60 µg/dose. Hence, this study served as a proof of concept for developing the E-TRANS® fentanyl HCl 40 µg/dose system. Observations from this study with regards to exposure-response of fentanyl indicated strong evidence of a dose-effect relationship based on both the patient global response and the visual analog scale. However, no correlation was observed between measures of pain relief or respiratory depression, and fentanyl concentration.

Mean (SD) Serum Fentanyl Pharmacokinetic Parameter Values Following E-TRANS® (fentanyl) Treatments

Parameters	Treatments		Statistical Outcome[a]
	E-TRANS® 40 µg (1 day)	E-TRANS® 40 µg (3 days)	
n	25	25	
C_{max} (ng/mL)	0.30 (0.13)	0.48 (0.19)	S p=0.0001
T_{max} (h)	1.66 (1.01)	1.33 (1.01)	NA
$t_{1/2}$ (h)[b] (terminal half-life)	11.4 (7.4)	14.2 (7.1)	S p=0.0001
$AUC_{0\text{-}5}$ (ng·h/mL)[c]	1.20 (0.55)	1.88 (0.71)	S p=0.0001
C_{pre} (ng/mL)[d]	0.21 (0.08)	0.34 (0.13)	S p=0.0001
$t_{1/2}'$ and $t_{1/2}''$ (h)[b] (half-life values for decline in concentration)	7.66 (2.22)	9.98 (9.13)	NA
Corrected $AUC_{0\text{-}5}$ (ng·h/mL)[c]	0.40 (0.29)	0.54 (0.32)	NS p=0.133

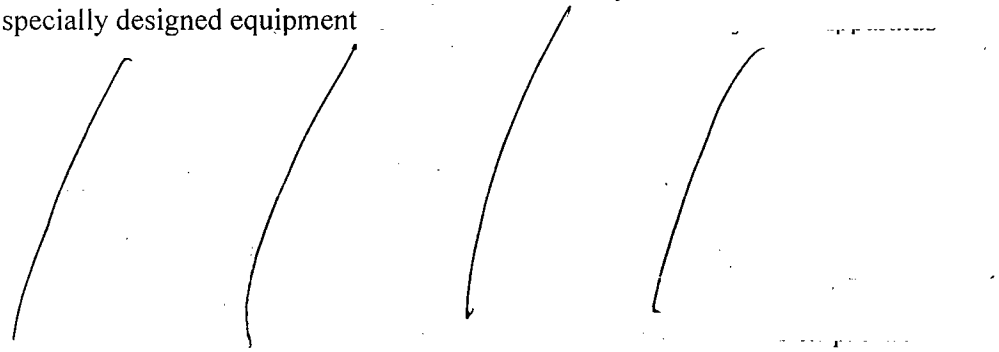
[a] α = 0.05, S=Significant, NA=Not applicable, NS=Not significant

Pharmacokinetics of fentanyl following different sequences of on-demand dosing with E-TRANS® system was studied. In comparison with IV bolus administration, fluctuations of fentanyl concentrations are small and therapeutic concentrations are achieved slowly. Passive absorption of fentanyl, equivalent to 16 to 192 µg (over 24 hours), was observed following a 24 hour application of the commercial formulation of E-TRANS® fentanyl HCl 40 µg system without activation (C-2002-027). Fentanyl pharmacokinetics is dose-dependent in that increase in elimination half-life of fentanyl was observed between one-day and three-day on-demand dosing regimen. The AUC of fentanyl increases with the more frequent administration and steady state levels are achieved at approximately 60 hours following two on-demand doses every 4 hours.

Application of E-TRANS® fentanyl HCl system to lower inner arm results in 20% less amount absorbed compared with application to the chest and upper outer arm (Study C-93-019). Amount of fentanyl absorbed was not significantly different in subjects belonging to different demographic groups such as age (18- 45 years vs >65 years), gender, race (Blacks vs Caucasians), body weight (lean vs obese) (Study C-94-060). Pharmacokinetics of fentanyl was not studied in patients with

hepatic or renal impairment. Pharmacokinetics of fentanyl absorbed from E-TRANS® systems were not evaluated with regards to drug interactions.

Alza Corporation developed an *in vitro* release method with intent to request bioequivalence study waiver for scale-up and post approval changes to the drug product. The *in vitro* release of fentanyl dose delivered over 10 minutes from E-TRANS® system was determined employing specially designed equipment

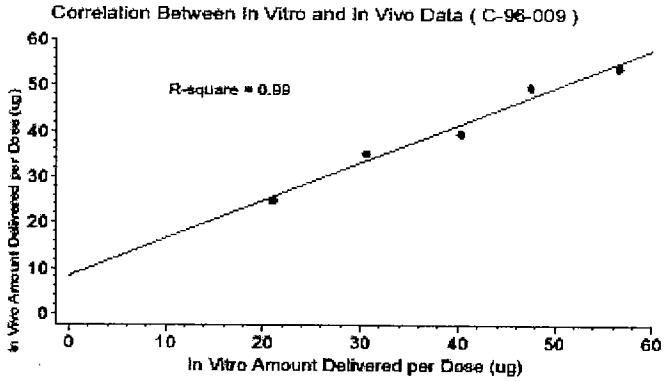


. Considering the novel nature and utility of the sponsor validated the equipment with regards to its performance and robustness in determining fentanyl dose delivered by E-TRANS® systems. Accuracy and precision of fentanyl dose released *in vitro* was determined with respect to changes in the Simultaneously, accuracy and precision of current output from E-TRANS® system was also determined. In addition, accuracy and precision of drug recovery from was determined. Based on the data provided, the is adequately validated for the purpose of evaluating *in vitro* release of fentanyl from E-TRANS® systems. Following validation, the sponsor determined the amount of fentanyl released following 1st, 25th, 47th and 77th activation of E-TRANS® systems (100 – 230 µA) utilized in clinical pharmacokinetic studies C-96-009 and C-97-001. In vivo studies involved administration of fentanyl by two on-demand doses every hour for upto 24 hours in naltrexone-blocked healthy volunteers. It appears that the scheduled *in vitro* dose activations 1, 25 and 47, were planned to coincide with the blood sampling at hour 0-1, 12-13 and 23-24 in clinical PK studies. Amount of fentanyl dose absorbed from E-TRANS® systems (100 – 230 µA) was determined by comparison of $AUC_{23\text{-}24}$ observations with intravenous bolus administration as shown in the equation below.

The E-TRANS® system is functional only upto 24 hours or 80 doses, which ever comes first, and in addition, it was assumed that steady absorption of fentanyl would be observed following 24 hour application *in vivo*. Hence, $AUC_{23\text{-}24}$ data obtained from the 47th dose activation *in vivo* was correlated with observations from 45th dose activation *in vitro*. The

$$\text{Amount absorbed}^{\text{E-TRANS}} = \frac{AUC^{\text{E-TRANS}}_{(23\text{-}24)}}{AUC^{\text{IV}}_{(23\text{-}24)}} \times Dose^{\text{IV}}_{(23\text{-}24)} \qquad \textbf{Equation 1}$$

amount of fentanyl released *in vitro* correlated very well with the amount of direct current applied by E-TRANS® systems. The individual amount absorbed *in vivo* for each E-TRANS® system was found to show a trend indicating direct relationship with the amount of current applied by the systems. Furthermore, good correlation was observed between the mean of observations of fentanyl delivered *in vitro* and *in vivo* (as shown in the figure below).



Based on observations from *in vitro* release of fentanyl from E-TRANS® systems (Code , utilized for stability studies, the sponsor arrived at the following specifications.

The sponsor indicated that the range limits for intervals 2, 3, and 4 were established at , assuming a plasma concentrations ≥ 1.2 ng/mL, and were based on the observed lot-to-lot variability. There is potential risk for safety with the proposed specification for individual delivery. In addition, review of fentanyl release from E-TRANS® systems used in clinical PK and stability studies indicates low variability of drug release at indicated dose attempts. Following consultation with the reviewing chemist Dr. Agarwal, the revised specifications are recommended.

2 QBR

2.1 General Attributes of the Drug

Marketed formulations of fentanyl: Fentanyl is an opioid analgesic administered to patients for the management of acute or post-operative pain or breakthrough cancer pain. Currently, fentanyl is approved for administration by intravenous (fentanyl citrate injection, NDA 16-619), transdermal (Duragesic®, NDA 19-813) and oral transmucosal routes (Actiq® lozenge on a stick, NDA 20-747). Highly lipid soluble fentanyl base is used in Duragesic® transdermal patch, while aqueous soluble fentanyl citrate is used in formulations for intravenous and oral transmucosal administration.

Mechanism of Action: Fentanyl acts as an analgesic by its μ-opioid receptor agonist activity in brain and spinal cord.

Pharmacokinetics: Fentanyl is poorly bioavailable following oral administration due to extensive metabolism in GIT and liver by CYP3A4 to a pharmacologically inactive metabolite norfentanyl. Following intravenous fentanyl administration, only 10% is recovered in urine unchanged, 75% of dose is recovered in urine as metabolites and approximately 9% of the dose is recovered in feces, mainly as metabolites. Plasma protein binding of fentanyl is about 80-85%. Terminal elimination half-life of fentanyl following intravenous administration is approximately 7 (3 – 12) hours. Following passive absorption, approximately 92% of fentanyl dose reaches systemic circulation from Duragesic® transdermal system. After Duragesic® system removal, serum fentanyl concentrations decline slower ($t_{1/2}$ in the range of 13-22 hours) compared to IV infusion.

Proposed Drug Product: In the current submission, Alza Corporation developed an electrotransport device (E-TRANS) for transdermal delivery of fentanyl hydrochloride. The E-TRANS (fentanyl HCl) System provides a nominal 40 μg dose of fentanyl (base equivalent) per activation, which is delivered over a 10-minute period with a current of 170 μA. To initiate administration of a fentanyl dose, the patient must press the recessed button on the top of the system firmly twice within 3 seconds. An audio tone (beep) indicates the start of delivery of each dose, and a red light from a light emitting diode (LED) remains on throughout the 10-minute dosing period. A maximum of six 40 μg doses per hour can be administered by the E-TRANS® (fentanyl HCl) System. Each system operates for 24 hours, or until 80 doses have been administered, whichever occurs first. The system becomes inoperable after this period. The maximum nominal amount of fentanyl that can be administered from a single system over 24 hours is 3.2 mg (80 individual 40 μg doses).

2.2 General Clinical Pharmacology

Clinical pharmacology studies performed to support dosing or claims of efficacy:

The sponsor performed four clinical studies evaluating safety and efficacy of E-TRANS® fentanyl HCl systems in adult patients with post-operative pain. Two E-TRANS® systems capable of delivering 25 μg/dose and 40 μg/dose fentanyl were compared in safety and efficacy study # C-93-023. In study # C-95-016, safety and efficacy of E-TRANS® fentanyl HCl system 40μg/dose system was compared to placebo. In study C-2000-007, safety and efficacy of E-TRANS® fentanyl HCl 40 μg/dose system was compared with intravenous PCA with morphine. The sponsor also investigated the postoperative analgesic effects of three demand doses of fentanyl administered IV by PCA pump (Study FEN-INT-006).

2.2.1 Exposure-Response Information

What are the response endpoints? What is the basis for their selection? How were they measured in clinical pharmacology studies?

The selected outcome measures for efficacy were a) pain intensity assessed on a visual analog scale (VAS) and quality of analgesia (excellent, good, fair and unsatisfactory) assessed immediately before and at several time points after the application of E-TRANS® fentanyl HCl , b) patient and investigator global assessment of pain relief, c) number of fentanyl demand doses requested. In addition, frequency of use of rescue IV fentanyl infusion in patients receiving E-TRANS® systems was also compared as an efficacy measure. The outcome measures for safety were respiratory depression and oxygen saturation, monitored continuously using a pulse oximeter.

What are the characteristics of the exposure-response relationship for efficacy or safety?

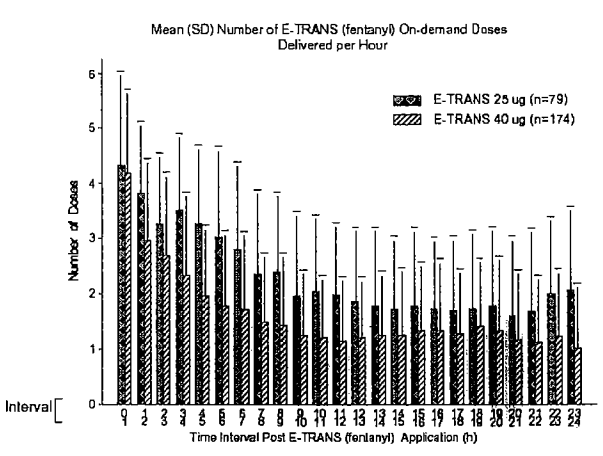
Plasma concentration of fentanyl did not correlate well with efficacy or safety measures described above. However, with an increase in fentanyl dose less number patients sought rescue medication and more patients expressed better pain relief. Clinically significant dose/concentration-response with regards to respiratory depression was not observed.

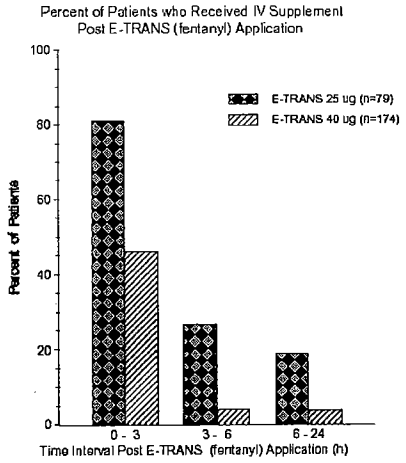
Studies C-93-023 and FEN-INT-006 were reviewed by Dr. He Sun, to draw information with regards to fentanyl dose-response or concentration response. A summary of study design and conclusions are presented below (See Appendix for Study synopsis on pages 60 and 69).

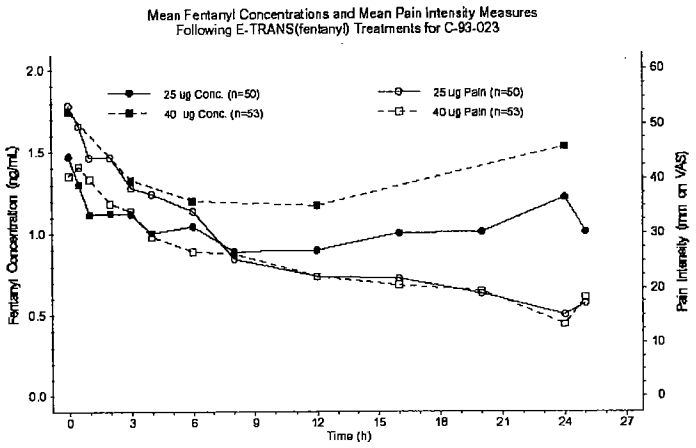
E-TRANS® Fentanyl HCl system Pilot Efficacy and Safety Study in the Treatment of Postoperative Pain (Study C-93-023)

The objective of this study was to compare safety and efficacy of PCA fentanyl doses of 25 µg and 40 µg. The study (n=253) was a multicenter, open-label, two-part design in patients expected to have moderate to severe pain after surgery performed under general or regional anesthesia. Postoperatively, patients had an E-TRANS® fentanyl system for 24 hours and could administer up to six on-demand fentanyl doses an hour as follows: 25 µg fentanyl delivered over 10 minutes (Part 1) or 40 µg fentanyl delivered over 10 minutes (Part 2). If the dosage did not provide adequate relief, single or multiple 10 µg doses of IV fentanyl were provided as rescue medication.

Study C-93-023 demonstrated that the 40 µg dosing regimen provided better efficacy than the 25 µg dosing regimen for management of postoperative pain. The 40 µg dosing regimen was associated with fewer on-demand doses (Figure below, left) and IV supplements (Figure below, right) as compared to the 25 µg dosing regimen.

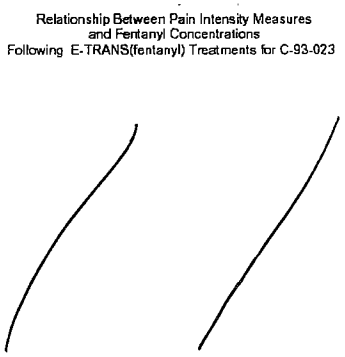


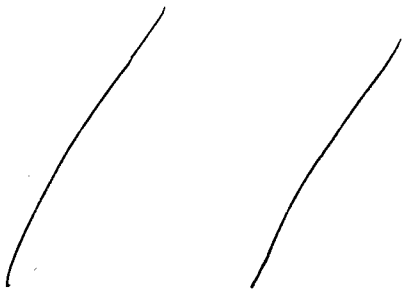




In addition, VAS scores for pain intensity (adjacent Figure) were lower during the first 6 hours and mean fentanyl concentrations were higher with the 40 µg dosing regimen as compared to 25 µg. After 6 hours, the mean VAS profiles were similar for the two treatments; however, the concentrations were still approximately 20% higher for the 40 µg dosing regimen compared to the 25 µg dosing regimen.

In the right hand side figure, the individual pain intensity scores versus the concentration of fentanyl was plotted. A placebo treatment was not included in this study, the likely course of postoperative pain intensity without fentanyl is not known. **A direct correlation between fentanyl concentration and pain scores cannot be established from these data.**





The adjacent figure presents the individual respiratory rate as a function of fentanyl concentration from Study C-93-023. A statistically significant trend of lower respiratory rates with higher fentanyl concentrations was observed. However, the numbers of observations are not evenly distributed, and the trend may be due to fewer numbers of observations at higher (greater than 6 ng/mL) fentanyl concentrations than at the lower concentrations (less than 2 ng/mL). Furthermore, no correlation was observed between oxygen saturation and fentanyl concentration. The presence of pain stimulus is known to increase respiratory rate and, therefore, the fentanyl concentration-respiratory rate relationship is confounded.

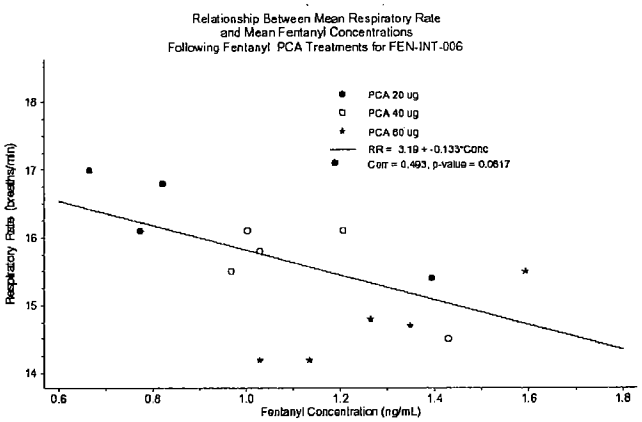
Investigation of the Postoperative Analgesic Effects of Three Demand Dose Sizes of Fentanyl Administered by PCA (Study FEN-INT-006)

The primary objective of this study was to examine the effects of three different on-demand dose levels of IV fentanyl (20, 40, and 60 μg) when administered over 10 minutes from a PCA device (See Appendix page 69 for study synopsis). The study was a multicenter, double-blind, randomized, parallel-group design. Fentanyl was delivered by PCA to 150 patients with moderate to severe pain after major abdominal surgery performed under general anesthesia with a volatile anesthetic (supplemented by fentanyl). Postoperatively, all patients were titrated with fentanyl in order to achieve an acceptable level of analgesia-a clinician administered 10 μg doses of IV fentanyl every 1-5 minutes until the pain intensity was <2 (on a VAS scale of 0-10). Thereafter, the PCA device was connected, and patients administered fentanyl according to one of these three regimens (dose duration and maximum number of doses allowed per hour were set to mimic the E-TRANS® fentanyl system design):

- 20 μg fentanyl over 10 minutes (Treatment A)
- 40 μg fentanyl over 10 minutes (Treatment B)
- 60 μg fentanyl over 10 minutes (Treatment C)

Patients could administer the drug up to six times per hour for a minimum of 24 hours unless the investigator decided to change the method of analgesia because of inadequate pain relief or severe opioid side effects. Blood samples for the determination of fentanyl plasma concentrations were collected in one trial center at the following times: before surgery; immediately after surgery but before the IV titration with fentanyl; at 9 minutes after the start of the IV titration with fentanyl; after the IV titration with fentanyl, just before the start of IV PCA fentanyl (0 h); and 4, 8, 12, and 24 hours after the start of the IV PCA fentanyl treatments. The primary measure was the patient's global assessment, and the secondary parameters were as follows: pain intensity assessed on a visual analog scale immediately before and after titration with IV fentanyl to acceptable analgesia, and at several time points after the start of PCA; and the number of fentanyl on- demand doses requested. Respiratory depression and oxygen saturation were monitored continuously using a pulse oximeter.

Results from Study FEN-INT-006 were consistent with those of Study C-93-023. **Study FEN-INT-006 also provided strong evidence of a dose-effect relationship based on both the patient global response and the visual analog scale.** The number of fentanyl demands made during the study was significantly lower with both 40 μg and 60 μg dose levels as compared to the 20 μg dose level. There was no significant difference in the number of fentanyl demands between the 40 μg and 60 μg dose levels.



The adjacent figure presents the mean respiratory rate as a function of fentanyl concentration from study FEN-INT-006 (individual data not show); as drug concentration increased, respiratory rate decreased, however, respiratory rates were within normal limits. **No correlation was observed between oxygen saturation and fentanyl concentration.**

2.2.2 Pharmacokinetics

What are the pharmacokinetic characteristics of the drug and its major metabolite?

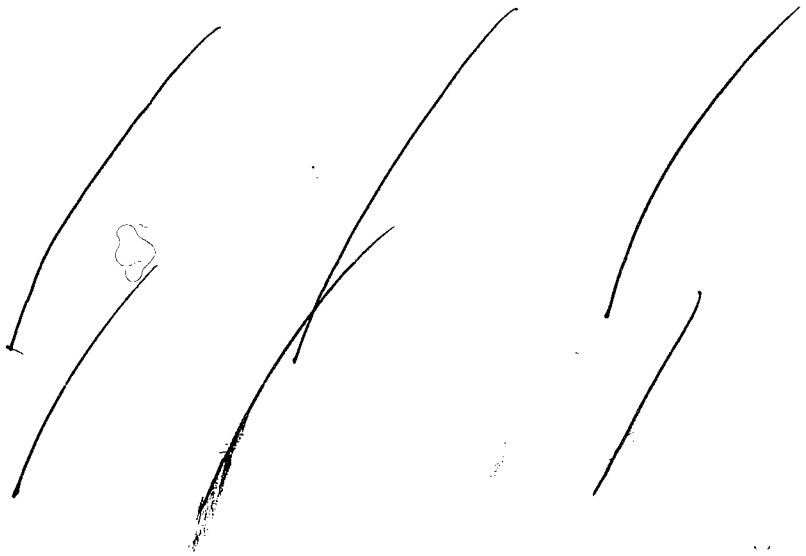
Dose of fentanyl delivered by E-TRANS® system correlates with the current delivered by the system. Compared with intravenous infusion, therapeutic serum fentanyl concentrations from E-TRANS® system are achieved slowly, have lower fluctuations, steady absorption of fentanyl is achieved following several on demand doses. Absolute bioavailability data indicates that a 40 µg of fentanyl dose is delivered by the proposed commercial E-TRANS® 170 µA fentanyl HCl system on demand.

Clinical pharmacokinetic studies were aimed at determining the dose of fentanyl absorbed following application of E-TRANS® fentanyl HCl system. Pharmacokinetics of norfentanyl which is the major and also inactive metabolite of fentanyl was not evaluated by the sponsor. The sponsor studied the relationship between the amount of current employed by E-TRANS® system and amount of fentanyl absorbed in healthy human volunteers (C-91-001, C-92-038, C-94-067). Based on the results from these studies fentanyl dose absorbed from E-TRANS® system was found to be directly proportional to the amount of current applied. These studies were not reviewed in detail since similar conclusions from later studies, reviewed below, were drawn using commercial E-TRANS® systems.

Clinical pharmacokinetic studies C-96-009 and C-97-001 were conducted to compare absolute bioavailability of fentanyl following application of different E-TRANS® systems capable of delivering 100, 140, 170, 200 and 230 µA of direct current. Overall, these studies were open-label, randomized, crossover design studies in naltrexone-blocked healthy adult volunteers. Details of study designs and treatments are provided in the study synopses in the Appendix (C-96-009 - page 73, C-97-001 – page 76). Subjects in study C-96-009 received the following treatments:

- IV infusion of fentanyl (80 µg) over 20 minutes administered once every hour for 22.33 hours and 40 µg infusion over 10 minutes at Hour 23
- E-TRANS® fentanyl systems administering fentanyl in two consecutive 10-minute doses every hour for 22.33 hours and one 10-minute dose at Hour 23.

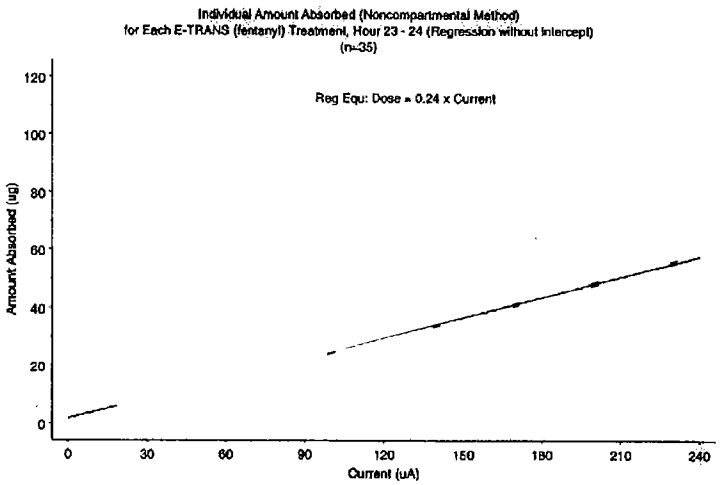
Serum fentanyl concentrations plotted against time intervals of Hours 0-1, 12-13 and 23-24 are presented in the figure below.



Mean fentanyl amounts absorbed, as calculated from the equation 1, are presented in the table below.

Pharmacokinetics	Treatment					
	IV (n=36)	200 µA (n=35)	230 µA (n=16)	170 µA (n=16)	140 µA (n=18)	100 µA (n=18)
Cmax (ng/mL)	2.157	2.225	2.636	1.954	1.404	1.024
Tmax (h)	23.187	23.319	23.291	23.427	23.340	23.227
AUC(0-1) (ng·h/mL)	0.440	0.120	0.103	0.171	0.120	0.049
AUC(12-13) (ng·h/mL)	1.228	1.296	1.575	1.097	0.863	0.660
AUC(23-24) (ng·h/mL)	1.624	1.962	2.350	1.760	1.251	0.899
Amount delivered/10-minute on-demand dose (µg)	NA	55.3	63.8	40.4	40.4	27.6
Mean amount absorbed/10- minute on-demand dose (µg) (noncompartmental method)	Ref	49.7	53.9	39.5	35.1	24.8

The sponsor correlated the amount of current (100 – 230 µA) with the individual amount absorbed at hour 23 as calculated from equation 1. At hour 23, the mean amount of fentanyl absorbed per 10-minute on demand dose was 53.9 µg, 49.7 µg, 39.5 µg, 35.1 µg, and 24.8 µg for currents of 230 µA, 200 µA, 170 µA, 140 µA, and 100 µA, respectively. Using linear regression, the amount of fentanyl absorbed (noncompartmental method) per 10-minute on-demand dose increased proportionally to the amount of current applied, with a slope of 0.23 and an intercept of 1.77. A new model (slope=0.24 µg/µA) without the intercept was fitted to the data as shown in the adjacent figure. Reanalysis of this data confirmed the sponsor proposed results where the regression line fit the data with an $R^2 = 0.4954$. In conclusion, there is good correlation between the current delivered by the E-TRANS® system and the amount of fentanyl dose absorbed *in vivo*.



A confirmatory study (C-97-001) was performed employing the E-TRANS® fentanyl HCl delivering 100 µA and 170 µA current in an open-label, randomized, crossover design in naltrexone-blocked healthy adult volunteers. The following treatments were administered:

IV infusion of Fentanyl citrate (equivalent to 80 µg fentanyl) delivered over 20 minutes every hour for 23.33 hours.

E-TRANS® fentanyl systems administering fentanyl in two consecutive

- 10-minute doses every hour for 23.33 hours.

- 25 µg system with anode surface area of 1.4 cm^2 and direct current of 100 µA

- 40 µg system with anode surface area of 2.75 cm^2 and direct current of 170 µA

Mean fentanyl amounts absorbed, as calculated from the equation 1, are presented in the table below.

Mean (SD) Fentanyl Pharmacokinetic Parameters at Hour 23 in Study C-97-001 (excluding subjects 1011, 1032, 1039, and 1040)

Parameter	E-TRANS® 25 µg (n=31)	E-TRANS® 40 µg (n=31)	IV fentanyl 40 µg (n=31)
C_{max} (ng/mL)	1.003 (0.653)	1.37 (0.30)	1.82 (1.23)
T_{max}	0.562 (0.238)	0.65 (0.25)	0.58 (0.27)
$t_{½}$ (h)[a]	11.28 (3.37)	11.0 (2.4)	12.6 (3.0)
$AUC_{(23-24)}$ (ng.h/mL)	0.80 (0.21)	1.23 (0.27)	1.34 (0.31)
Amount absorbed (µg)[b]	48.8 (13.9)	74.3 (12.5)	Reference
Amount absorbed, mean (µg/dose)	24.4	37.2	Reference

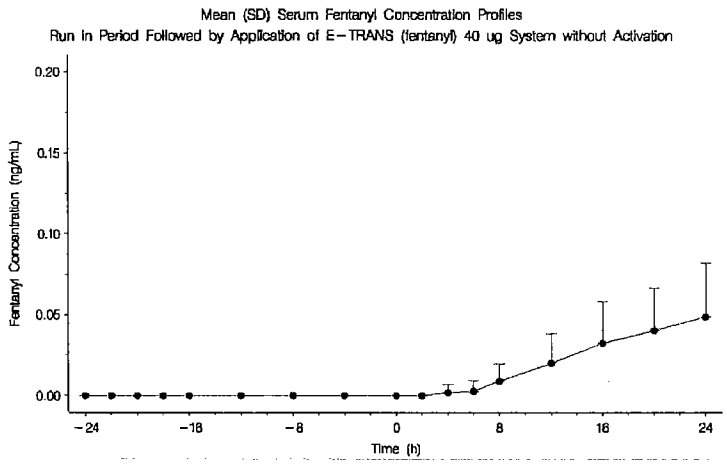
[a] 25 µg, n=26; 40 µg, n=31; IV fentanyl, n=30
[b] From two 10-minute, consecutive doses (Equation 1)

The sponsor intends to market the E-TRANS® fentanyl HCl 170 µA system which would deliver approximately 40 µg/dose over a 10 minute interval and upto 240 µg fentanyl can be administered over one hour. The rise and fall of serum fentanyl concentrations are blunted with E-TRANS®-mediated transdermal delivery in comparison with intravenous fentanyl infusion.

Passive delivery and pharmacokinetics of fentanyl from E-TRANS® system following sequential administration for different durations:

Passive delivery:

The sponsor conducted two clinical pharmacokinetic studies C-91-001 and C-2002-027, where in naltrexone-blocked healthy volunteers received E-TRANS® fentanyl HCl systems without activation. Four subjects in study C-91-001 received E-TRANS® fentanyl HCl system without current for 24 hours and fentanyl was not detected in serum from any of the 15 blood samples collected predose and upto 24 hours post application. An experimental E-TRANS® platform capable of delivering 0- 1.2 mA of current using an ——— was utilized in study C-91-001. However, study C-2002-027 involved use of a functional drug product similar to the final to-be-marketed E-TRANS® fentanyl HCl 40 µg/dose system which was not activated. Maximum serum fentanyl concentrations in the range of — to — ng/mL were detected by 16 – 24 hours post drug product application in a total of twenty eight naltrexone-blocked healthy volunteers.



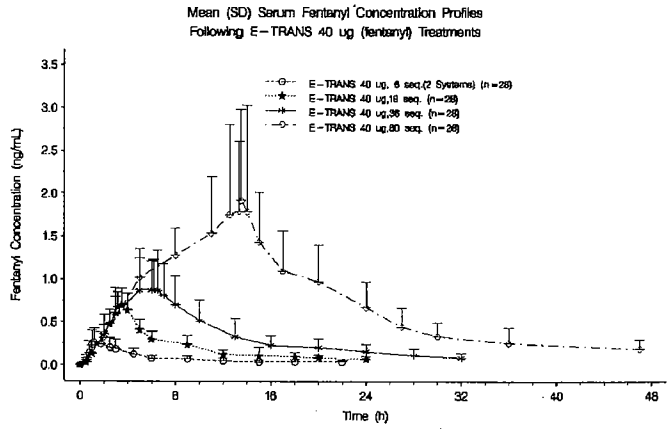
The serum fentanyl concentration profile following E-TRANS® system application without activation is provide in the adjacent figure. Based on numerical deconvolution of the serum fentanyl profile observed during treatment A, the mean cumulative amount of fentanyl absorbed was calculated as 57.4 µg (range: — to — µg). In different terms, the maximum passive absorption of fentanyl would relate to approximately 0.5 - 5 extra doses over a period of 24 hours. The mean fentanyl average absorption rate was 2.3 µg/h (range: 0.7 to 7.9 µg/h) over the 24-hour application (blood samples were collected through 0.5 hours post system removal). It is noteworthy that highest individual fentanyl C_{max} (— , ng/mL) observed in Treatment A is comparable to the mean C_{max} in Treatment B. However, it should also be noted that such C_{max} levels in treatment A are achieved only after 24 hour application of E-TRANS® fentanyl HCl 40 µg/dose without activation. It is anticipated that the patients will administer two to four 40 µg doses per hour, resulting in approximate absorption of 1.9 mg to 3.8 mg fentanyl dose over 24 hours.

Fentanyl pharmacokinetics following different sequences of E-TRANS® system application upto 24 hours was determined in study C-2002-027:

Mean (SD) Serum Fentanyl Pharmacokinetic Parameter Values Following Treatments

Parameter	Treatments				
	A E-TRANS® 40 µg without current activation 24 h n=28	B E-TRANS® 40 µg 6 sequential doses over 1 h n=20	C E-TRANS® 40 µg 18 sequential doses over 3 h n=20	D E-TRANS® 40 µg 36 sequential doses over 6 h n=20	E E-TRANS® 40 µg 80 sequential doses over 13.33 h n=20
C_{max} (ng/mL)	0.06 (0.05)	0.27 (0.18)	0.72 (0.20)	1.08 (0.48)	2.00 (1.24)
T_{max} (h)	24.15 (1.58)	1.86 (1.79)	3.45 (0.33)	6.12 (0.68)	13.00 (1.93)
$t_{1/2}$ (h) (terminal half-life)	NA	19.2 (6.0)[a]	10.5 (2.5)	10.4 (4.6)	20.5 (7.2)[b]
k (h^{-1}) (elimination rate constant)	NA	0.040 (0.013)[a]	0.070 (0.016)	0.076 (0.025)	0.038 (0.015)[b]
AUC_t[c] (ng·h/mL)	0.53 (0.40)	1.68 (0.83)	4.67 (1.61)	11.26 (4.25)	33.36 (14.04)
AUC_{Inf} (ng·h/mL)	NA	2.79 (1.43)	5.75 (2.13)	12.87 (5.32)	39.88 (18.34)
AUC_n = AUC_{Inf}/#dose (ng·h/mL)	NA	0.23 12 doses	0.32 18 doses	0.36 36 doses	0.50 80 doses

NA=Not applicable [a] n=17 [b] n=19 [c] AUCt = AUC up to the last detectable point

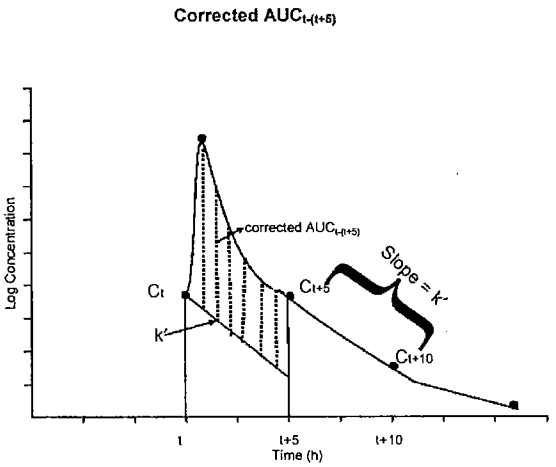


Synopsis of this study is attached (see Appendix page 81). The treatments and the pharmacokinetic parameters of fentanyl are presented in the table below. For treatment B, two E-TRANS® systems were simultaneously applied for one hour to ensure that serum fentanyl concentrations achieved were above the limit of quantitation to adequately characterize the pharmacokinetic profile following 1 hour of dosing. Dose-normalized AUC values for Treatments B, C, and D were each significantly (p=0.001) different from those for Treatment E. Dose-normalized AUC values for Treatments B, C, and D were 44%, 65%, and 72% of Treatment E, respectively. Higher serum fentanyl concentrations are achieved with more frequent dosing with E-TRANS® system. Results of the noncompartmental pharmacokinetic

analysis suggest that the dose-normalized AUC increases linearly with both time and number of doses administered.

Study # 2001-009 (synopsis on page 85) evaluated effect of E-TRANS® system dosing sequences (different from those employed in Study # C-2002-027) on the pharmacokinetics of fentanyl. Noncompartmental analysis of data indicates E-TRANS® system dosing frequency-dependent increase in AUC of fentanyl.

Pharmacokinetics of fentanyl following Single and Multiple-day application of E-TRANS® system:



Corrected $AUC_{20-25} = AUC_{20-25} - (C_{20} / k') (1- e^{-k'x5})$
Corrected $AUC_{68-73} = AUC_{68-73} - (C_{68} / k'') (1- e^{-k''x5})$
where k' and k'' are the rate of decline from Hour 25 to 30 and Hour 73 to 78, respectively.

Significant accumulation of fentanyl occurs with increased elimination half-life following multiple-day application of E-TRANS® system. Following two simultaneous doses of 10 min every 4 hours, steady state concentrations of fentanyl were observed by day 3. Depending on the frequency of the doses administered the time to achieve steady state and concentrations achieved may vary.

Study # C-94-068 is an open-label, two-period, two-treatment, crossover study to evaluate fentanyl pharmacokinetics following single- and multiple-day (3 days) dosing of E-TRANS® fentanyl HCl delivery two simultaneous 40 µg dose over 10 minutes in naltrexone-blocked healthy volunteers (See Appendix page 89 for synopsis).

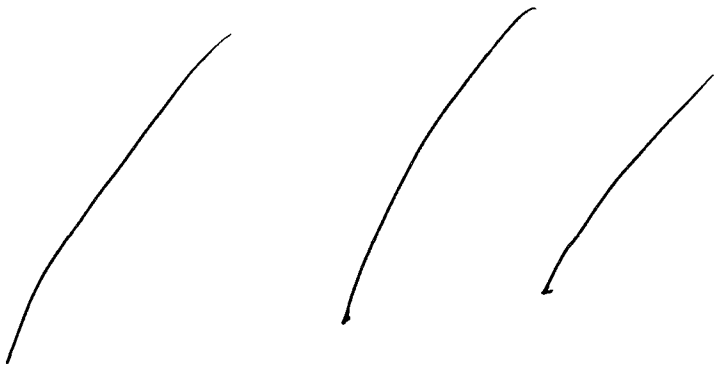
Mean (SD) Serum Fentanyl Pharmacokinetic Parameter Values Following E-TRANS® (fentanyl) Treatments

Parameters	Treatments		Statistical Outcome[a]
	E-TRANS® 40 µg (1 day)	E-TRANS® 40 µg (3 days)	
n	25	25	
C_{max} (ng/mL)	0.30 (0.13)	0.48 (0.19)	S p=0.0001
T_{max} (h)	1.66 (1.01)	1.33 (1.01)	NA
$t_{1/2}$ (h)[b] (terminal half-life)	11.4 (7.4)	14.2 (7.1)	S p=0.0001
AUC_{0-5} (ng·h/mL)[c]	1.20 (0.55)	1.88 (0.71)	S p=0.0001
C_{pre} (ng/mL)[d]	0.21 (0.08)	0.34 (0.13)	S p=0.0001
$t_{1/2}'$ and $t_{1/2}''$ (h)[b] (half-life values for decline in concentration)	7.66 (2.22)	9.98 (9.13)	NA
Corrected AUC_{0-5} (ng·h/mL)[c]	0.40 (0.29)	0.54 (0.32)	NS p=0.133

[a] α = 0.05, S=Significant, NA=Not applicable, NS=Not significant

As shown in the adjacent table, the mean maximum serum concentrations (C_{max}) following the on-demand dose at Hour 20 (1-day treatment) and Hour 68 (3-day treatment) were significantly different (p=0.0001) at 0.30 and 0.48 ng/mL, respectively, occurring at approximately 1.66 and 1.33 hours, respectively. The terminal half-life was significantly different (p=0.0001) for the 1-day and 3-day treatments at 11.4 and 14.2 hours, respectively. The mean AUC_{20-25} value of 1.20 ng·h/mL was significantly lower (p=0.0001) than the mean AUC_{68-73} value of 1.88 ng·h/mL. It appears that fentanyl accumulates during multiple-daily dosing and steady state concentrations were observed at

approximately 60 hours, where mean serum concentrations were not significantly different than those observed at 68 hours, the last evaluated predose concentration. The sponsor recalculated AUC_{0-5} for single and three day regimens, in order to correct for previous dose accumulation using the following equations and the basis for correction is explained by the figure above. Considering that only few serum samples were utilized in calculating the k`, the corrected AUC value is only an approximation.



The 90% Confidence Interval (CI) was constructed for the ratio of the mean corrected AUCt-(t+5) (log transformed) values. The point estimate was 78% and the CI was 59.2 to 102.6%. The CI estimate does not meet the 80 to 125% criterion for bioequivalence. The sponsor indicates that this possibly could be due to low statistical power.

2.3 Intrinsic Factors

Does the site of application have an effect on the amount of fentanyl absorbed from E-TRANS® fentanyl HCl system?

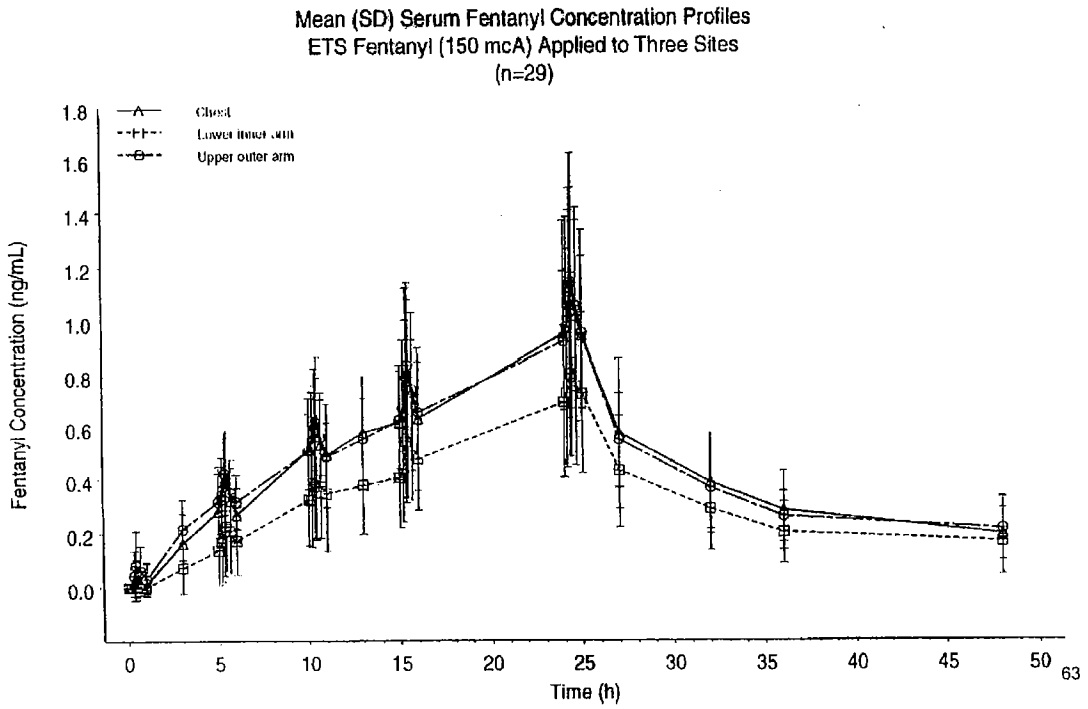
Application of a developmental E-TRANS® fentanyl HCl at chest and upper outer arm skin sites produced higher (~20%) fentanyl exposure over that produced by application at the inner lower arm skin site.

The observations from study C-93-019 were reviewed by Dr. Suresh Doddapaneni on January 2, 1996 and the synopsis is attached to the QBR (See Appendix page 93). The following table from Dr. Doddapaneni's review shows, pharmacokinetic parameters (mean (% CV)) of fentanyl after application at chest, lower inner arm, upper outer arm and upper outer arm (15 minutes prior to initiation).

Pharmacokinetic Parameters	Chest	Upper Outer Arm	Lower Inner Arm
C_{max} (ng/mL)	1.176 (40)	1.193 (27)	0.859 (39)
t_{max} (hour)	23.6 (13)	23.5 (16)	24.7 (6)
AUC $_{0-48}$ (ng hour/mL)	25.372 (40)	25.835 (29)	18.93 (40)

nd- not determined* - Standard deviation could not be calculated as only one subject had measurable concentrations.

The following figure depicts the mean ± SD serum fentanyl concentration profiles observed following application of the developmental E-TRANS® system to the chest (triangle, solid line), upper outer arm (circle, long-dashed line) and lower inner arm (square, dotted line).



The developmental E-TRANS® system employed in study C-93-019 is different from the commercial formulation for the following reasons:

- The E-TRANS® system provided 150 µA of direct current.
- The anode hydrogel contained fentanyl HCl as 5 mg base equivalent.

Clinical studies (C-93-023, C-95-016, C-2000-007, C-2001-006) evaluating safety and efficacy employed E-TRANS® fentanyl system on the chest or upper outer arm. Based on these results, the commercial formulation is intended for application to the chest or upper outer arm. Considering strong evidence of relationship between current delivered by E-TRANS® fentanyl HCl system and the dose absorbed, results obtained in this study using the developmental E-TRANS® may be extrapolated to the proposed commercial E-TRANS® 170 µA fentanyl system.

Do any demographic factors have an effect on the amount of fentanyl absorbed from E-TRANS® fentanyl HCl 40 µg/dose system?

Demographic factors such as age, race (black vs caucasian only), gender or weight did not show significant effect on the AUC_{inf} of fentanyl following E-TRANS® fentanyl treatment.

Study # C-94-060 was an open-label, non-randomized, sequential, two-treatment study in eight groups of naltrexone-blocked healthy subjects. The synopsis of study design, results and conclusions are attached (see Appendix page 97 for synopsis). Briefly, each group was characterized by three demographic factors and each subject received an E-TRANS® fentanyl

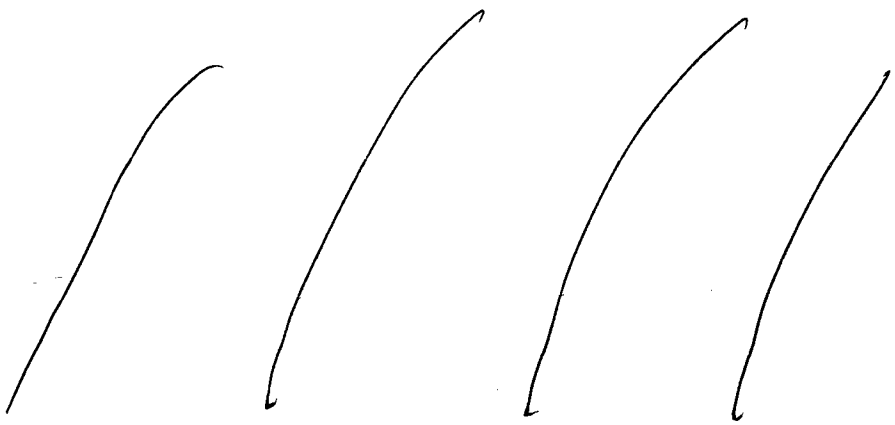
40 µg/dose system treatment (three sequential 10 minute treatments delivered every hour for 3 hours). Following a 5-10 day washout period subjects in each group received IV fentanyl citrate treatment (thirty minute infusion every hour for 3hours).

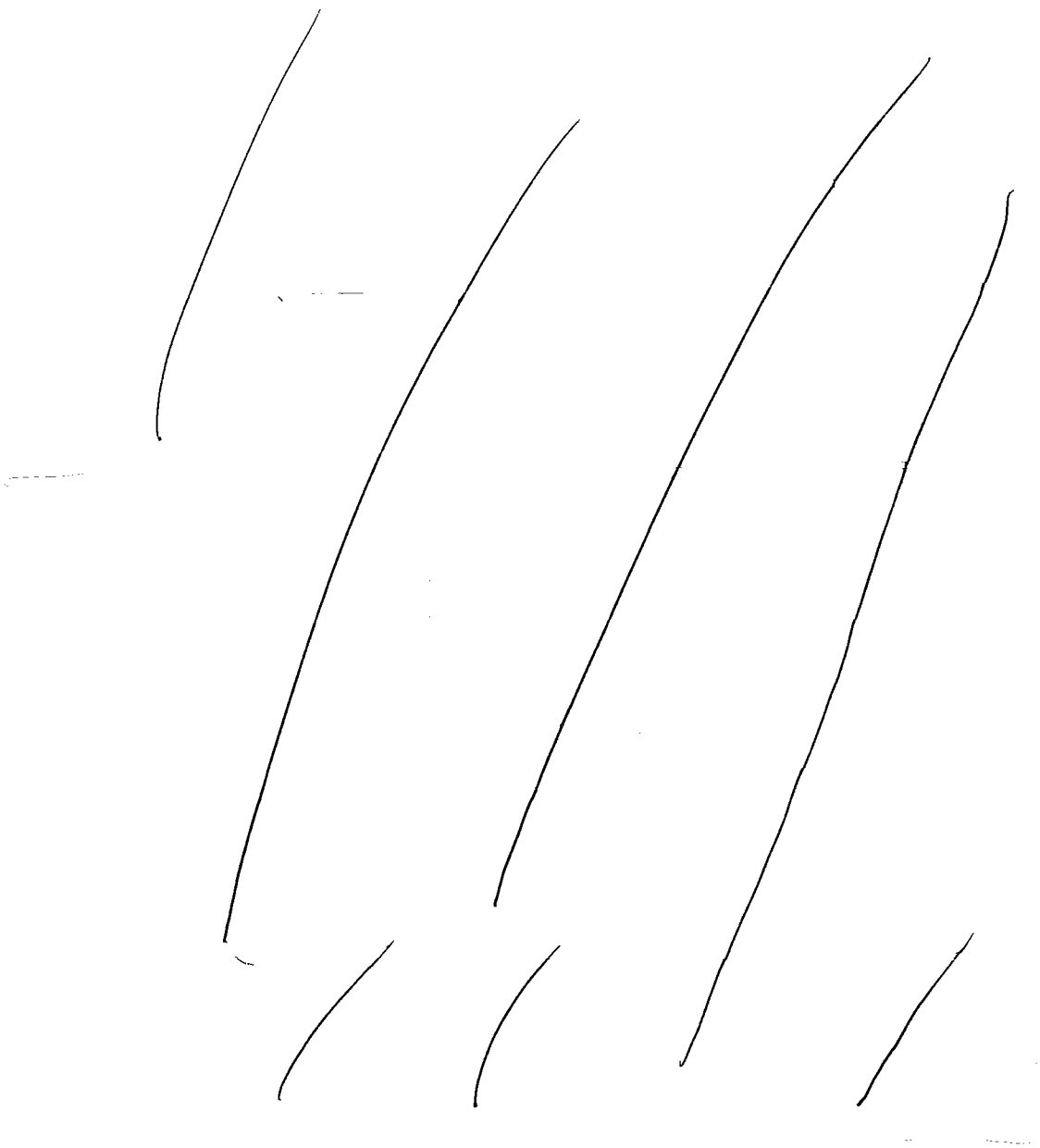
The sponsor proposed to determine the amount of fentanyl absorbed from E-TRANS® system by determining absolute bioavailability. However, the sponsor indicated that due to difficulties encountered while analyzing IV infusion data, AUC_{inf} was not calculated and hence did not attempt to determine the amount of fentanyl absorbed from E-TRANS® system in subjects different groups. Hence, AUC_{inf} of fentanyl in only subjects receiving E-TRANS® was compared. The following table indicates the demographics of subjects and also shows comparison of the pharmacokinetic parameters of fentanyl following treatment with E-TRANS® systems. The numbers in parenthesis under each PK parameter indicates the number of subjects in each group.

Mean ± SD (n) Fentanyl Pharmacokinetic Parameters Following E-TRANS® (fentanyl) Treatment All Available Subject Data

Age (yrs)	Race/Ethnic Origin	Body Mass	C_{max} (ng/mL)	[a]$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)
18–45	White	Lean	0.56 ± 0.17 ([b]11)	5.96 ± 3.44 (9)	3.86 ± 1.79 (11)
		Obese	0.53 ± 0.18 (8)	3.45 ± 0.92 (7)	2.80 ± 1.01 (8)
	Black	Lean	0.89 ± 1.88 (12)	4.98 ± 1.90 (4)	5.32 ± 9.9 (11)
		[c](Excluding # 3011)	0.35 ± 0.22 (11)	Not Applicable	2.35 ± 1.19 (10)
		Obese	0.49 ± 0.17 (9)	4.58 ± 1.53 (9)	2.69 ± 0.8 (9)
> 65	White	Lean	0.48 ± 0.27 (7)	8.34 ± 7.04 (6)	3.43 ± 1.89 (7)
		Obese	0.43 ± 0.12 (10)	4.75 ± 1.81 (9)	3.13 ± 1.49 (10)
	Black	Lean	0.41 ± 0.42 (3)	3.91 ± 0.02 (2)	2.72 ± 1.12 (2)
		Obese	0.21 ± 0.29 (10)	4.55 ± 0.77 (3)	1.93 ± 1.31 (6)

[a] $t_{1/2}$ values were not estimable for all subjects.
[b] Numbers in parentheses indicate the number of subjects in each group.
[c] This subject had relatively high concentrations following the E-TRANS® (fentanyl) treatment.





2.4 Extrinsic Factors

Effect of extrinsic factors such as drug-drug interactions on fentanyl pharmacokinetics following application of E-TRANS® system was not studied.

Considering the extensive metabolism of fentanyl by hepatic CYP3A4, drug interactions may be possible upon coadministration with strong CYP3A4 inhibitors or inducers. Coadministration of a potent CYP3A4 inhibitor, ritonavir, significantly reduced clearance of intravenously administered fentanyl (*Olkkola et al., Anesthesiology 91: 681-685, 1999*).

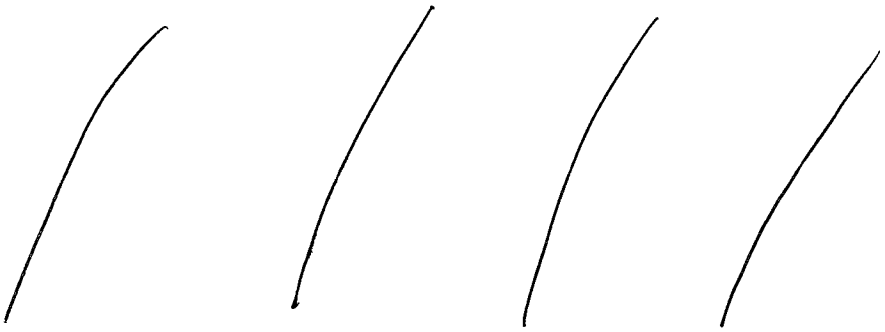
Coadministration of strong CYP3A4 inhibitors may result in decreased metabolic clearance of fentanyl. On the other hand, CYP3A4 induction may result in faster clearance of fentanyl requiring more number of doses per hour (maximum upto 6 per hour).

2.5 General Biopharmaceutics

The E-TRANS® (fentanyl HCl) System is a novel electrically-assisted transdermal delivery system designed for the management of acute pain in patients requiring opioid analgesia. This product is recommended for use in a medically-supervised setting. The system is patient-activated and provides on-demand systemic delivery of fentanyl by means of a small electric current, which is a process known as electrotransport.

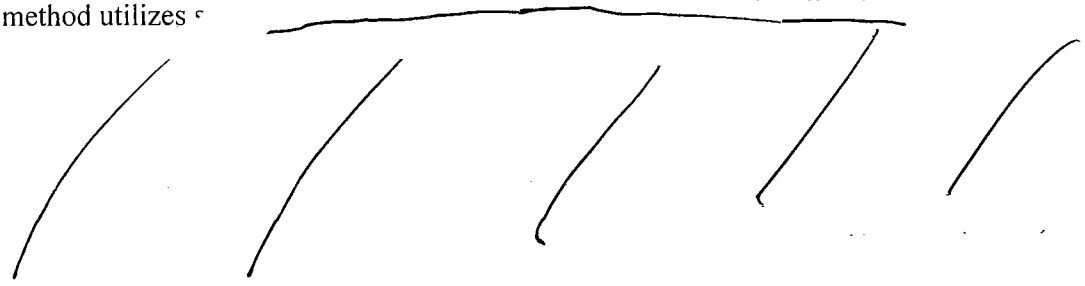
2.5.1 Drug Product

Electrotransport System (ETS) is a device for delivering active ingredient (drug) from a hydrogel reservoir by application of electric current. In addition to the drug hydrogel, the ETS contains delivery and return electrodes, a hydrogel at the site of the return electrode, electronic control circuitry, associated housings to contain components, and adhesive for attachment to the skin of a patient. A schematic of the E-TRANS® (fentanyl HCl) System's transdermal electrotransport of fentanyl cation is shown below. A source of electrical energy, such as a battery, is part of a printed circuit board assembly (PCBA) that supplies electric current to the body through two electrodes. The anode electrode and hydrogel deliver the positively-charged therapeutic agent into the body. The cathode electrode and hydrogel close the electrical circuit. Each hydrogel is placed in contact with the patient's skin on the upper arm and contains either the drug (for the anode electrode assembly) or a pharmacologically inactive electrolyte (for the cathode electrode assembly).



2.5.2 In Vitro Release Method

The sponsor developed an *in vitro* release method for the E-TRANS® (fentanyl HCl) System. The method utilizes



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✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

2.5.3 In Vitro In Vivo Correlation

Good correlation was established between the in vitro fentanyl dose delivered and in-vivo fentanyl dose absorbed at steady state as a function of electrical current. Both internal and external validation of the IVIVC model was performed. The mean prediction errors were less than 5% and 10%, respectively.

Dr. He Sun reviewed the IVIVC data provided by the sponsor. Since the IVIVC is to predict bioavailability (BA) of drug delivered over 10 minutes (one of 80 programmed dose), not for predicting the concentration-time profile, and also considering that topical absorption requires some time to "saturate" the skin disposition, it is important to check the time course of BA. There appears to be an increase in amount of fentanyl absorbed as a function of time, but the time-dependent increase in BA does not appear to be dependent on frequency of dosing.

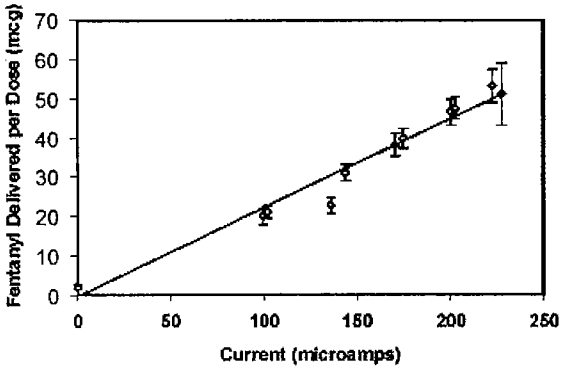
Mean* In Vitro Amount

Study	Current (μA)	No. of Systems*	Amount (ug/Dose)**
C-96-009	100	2	21.1
	140	8	30.6
	170	8	40.3
	200	2	47.5
	230	8	56.6
C-97-001	100	6	22.2
	170	6	39.8

* Individual data are provided in CMC Section 3.2.P.2.2
** Amount delivered at Dose # 45 in the SFTA test in Study C-97-001; amount delivered at Dose # 45 or 46 in SFTA test in Study C-96-009

The IVIVC was examined using *in vivo* data from two pharmacokinetic studies (C-96-009 and C-97-001) and from in-vitro data obtained via the [redacted]. Data from Study C-96-009 were used to establish the IVIVC and to perform internal validation, and data from Study C-97-001 were used to perform external validation.

Average Amount of Fentanyl Delivered In Vitro as a Function of Current



To assess the IVIVC, the amount absorbed *in vivo* was estimated at 23 hours after treatment was initiated, following the delivery of the 47th and 48th doses over 10 min. The amount released *in vitro* was the amount delivered at approximately the same dose number (dose 45). The in-vitro data collected for the various lots of E-TRANS® fentanyl systems used in Studies C-96-009 and C-97-001 are summarized in Table above (the amount delivered at dose 45 was evaluated to allow consistency among data from the *in vivo* studies).

Data from Study C-96-009 were used to establish the IVIVC and to perform internal validation, and data from Study C-97-001 were used to perform external validation. Figure below shows the correlation between the fentanyl amount delivered *in vitro* and the amount absorbed *in vivo*. There was good correlation between the in-vivo and in-vitro data as a function of current. The regression equation presented in the figure below was used to predict the *in vivo* BA from the *in vitro* amount released.

In Vitro/In Vivo Correlation

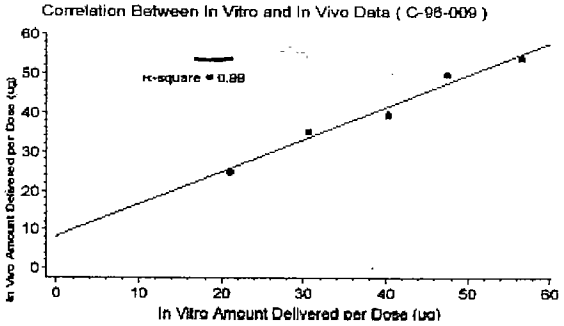


Table below presents the amount absorbed *in vivo*, and the predicted amount and the prediction errors for both the internal and external validation. The mean prediction errors were less than 5% and 10%, respectively.

Observed and Predicted Amount Absorbed to Evaluate the Internal and External Predictability of the IVIVC

Study	Current	Mean In-Vitro Amount[a]	Mean In-Vivo Amount	Prediction	Prediction Error[a]
	µA		(ug/Dose)		PE (%)
Internal Validation C-96-009	100	21.1	24.8[b]	25.5	2.8
	140	30.6	35.1[b]	33.3	5.1
	170	40.3	39.5[b]	41.4	4.8
	200	47.5	49.7[b]	47.4	4.6
	230	56.6	53.9[b]	54.9	1.9
	Mean				*3.8*
External Validation C-97-001	100	22.2	24.4[c]	26.4	8.2
	170	39.8	37.2[c]	41.0	10.2
	Mean				*9.2*

2.6 Analytical Section

The sponsor employed adequately validated analytical methods for the analysis of fentanyl in human plasma. Table below (next page) provides an overview of the studies, the techniques used to analyze the samples, and the laboratories that conducted the analyses. [redacted] developed and validated a method for the determination of morphine in human serum samples ([redacted] Method 18001_4) obtained from the C-2000-007 clinical study. Study C-2000-007 was a safety and efficacy trial in which half of the patients were treated with the 40 µg E-TRANS® fentanyl system and the other half were treated with a standard IV PCA morphine regimen. Validation reports submitted as a part of each separate pharmacokinetic study were reviewed and are acceptable. The summary of validation results for the analytical methods used in the analysis of fentanyl in human plasma are attached to this review (see Appendix page 123).

Summary of Clinical Studies and Methodologies Employed

Study No.	Type of Study	Analyte	Methodology	Laboratory
C-93-019	Bioavailability/Effect of Application Site	Fentanyl	RIA	Janssen
C-93-023	Pharmacokinetics/Safety and Efficacy	Fentanyl	RIA	Janssen
C-94-060	Bioavailability/ Demographics	Fentanyl	RIA	Janssen
C-94-068	Bioavailability/ Single, Repeated dose	Fentanyl	RIA	Janssen
C-95-016	Safety and Efficacy	Fentanyl	RIA	Janssen
C-96-009	Bioavailability	Fentanyl	RIA	Janssen
C-97-001	Bioavailability/Dose Proportionality	Fentanyl	RIA	Janssen
FEN-INT-006	Dose-Ranging	Fentanyl	RIA	Janssen
C-92-038	Bioavailability	Fentanyl	RIA	Janssen
C-98-013	Pharmacokinetics	Fentanyl	LC/MS/MS	—
C-94-067	Pharmacokinetics/Effect of Dosing Regimens	Fentanyl	LC/MS/MS	—
C-2000-007	Safety and Efficacy	Fentanyl Morphine	LC/MS/MS	—
C-2001-006	Pharmacokinetics/ Pediatric	Fentanyl	LC/MS/MS	—
C-2001-009	Pharmacokinetics/Effect of Dosing Regimens	Fentanyl	LC/MS/MS	—
C-2002-027	Pharmacokinetics/ Following Sequential Application	Fentanyl	LC/MS/MS	—

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_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

4.2 Individual Study synopses

4.2.1 C-93-023 synopsis

Original NDA 21-338: E-TRANS® (Fentanyl HCl)

C-93-023-00, BROWN: FINAL REPORT (Amended 07/17/01)

STUDY SYNOPSIS

PROTOCOL NUMBER	C-93-023-00
PROTOCOL TITLE	ETS (fentanyl) Pilot Efficacy and Safety Study in the Treatment of Postoperative Pain
STUDY DATES	Part 1 (25 µg): December 15, 1993 - August 5, 1994 Part 2 (40 µg): August 8, 1994 - August 9, 1995
INVESTIGATORS AND FACILITIES	
SPONSOR	ALZA Corporation 1900 Charleston Road PO Box 7210 Mountain View, CA, USA 94039-7210
REPORT DATE	November 1995 Amended: 22 January 1996 Changes to report: Page xvi: changed Appendix 4 to Appendix 4-A, added Appendix 4-B; changed Appendix 8 to Appendix 8-A, added Appendix 8-B Page 32: changed reference from Appendix 4 to Appendix 4-A, added reference to Appendix 4-B Page 47: changed reference from Appendix 8 to Appendix 8-A, added reference to Appendix 8-B Changed Appendix 4 to Appendix 4-A, added Appendix 4-B; changed Appendix 8 to Appendix 8-A, added Appendix 8-B

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Amended: 17 July 2001

Changes to report:
In the Synopsis: The Sponsor's address was updated. In Conclusions, the percent of patients receiving the 25 µg on-demand dosing regimen of ETS (fentanyl) who required supplemental intravenous fentanyl during Hours 0-3 was corrected to read 81% (was 79%).

In Section 10.0 Conclusions: The percent of patients receiving the 25 µg on-demand dosing regimen of ETS (fentanyl) who required supplemental intravenous fentanyl during Hours 0-3 was corrected to read 81% (was 80%).

In Figures Following the Text: For both Figures 2 and 8, the Y axis label, "Number of Patients," was corrected to read "Percentage of Patients (%)."

STUDY SYSTEM

ETS (fentanyl) consisting of the following components:
ALZA Model — On Demand-ETS Reusable Controller
Code number — control numbers —

Disposable cathode
Code number —

Anode gel containing 5 mg fentanyl
Code number —

Replaceable power supply consisting of three 3-volt lithium batteries
Code number —

PATIENTS

<u>25 µg On-demand dosing regimen</u>
Seventy-nine patients, men or women 19 to 73 years of age, who had undergone surgery, required parenteral opioids for the treatment of postoperative pain, and were expected to have moderate to severe pain, used the 25 µg on-demand dose ETS (fentanyl) in this part of the trial.

40 µg On-demand dosing regimen
A total of 174 patients, men or women 18 to 75 years of age, who had undergone surgery, required parenteral opioids for the treatment of postoperative pain, and were expected to have moderate to severe pain, used the 40 µg on-demand dose ETS (fentanyl) in this part of the trial.

OBJECTIVES

25 µg On-demand dosing regimen
The objective of Part 1 of this open-label study was to determine if a regimen of up to six 25 µg fentanyl on-demand doses per hour for 24 hours administered by the patient provided safe and effective management of post-operative pain.

40 µg On-demand dosing regimen
The objective of Part 2 of this open-label study was to determine if a regimen of up to six 40 µg fentanyl on-demand doses per hour for 24 hours administered by the patient provided safe and effective management of post-operative pain.

The secondary objective of this study was to evaluate the outcome measures to be used in the pivotal efficacy and safety studies.

STUDY PLAN

An ETS (fentanyl) was applied for 24 hours to each patient who satisfied the inclusion and exclusion criteria and met specified conditions after surgery. During the treatment period, the patient pressed the on-demand button as needed for analgesia. If required, the patient could be titrated with single or multiple 10 µg doses of fentanyl administered intravenously as a supplement. Efficacy was evaluated by the patient and investigator, and systemic safety was evaluated by observation, measurement, and querying the patient. Topical safety was evaluated 1, 6, and 24 hours after ETS (fentanyl) removal. During the 24-hour treatment period and for 12 hours after ETS (fentanyl) removal, blood samples were taken (from the first 50 patients in Part 1 and the first 52 patients in Part 2) for determination of pharmacokinetic parameters. Part 2, in which 40 µg on-demand doses were administered, was conducted

because an interim analysis demonstrated that the 25 µg on-demand doses were not as effective as desired.

RESULTS

25 µg On-demand dosing regimen
The following results demonstrate that the 25 µg on-demand dosing regimen for ETS (fentanyl), with supplemental intravenous fentanyl available as needed, was effective and safe in the management of pain after surgery:

Efficacy

- Mean pain intensity visual analogue scores (0=no pain, 100=worst possible pain) by patients decreased as the 24-hour treatment progressed: at Hour 6, 35% of the patients rated their pain ≤20, as did 57% at Hour 12, 67% at Hour 20, and 81% at Hour 24.

- The quality of analgesia was rated as good or excellent by 75% of the patients at Hour 6 and 91% of the patients at Hours 12 and 24.

- The investigator and the patients rated ETS (fentanyl) highly based on global assessment data: the investigator rated ETS (fentanyl) as good or excellent for 72 (91%) of 79 patients; 68 (86%) of the patients rated ETS (fentanyl) as good or excellent.

- Of the 64 patients from whom answers to the preference questions were recorded, 40 (62%) would have liked to use ETS (fentanyl) for another 24 hours and 54 (84%) would request the use of ETS (fentanyl) for future surgeries. Of the 47 patients who had previous surgeries, 41 (87%) said the pain control provided by ETS (fentanyl) was better than that provided by other methods for previous surgeries.

- The frequency of on-demand dose administration declined from an average of 4-5 doses in the first hour after ETS (fentanyl) application to an average of approximately two doses per hour from Hours 9 to 24.

- The number of on-demand doses delivered by each patient after being discharged from the recovery room to the ward ranged from 3 to 110 with the majority in

the range of 20-80 doses.

- Supplemental intravenous fentanyl was administered to 81% of the patients during Hours 0-3, to 27% of the patients during Hours 3-6, and to 19% during Hours 6-24.

- The mean rates of fentanyl delivery from ETS (fentanyl) were 102 µg/h during Hours 0-3, 82 µg/h during Hours 3-6, and 48 µg/h during Hours 6-24.

- No patients withdrew due to inadequate pain control.

Safety

Hypoventilation or hypoxia or both were reported in six patients. All of these events were determined to be either related to treatment or of unknown relationship and resolved with or without nasal oxygen. Four patients had episodes of hypotension and two patients had intermittent episodes of tachycardia. There were no episodes of respiratory depression. No patients were withdrawn from the Part 1 of the study due to safety considerations.

Of the 79 patients enrolled in Part 1 of the trial, 69 (87%) reported adverse events. The most frequently reported adverse events were nausea (61%) and vomiting (38%); all but one episode of nausea were judged to be mild to moderate. Other commonly reported adverse events included nausea and vomiting (18%), dizziness (14%), back pain (13%), and headache (13%).

Topical effects following use of ETS (fentanyl) were mostly mild: 78% of the patients had no or barely perceptible erythema at the (fentanyl) anode site and 95% had no or barely perceptible erythema at the cathode site 24 hours after removal. The following were the incidences of other topical effects 24 hours after removal: 11% of patients had edema, 9% had some itching, and 8% had papules at the anode site while 6% of patients had edema, 9% had itching, and 13% had papules at the cathode site.

<u>40 µg On-demand dosing regimen</u>
The following results demonstrate that the 40 µg on-

demand dosing regimen for ETS (fentanyl), with supplemental intravenous fentanyl available as needed, was effective and safe in the management of pain after surgery.

Efficacy

- Mean pain intensity visual analogue scores (0=no pain, 100=worst possible pain) by patients decreased as the 24-hour treatment progressed: at Hour 6, 43% of the patients rated their pain ≤20, as did 51% at Hour 12, 64% at Hour 20, and 70% at Hour 24.

- The quality of analgesia was rated as good or excellent by 87% of the patients at Hour 6 and 94% and 95% of the patients at Hours 12 and 24, respectively.

- The investigator and the patients rated ETS (fentanyl) highly based on global assessment data: the investigator rated ETS (fentanyl) as good or excellent for 162 (95%) of 171 patients; 158 (93%) of 170 patients rated ETS (fentanyl) as good or excellent.

- Of the patients for whom answers to the preference questions were recorded, 146 of 168 (87%) would have liked to use ETS (fentanyl) for another 24 hours and 158 of 167 (88%) would request the use of ETS (fentanyl) for future surgeries. Of the 124 patients who had previous surgeries, 98 (92%) said the pain control provided by ETS (fentanyl) was better than that provided by other means for previous surgeries, 8 (8%) said it was not better, and 18 did not respond.

- The frequency of on-demand dose administration declined from an average of 4-5 doses in the first hour after ETS (fentanyl) application to an average of approximately one dose per hour from Hours 9 to 24.

- The number of on-demand doses delivered by each patient after being discharged from the recovery room to the ward ranged from 2 to 80, with the majority in the range of 20-60 doses.

- Supplemental intravenous fentanyl was administered to approximately 46% of the patients during Hours 0-3, to 4% of the patients during Hours 3-6 and 3% during Hours 6-24.

- The mean rates of fentanyl delivery from ETS (fentanyl) were 137 µg/h during Hours 0-3, 80 µg/h during Hours 3-6, and 50 µg/h during Hours 6-24.

- No patients withdrew due to inadequate pain control.

Safety

Hypotension was reported for fifteen patients; of these, three were categorized as severe. Two patients were withdrawn from the study: one who became hypotensive due to blood loss during her abdominal hysterectomy and one who had an episode of lowered oxygen saturation, shallow respiration, hypotension, and stupor 20 minutes after a dose of ETS (fentanyl). Following intravenous administration of 0.2 mg Narcan, oxygen saturation, blood pressure, and mental status of the latter patient returned to normal. Hypertension was reported for eight patients; all were categorized as mild or moderate.
Bradycardia was reported for two patients. The bradycardia of one resolved within 4 hours. The other patient had bradycardia and hypertension throughout the study.

Hypoxia was reported for five patients; two required supplemental oxygen but none were withdrawn from the study. Hypoventilation was reported for two other patients whose symptoms were either of unknown relationship to the study drug or judged to be probably not related. There were no episodes of respiratory depression.

Of the 174 patients enrolled in Part 2 of the trial, 160 (92%) reported adverse events. The most frequently reported adverse events were nausea (56%), vomiting (36%), and nausea and vomiting (18%); 99% of the episodes of nausea, 98% of the episodes of vomiting, and 100% of episodes of nausea and vomiting were judged to be mild to moderate in severity. Other frequently reported adverse events were fever (18%), headache (17%), back pain (14%), nausea and vomiting (14%), and pain (13%).

Topical effects following use of ETS (fentanyl) were mostly mild by 24 hours after removal: 80% of the patients had no or barely perceptible erythema at the (fentanyl) anode site, as did 95% at the cathode site. Edema was observed at 19 (11%) anode sites and at 8 (4%) cathode sites 24 hours after removal. The following were the incidences of other topical effects 24 hours after removal: 4% of patients had itching, 3% had pustules, and 1% had papules at the anode site while 3% had itching, 5% had papules, and 1% had papules at the cathode site.

Pharmacokinetics

A total of 899 samples were drawn from 102 patients (50 from Part 1 and 52 from Part 2) and analyzed for serum fentanyl concentrations. The mean fentanyl clearance estimated for the post-operative patients in this study was 35.1 L, similar to that estimated for healthy subjects.

CONCLUSIONS

25 µg on-demand dosing regimen

The results of Part 1 of this study demonstrated that an ETS (fentanyl) dosing regimen comprised of six 25 µg on-demand doses of fentanyl available per hour provides good efficacy for management of moderate to severe post-operative pain during the first 24 hours after surgery. This efficacy is indicated in the VAS scores that decreased over the 24-hour treatment period, the patient ratings of quality of analgesia that improved over the 24-hour treatment period, and the high percentage of patient and investigator global assessment ratings of "good" or "excellent". In addition, the safety of this on-demand dosing regimen was confirmed by Part 1 of this study.

However, 81% of the patients receiving the 25 µg on-demand dosing regimen of ETS (fentanyl) required supplemental intravenous fentanyl during Hours 0-3, and 27% of the patients required supplemental fentanyl during Hours 3-6. In addition to this supplementary fentanyl, patients delivered an average of 4-5 on-demand doses of fentanyl during the first hour and about 2 doses per hour from Hours 9-24. Because the 25-µg on-demand ETS (fentanyl) regimen required both large numbers of on-

demand doses and substantial supplement with intravenous fentanyl to provide adequate pain management, and because there were no safety concerns with the 25 µg ETS (fentanyl) dosing regimen, a decision was made to investigate the safety and efficacy of a higher (40 µg) on-demand dose level.

40 µg on-demand dosing regimen

The results of Part 2 of this study demonstrated that an ETS (fentanyl) dosing regimen comprised of six 40 µg on-demand doses of fentanyl available per hour provides better efficacy for management of moderate to severe post-operative pain during the first 24 hours after surgery than does a regimen comprised of six 25 µg on-demand doses of fentanyl available per hour. The improved efficacy of the 40 µg relative to the 25 µg on-demand dosing regimen is indicated by the lower VAS scores over the 24-hour treatment period for the 40 µg regimen, the lower average number of 40 µg than of 25 µg on-demand doses of fentanyl delivered over the 24-hour treatment period, the higher proportion of patients rating the quality of anesthesia as "good" or "excellent" at intervals during the 24-hour treatment period with 40 µg versus 25 µg on-demand doses, and the higher percentage of patients and investigators giving global assessment ratings of "good" or "excellent" for the 40 µg regimen. In addition, a good safety profile was demonstrated with the 40 µg on-demand dose ETS (fentanyl) regimen.

Overall Conclusion

Based on the improved efficacy for the 40 µg on-demand dose regimen (Part 2) for ETS (fentanyl) compared with that for the 25 µg on-demand dose regimen (Part 1), as well as on the comparable safety profiles for both dosing regimens, the combined results of this study indicate that, of the two dose levels tested, the 40 µg on-demand dose regimen is preferable for use in the commercial ETS (fentanyl) product.

4.2.2 FEN-INT-006 study synopsis

SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN PHARMACEUTICA NV **Finished product: Fentanyl** **Active ingredient: fentanyl (R 4263)**		
Title: Investigation of the postoperative analgesic effects of three demand dose sizes of fentanyl administered by PCA	**Trial No.: FEN-INT-006** **Clinical phase: II**	
Investigator: ———	**Country: Belgium/Netherlands**	
Reference: JRF, Clinical Research Report FEN-INT-006, September 1995 (N 114336/1)		
Trial period: Start: 4 July 1994 End: 21 April 1995	**No. of investigators: 12** **No. of patients: 150**	
Indication / objectives: PCA in moderate to severe postoperative pain / Primary objective to prove the superiority in efficacy of 40 µg fentanyl over 20 µg fentanyl for use in PCA. Secondary to compare the safety of fentanyl at 20 µg, 40 µg and 60 µg.		
Trial design: Randomized, double-blind, parallel group, multicentre		

Patient selection

- Inclusion criteria:

  Preoperative
  - male or female patients
  - age 21-75 years
  - ASA Class I, II or III
  - scheduled major abdominal surgery, such as major colon surgery or rectal surgery lasting >1 hour
  - moderate to severe pain requiring parenteral opioids for a minimum of 24 hours postoperatively
  - signed informed consent.

  Postoperative
  - extubated
  - responsive to name and place.
  - respiratory rate of 8 bpm or greater.
  - O_2 saturation greater than 90%
  - moderate to severe pain (i.e.VAS ≥ 5)
  - titrated to acceptable analgesia (i.e. VAS ≤ 2).
- Exclusion criteria:
  - procedures requiring postoperative sedation, ventilatory support, treatment with vasoactive agents, or admission to an intensive care unit
  - likely to require another surgical procedure within 36 hours of the end of surgery
  - opioid treatment for chronic pain within 3 days before surgery
  - history of substance or alcohol abuse.
  - significant CNS or cardiopulmonary disease, hepatic or renal insufficiency
  - significant blood loss prior to surgery
  - allergy or hypersensitivity to fentanyl
  - 50% below or 50% above ideal body weight
  - treatment with an investigational drug in the previous 30 days
  - fertile women who were pregnant, breast feeding or not using adequate birth control
  - unable to operate a PCA device
  - not expected to remain in the hospital for the 24-hour observation period

Treatment					
Form - dosing route	PCA device				
Medication	Fentanyl 20 µg		Fentanyl 40 µg		Fentanyl 60 µg
Batch number	Batch 94H09/328 and commercially available Fentanyl				
Dosage	As required by patient Maximum doses of 120, 240 and 360 µg/h				
Duration	24 hours				
Disallowed medication	Other opioid analgesics				
Assessments	Before surgery	Before iv dose titration	After iv dose titration	0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 20 hours	24 hours
• Entry					
- History and physical examination	X				
• Efficacy					
- VAS pain score		X	X	X	X
- Number of demand doses				X	X
- Patients' global assessment					X
- Investigators' global assessment					X
• Safety					
- Adverse Events		X	X	X	X
- Pulse oximetry		X	X	X	X
- Respiratory rate		X	X	X	X
- Heart rate and BP		X	X	X	X
• Fentanyl plasma concentrations (not required according to protocol)	X	X	X	X	X
Statistical methods	Intent-to-treat analysis, Kruskal Wallis analysis of variance, Fisher exact probability test, Cochran Mantel-Haenszel test, Van Elteren test, Cochran-Armitage test, Jonckheere-Terpstra test, Breslow-Day test				

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Main features of the trial sample and summary of the results

Baseline characteristics - patient disposition	Fentanyl 20 µg	Fentanyl 40 µg	Fentanyl 60 µg
Number of patients entered (M/F) Age: median (min-max), yrs	23/27 55.5 (28-73)	24/26 55.0 (22-70)	27/23 59.0 (21-74)
Drop-outs - reason • adverse event • insufficient response • insufficient response + withdrew consent • ran out of trial material	 1 1	 2 1	 1 1

Effectiveness (n = 150)	Fentanyl 20 µg n=50	Fentanyl 40 µg n=50	Fentanyl 60 µg n=50
Primary parameter • Responders (patient's global assessment score of "very good" or "excellent" and no severe opioid adverse effects)	42%	52%	68%
	60 µg > 20µg; 40 µg = 20 µg; 40 µg = 60 µg		
• Global evaluations (% of patients): - Patient / investigator poor fair good very good excellent	 6/2 12/20 40/36 26/26 16/16	 8/6 4/4 27/22 37/49 24/18	 8/8 4/6 16/14 42/44 30/28
Secondary parameters • Pain scores: mean % AUC standardized to the maximum possible score - rest - movement	 23.9 36.8	 22.0 34.6	 18.1 28.9
	Rest: 60 µg > 20 µg; 60 µg > 40 µg; Movement: 60 µg > 20 µg		
• Mean total number of demand doses - valid demands* - invalid demands*	 51.8 123.6	 41.1 74.4	 35.7 84.7
* a valid demand results in a fentanyl delivery, an invalid demand delivers no fentanyl	Valid: 40 µg > 20 µg; 60 µg > 20 µg; 40 µg = 60 µg Invalid: 40 µg > 20 µg; 60 µg > 20 µg; 40 µg = 60 µg		

> indicates significantly more effective; = indicates no significant difference in efficacy

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Safety (n = 150)	Fentanyl 20 µg n=50	Fentanyl 40 µg n=50	Fentanyl 60 µg n=50
Adverse events (AE)			
• Prestudy to end titration			
No. (%) with one or more AE	13 (26)	8 (16)	13 (26)
No. (%) with one or more severe AE	5 (10)	1 (2)	3 (6)
No. (%) with one or more serious AE	0 (0)	0 (0)	0 (0)
No. (%) treatment stopped due to AE	0 (0)	0 (0)	0 (0)
• Double-blind phase, n (n severe)			
Respiratory system disorders			
bradypnoea	0	0	3 (1)
hypoxia	0	1	0
respiratory depression	0	1	1 (1)
respiratory insufficiency	0	0	2 (1)
Other adverse events, reported in more than 2 patients in any group			
nausea	12 (1)	18	12
vomiting	7	3	2
somnolence	2 (2)	2 (1)	3 (1)
No. (%) with one or more AE	21 (42)	27 (54)	22 (44)
No. (%) with one or more severe AE	1 (2)	2 (4)	3 (6)
No. (%) with one or more serious AE	0 (0)	0 (0)	0 (0)
No. (%) treatment stopped due to AE	0 (0)	2 (4)	1 2)
Heart rate and Blood Pressure	No clinically significant chne at any dose level		
Respiratory rate: No. (%) of patients with <8 breaths/min	0 (0)	3 (6)	3 (6)
	respiratory rate at 4 to 12 h after start of PCA treatment was significantly lower at 60 µg than at 20 µg; at 6 h it was lower with 60 µg than with 40 µg		
Fentanyl plasma concentrations			
Average fentanyl plasma concentration, ng/ml	0.7 - 1.2	1.0 - 1.2	1.0 - 1.6
No. (%) of patients with ≥1 observation >2 ng/ml	1 (8)	0	5 (50)

Conclusions

The results of the present trial demonstrate that:

- fentanyl at 40 µg on-demand dose is of similar efficacy to fentanyl at 60 µg on-demand dose and is superior to 20 µg on-demand dose in controlling postoperative pain in patients who have undergone major abdominal surgery.
- the 40 µg dose level is associated with a lower incidence of respiratory adverse events than the 60 µg and is the preferred dose for this form of analgesia.
- with the 40 µg dose, fentanyl plasma concentrations are on average approximately 1 ng/ml.

J20

4.2.3 C-96-009 study synopsis

Original NDA 21-338: E-TRANS® (Fentanyl HCl)

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Title of Study: Pharmacokinetic Characterization of E-TRANS® (fentanyl) On-demand Doses Delivered by Various Currents in Healthy Volunteers (Protocol C-96-009-02)

Investigator(s)/Study Center:

Publication (reference): none

Study period: August 26 to September 9, 1996 | **Phase of development:** I

Objectives: The primary objective of this study was to estimate the amount of fentanyl administered over a 10-minute period from various E-TRANS® (fentanyl HCl) System treatments with different currents.

Methodology: This was a single-center open-label, incomplete block, randomized, 4-period, 6-treatment, 12-sequence crossover study. Subjects were divided into 2 groups. Those in group 1 were randomized to sequences 1 to 6 to receive treatments A, B, C, and D. Those in group 2 were randomized to sequences 7 to 12 to receive treatments A, B, E, and F. All subjects received the intravenous (IV) treatment (Treatment A) in the first period. Treatments B through F used the E-TRANS® fentanyl systems and were differentiated by the electrical current and fentanyl dose delivered. The opioid effects of fentanyl were blocked with concomitant administration of the opiate antagonist naltrexone. The IV treatment was 80 µg over 20 minutes every hour for 22.33 hours and 40 µg over 10 minutes at hour 23; E-TRANS® treatment was two consecutive doses over 10 minutes every hour for 22.33 hours and one dose over 10 minutes at hour 23. Treatments were separated by a 3-day (or longer) washout period.

Number of patients (planned and analyzed): A sample size of 36 volunteers was targeted to ensure completion by at least 30 subjects. Thirty-six subjects enrolled and 34 completed the study.

Diagnosis and main criteria for inclusion: Subjects were healthy male volunteers 18 to 45 years old, with no clinically relevant abnormalities as determined by medical history, physical examination, clinical laboratory tests, and electrocardiogram. They weighed between 60 and 90 kg; were within 10% of ideal body weight, were normotensive, had negative urine drug screen results at the time of the study screening and at check-in before commencement of the study period, agreed to use a medically acceptable method of contraception throughout the study and for 1 week after study completion; passed an opioid withdrawal test (prestudy Nalaxone challenge); and were able to read and understand English.

Test product, dose and mode of administration, batch number:

E-TRANS® fentanyl: There were five E-TRANS® fentanyl treatments (Treatments B through F), providing transdermal delivery of fentanyl by iontophoresis at different current and dose levels. Doses from all E-TRANS® fentanyl treatments were delivered for two consecutive 10-minute doses every hour for 22.33 hours, and were expected to be 40 µg, 46 µg, 34 µg, 28 µg, and 20 µg, respectively, over a 10-minute period for Treatments B through F. Treatment B (200 µA): Code No. Treatment C (230 µA): Code No Treatment D (170 µA): Code No. Treatment E (140 µA): Code No. Treatment F (100 µA): Code No E-TRANS® fentanyl anode gel surface areas were 2.75 cm^2 in treatments B-E, 1.38 cm^2 in treatment F.

Opioid antagonist: Naltrexone hydrochloride, 50 mg, was administered orally every 12 hours beginning 14 hours before the start of each fentanyl treatment and was continued until 11 hours after each treatment regimen was completed.

Challenge and Rescue medication: Naloxone hydrochloride

Duration of treatment: 24 hours for each treatment

Reference therapy, dose and mode of administration, batch number: Treatment A was IV

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

fentanyl citrate, Batch No. 96B22/740 80 µg over 20 minutes once every hour for 22.33 hours and 40 µg over 10 minutes at Hour 23.

Criteria for evaluation:

Pharmacokinetics: Blood samples were drawn frequently during the 24-hour treatment periods for quantitation of serum fentanyl concentrations.

Safety: Systemic adverse events and vital signs were monitored throughout the study during each fentanyl treatment and for 13 hours after the end of each treatment. Physical examinations and laboratory tests were performed at screening and on the final day of the study. Topical effects were evaluated at 1, 6, and 24 hours following removal of the E-TRANS® systems.

Statistical methods: Noncompartmental parameters C_{max}, T_{max}, $AUC_{(12-13)}$, $AUC_{(23-24)}$ values were calculated. The amount of fentanyl absorbed following a 10-minute on-demand dose at Hour 23 from an E-TRANS® fentanyl treatment was calculated by comparing the observed $AUC_{(23-24)}$ value with that observed following the administration of a known dose (40 µg/10 minutes) of the reference IV treatment.

The amount absorbed following each E-TRANS® fentanyl treatment was also estimated using nonlinear regression using NONMEM. The IV treatment was modeled to a two-compartment model. A first-order absorption process was used to describe the absorption of fentanyl following E-TRANS® fentanyl administration and the absorption parameters (amount and absorption rate constants) were estimated with the disposition parameters resulting from modeling the intravenous data as fixed parameters.

The amount of fentanyl absorbed, estimated by noncompartmental methods as a function of current, was examined by regression analysis (alpha=0.05). The amount of fentanyl absorbed (by subjects during each treatment), estimated by compartmental and noncompartmental methods, was compared by regression analysis; a similar magnitude of error was assumed in each method.

Summary:

The mean $AUC_{(23-24)}$ value for the E-TRANS® fentanyl treatments increased proportionally with the total amount of current applied. The coefficient of variation (CV) values were similar for the IV and the five E-TRANS® fentanyl treatments, suggesting that E-TRANS® fentanyl drug delivery does not add to the inherent variability in fentanyl serum concentrations.

Reducing the current and anode surface area of the target treatment by half (200 µA/2.75 cm^2 to 100 µA/1.38 cm^2), thereby maintaining the same current density, resulted in a proportional decrease in the amount of fentanyl delivered.

Good correlation was observed when the noncompartmental and compartmental methods were used to estimate the amounts of fentanyl absorbed.

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Treatment	C_{max} (ng/mL)	$AUC_{(0-1)}$ (ng•h/mL)	$AUC_{(12-13)}$ (ng•h/mL)	$AUC_{(23-24)}$ (ng•h/mL)	Mean amount absorbed per dose[a] (µg)
A: IV (n=36)	2.157	0.440	1.228	1.624	Ref
B: 200 µA (n=35)	2.225	0.120	1.296	1.962	49.7
C: 230 µA (n=16)	2.636	0.103	1.575	2.350	53.9
D: 170 µA (n=16)	1.954	0.171	1.097	1.760	39.5
E: 140 µA (n=18)	1.404	0.120	0.863	1.251	35.1
F: 100 µA(n=18)	1.024	0.049	0.660	0.899	24.8

[a]mean amount absorbed per 10-minute dose (µg) calculated by noncompartmental method

Safety results: No serious adverse events were reported and no clinically significant changes in vital signs were noted for any treatment. During the IV treatment, three subjects reported headache, and two reported dizziness. Moderate dizziness, mild sweating, and mild vasodilatation were reported by a single subject, and mild nausea and chills by another (both of these events were of probable or unknown relationship to drug). During E-TRANS® fentanyl treatments, adverse events were reported for 5 (14%) of 35 subjects during Treatment B (200 µA), 2 (13%) of 16 subjects during Treatment C (230 µA), 5 (31%) of 16 subjects during Treatment D (170µA), 4 (22%) of 18 subjects during Treatment E (140 µA), and none during Treatment F (100 µA). No single adverse event was reported by more than one subject during any of the E-TRANS® fentanyl treatments. AEs of probable or unknown relationship to study drug during E-TRANS® fentanyl treatments were mild application site pain in one subject, mild ecchymosis at the edge of the application site in one subject, and mild abdominal pain in one subject. Topical effects consisted primarily of erythema and were mild to moderate in severity. Of those topical effects followed to conclusion, all resolved within 96 hours of system removal. The incidence and severity of erythema were greatest during treatments with the highest current densities; scores of 3 (beet redness) were rare and observed only at the highest currents (230 µA and 200 µA). At the 24-hour assessment after system removal, topical effects (combined percentage of subjects with scores for erythema of ≥ 2 [definite redness] and for papules of ≥ 2 [>50% of occluded area]) were highest for the 230 µA (43.8%), 200 µA (32.9%) and 170 µA (36.7%) treatments.

Conclusions: The amount absorbed from the E-TRANS® fentanyl system increased proportionally to the amount of electric current applied. The 170 µA and 100 µA currents applied over 10 minutes were identified to deliver a nominal fentanyl dose of 40µg and 25 µg, respectively. The majority of topical effects were mild to moderate after removal of the E-TRANS® fentanyl systems.

Date of the report: July 1998

SYNOPSIS – AMENDED FINAL REPORT

Trial identification and protocol summary:

Company: JANSSEN PHARMACEUTICA N.V. ALZA CORPORATION **Finished product:** E-TRANS™ (fentanyl) **Active ingredient:** fentanyl hydrochloride (R183119); fentanyl citrate (R4263)		
Title: Dose relationship of two E-TRANS™ (fentanyl) systems 25 µg (100µA/1.4 cm²) and 40 µg (170µA/2.75 cm²)	**Trial No.:** FEN-USA-63 C-97-001-01 **Clinical phase:** I	
Investigator: [redacted]	**Country:** USA	
Reference: JRF, Clinical Research Report FEN-USA-63, August 1999 (N 140687); Amended, 8 February 2002		
Changes in amended report: The study schema was corrected. Cross-references to tables, figures, and appendices were added. Subject numbers were added when findings from specific subjects were discussed. In-text Table 1 was revised to clarify data presentation. In-text Table 3 was revised to include the derivation of nC_{max} and $nAUC_{0-\infty}$. The analytical report in Annex 3 was revised. Appendix 1.1 now contains the signed final version of the protocol, along with the signature pages from the previous version. The addresses of ALZA and the Institutional Review Board were updated. Minor editorial changes were made for clarity.		
Trial period: Start: 01 November 1997 End: 19 November 1997	**No. of investigators:** 1 **No. of subjects:** 40	
Indication/objectives of the trial: The objectives of this trial were to establish dose-proportionality for fentanyl delivered by E-TRANS™ (fentanyl) 25 µg and 40 µg systems and to determine the amount of fentanyl absorbed after on-demand delivery of fentanyl from each system.		
Trial design: Single-center, open-label, randomized, 3-period, 3-treatment, 2-sequence crossover in naltrexone-blocked subjects.		

Subject selection:

- Inclusion criteria:
  - Males or females between 18 and 45 years of age;
  - Within 15% of ideal weight for height;
  - Healthy volunteers with no clinically relevant abnormalities;
  - Consented to use a medically acceptable method of contraception throughout the entire trial period and for 1 week after the trial was completed;
  - Normotensive blood pressure between 100-140 mm Hg systolic and 50-90 mm Hg diastolic after sitting for 5 minutes;
  - Negative urine drug screen and alcohol breath test results at screening and within 24 hours before each fentanyl dosing period;
  - Negative screening pregnancy test for women of childbearing potential.
- Exclusion criteria:
  - Clinically significant medical problems;
  - History of carbon dioxide (CO_2) retention, prior lung disease, or asthma;
  - Active skin disease on the upper outer arm;
  - Males with hemoglobin less than 12.5 g/dL and females with hemoglobin less than 11.5 g/dL;
  - History of allergy or hypersensitivity to fentanyl and/or skin adhesives and/or cetylpyridinium chloride;
  - Subjects who would normally be excluded from the use of opioid agents;
  - Pregnant or breast feeding females;
  - Planned use of disallowed medications while in the trial;
  - Use of an investigational drug within the month prior to trial entry or, if longer than 1 month, within a period of less than 5 times the drug's half-life;

Subject selection (continued):

- Exclusion criteria (continued):
  - History or presence of drug or alcohol dependence/abuse or consumption of more than 2 drinks every day;
  - History of smoking or tobacco use within the previous 3 months;
  - Consumption of more than 36 ounces of a caffeine-containing beverage per day;
  - One or more signs of opioid withdrawal following a naloxone challenge test;
  - Unable to read and understand English;
  - Unable to understand the trial procedures.

	Treatment A	Treatment B	Treatment C
Medication	Fentanyl[1]	Fentanyl[1]	Fentanyl citrate
Form - dosing route	E-TRANS™ 25 µg (100µA/1.4 cm^2) Transdermal Electrotransport System	E-TRANS™ 40 µg (170µA/2.75 cm^2) Transdermal Electrotransport System	IV infusion
Batch number	Code #: 0007075 Control #: MV9720392	Code #: 0007074 Control #: MV9720363	21576
Dosage	2 consecutive on-demand doses each delivered over 10 minutes q 1h for 23.33 hours	2 consecutive on-demand doses each delivered over 10 minutes q 1h for 23.33 hours	equivalent to 80 µg fentanyl over 20 minutes q 1h for 23.33 hours
	Naltrexone 50 mg was administered orally (PO) q 12h during each treatment regimen, beginning 14 hours before the start of each treatment and ending approximately 11 hours after completion of each treatment.		
Duration of treatment	Up to 24 h		
Duration of trial	4 weeks		
Disallowed medication	Prescription medication (except for sex hormone replacement or birth control medications) 14 days prior to trial start and throughout the trial period, and over-the-counter medications (except for acetaminophen and birth control medications) 3 days prior to starting the trial and throughout the trial period.		

[1] Fentanyl hydrochloride.

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Assessments	Prestudy	Before Each Study Period	During Each Study Period	Post-study
Medical history	x			
Physical examination	x			x
Vital signs	x		x	x
Nighttime respiratory rate			x	
ECG	x			x
Clinical lab tests	x			x
Urine drug screen	x	x		
Alcohol breath test	x	x		
Urine pregnancy test[1]	x	x		
Naloxone challenge		x[2]		
Blood sampling			x	
System adherence			x	
Adverse events			x	
Assessment for topical adverse events in the 2 hours after E-TRANS™ removal			x[3,4]	
Erythema assessment 24 hours after E-TRANS™ removal			x[4]	

[1] Only for women of childbearing potential
[2] Assessment was performed only before the first treatment period.
[3] Effects noted during this observation period were categorized as adverse events (AEs).
[4] Assessment was only performed in study periods that evaluated E-TRANS™.

Pharmacokinetic parameters: Maximum observed serum concentration (C_{max}), time to maximum concentration (T_{max}), the area under the serum concentration time profile (AUC_t), apparent elimination rate constant (k), apparent half-life ($t_{1/2}$), and amount absorbed
Measurement of serum fentanyl concentrations: Validated radioimmunoassay with a quantification limit of 0.10 mg/mL
Statistical methods: A mixed effects model, which included fixed effects treatment, period and sequence and the random effect subject-within-sequence, was used for the analysis of the log-transformed fentanyl parameters (C_{max} and $AUC_{(23-24)}$) from the 2 E-TRANS™ (fentanyl) treatments normalized by dose.

Main features of the subject sample and summary of the results:

	All subjects	E-TRANS™ (fentanyl)		IV fentanyl
		25 µg	40 µg	
Planned/Randomized	40	40	40	40
Entered treatment	40	39	40	37
Completed treatment	35	39	38	36
Dropouts[1] - reason	5[3]	0	2	1
• Withdrew consent	1	0	1	0
• Personal reasons	1	0	0	0
• System failure	1	0	1	0
• Adverse event (AE)	2	0	0	1
Evaluable subjects[2]	31	31	31	31

[1] Premature discontinuation from treatment.

[2] All subjects who completed all 3 treatments (n=35), excluding 4 subjects with unexpectedly high serum fentanyl concentration during Treatment C (IV fentanyl) (i.e., Subject #1011, 1031, 1039, 1040)

[3] Two subjects withdrew (Subject #1020 for personal reasons; #1004 for AE) after completing both E-TRANS™ treatment periods but prior to entering the IV fentanyl treatment period.

Pharmacokinetics: Parameters	E-TRANS™ (fentanyl) 25 µg (n=31)	E-TRANS™ (fentanyl) 40 µg (n=31)	IV fentanyl (n=31)	90% Confidence Intervals[5]
C_{max} (ng/mL), mean [SD][1]	1.00 [0.65]	1.37 [0.30]	1.82 [1.23]	—
nC_{max} (ng/mL)[2]	1.45[5] (log transformed LS mean=0.373)	1.33[5] (log transformed LS mean=0.286)	—	96.79, 123.06
T_{max} (h), mean [SD]	0.56 [0.24]	0.65 [0.25]	0.58 [0.27]	73.20, 101.21
$t_{1/2}$ (h), mean [SD][3]	11.3 [3.4]	11.0 [2.4]	12.6 [3.0]	93.24, 111.82
$AUC_{(23-24)}$ (ng.h/mL), mean [SD]	0.80 [0.21]	1.23 [0.27]	1.34 [0.31]	—
$nAUC_{(23-24)}$ (ng.h/mL)[2]	1.23[5] (log transformed LS mean=0.207)	1.20[5] (log transformed LS mean=0.180)	—	95.56, 110.45
Amount absorbed (µg), mean [SD][4]	48.8 [13.9]	74.3 [12.5]	Reference	—

[1] SD=standard deviation.

[2] nC_{max} and $nAUC_{(23-24)}$ - log transformed LS mean values (normalized to 80 µg) from analysis of variance (ANOVA) table converted to normal scale (Display 7.1.2; Appendix 3.8 pages 2 of 8, pages 4 of 8).

[3] 25 µg, n=26; 40 µg, n=31; IV fentanyl, n=30.

[4] From 2 consecutive doses.

[5] Analysis of the log transformed dose normalized pharmacokinetic parameters for the 25 µg and 40 µg E-TRANS™ (fentanyl) systems, with the 40 µg system as reference (Display 7.1.2, post-text Table 8).

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Safety:	E-TRANS™ (fentanyl)		IV fentanyl (n=37)
	25 µg (n=39)	40 µg (n=40)	
Reporting at least 1 AE	39 (100.0)	39 (97.5%)	5 (13.5%)
Deaths	0	0	0
Serious AEs	0	1[1]	0
Discontinued due to AE	0	1[2]	1[3]
Most frequently reported AEs (≥10% subjects reporting)			
Application site reaction-erythema[4]	38 (97.4)	39 (97.5)	0
Nausea	7 (17.9)	6 (15.0)	2 (5.4)
Headache	7 (17.9)	4 (10.0)	1 (2.7)

[1] Subject #1004 developed acute appendicitis that occurred after completion of E-TRANS™ (fentanyl) 40 µg and before IV fentanyl.
[2] Subject with acute appendicitis, see above.
[3] Subject #1027 developed nausea less than 3 hours after start of IV fentanyl.
[4] The majority of application site reaction-erythema reports were judged mild in severity.

Safety (continued): Erythema assessment 24 hours after system removal or at time of discharge[1], n (%)	E-TRANS™ (fentanyl)		IV fentanyl (n=37)
	25 µg (n=39)	40 µg (n=40)	
• Anode			—
– None	5 (12.8)	3 (7.7)	
– Mild	27 (69.2)	30 (76.9)	
– Moderate	7 (17.9)	6 (15.4)	
– Severe	0	0	
• Cathode			—
– None	7 (17.9)	2 (5.1)	
– Mild	23 (59.0)	25 (64.1)	
– Moderate	9 (23.1)	12 (30.8)	
– Severe	0	0	

[1] Severity is the erythema severity reported for a subject at 24 hours after system removal.

Conclusions: Results of this trial indicate that the pharmacokinetic parameters following 25 µg and 40 µg E-TRANS™ (fentanyl) were dose-proportional. The amounts absorbed over a 10-minute period following 25 µg and 40 µg E-TRANS™ (fentanyl) were 24.4 and 37.2 µg, respectively. E-TRANS™ (fentanyl) was associated with mostly mild application site erythema. No serious adverse events were attributed to E-TRANS™ (fentanyl) blocked with naltrexone.

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SYNOPSIS

Company: ALZA Corporation **Investigational product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Title: Pharmacokinetics of E-TRANS® (Fentanyl HCl) 40 µg System Following Sequential Administration of Doses Over Various Durations and Evaluation of Passive Delivery (Protocol C-2002-027-02)	
Investigator(s)/Study Center: ———	
Publication (reference): none	
Study period: Date first E-TRANS® system applied: 31 August 2002 Date last subject completed: 3 October 2002	**Phase of Development:** I
Objective: To evaluate the pharmacokinetics of fentanyl following sequential administration of doses over various durations (approximately 1, 3, 6 and 13.33 hours) from E-TRANS® (fentanyl HCl) (E-TRANS® fentanyl) 40 µg system. To evaluate passive drug absorption from E-TRANS® fentanyl 40 µg system.	
Methodology: This was a single-center, open-label study. Each subject received five treatments: Treatment A first followed by the remaining four treatments according to a randomly assigned treatment sequence (four-way crossover). A 6-to-10-day washout period separated the treatment periods. Naltrexone (50 mg) was administered orally every 12 hours, beginning at approximately 14 hours before the start of each treatment period, to antagonize the opioid effects of fentanyl.	
Number of subjects (planned and analyzed): Planned (n=28). Enrolled and received at least one E-TRANS® fentanyl system (n=28). Received Treatments A, B, C, and D (n=28); Received Treatment E (n=26). Completed five treatments with no suspected technical failures (n=20).	
Diagnosis and main criteria for inclusion: Healthy adults between 18 and 45 years of age who provided written consent to participate were allowed to enroll in the study. The following subjects were excluded from participating in the study: subjects with a history or the presence of drug or alcohol dependence/abuse as defined per DSM-IV; a history of smoking or tobacco use within the last 3 months, or subjects who consumed more than 450 mg of caffeine per day.	
Test product, dose and mode of administration, batch number:	
Test Product	E-TRANS® fentanyl 40 µg System
Dose	Treatment A: 24 hours (h) run-in period without an E-TRANS® system followed by an E-TRANS® system applied for 24 h with no current Treatment B: 2 E-TRANS® fentanyl 40 µg systems, 6 sequential doses (each delivered over 10 minutes), given over approximately 1 h Treatment C: E-TRANS® fentanyl 40 µg system, 18 sequential doses (each delivered over 10 minutes), given over approximately 3 h Treatment D: E-TRANS® fentanyl 40 µg system, 36 sequential doses (each delivered over 10 minutes), given over approximately 6 h Treatment E: E-TRANS® fentanyl 40 µg system, 80 sequential doses (each delivered over 10 minutes), given over approximately 13.33 h
Mode of administration	Transdermal delivery by iontophoresis
Applied current/ anode surface area	170 µA/2.75 cm^2
Code Number	0012096
Control Number	0116435

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Company: ALZA Corporation **Investigational product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Test product, dose and mode of administration, batch number continued:

Fentanyl content	10 mg	
Duration of treatment	Treatment A	System worn for 24 hours with no current activation (no doses given)
	Treatment B	Approximately 1 h
	Treatment C	Approximately 3 h
	Treatment D	Approximately 6 h
	Treatment E	Approximately 13.33 h
Duration of trial	4 weeks	

Reference therapy: none

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected during each E-TRANS® system treatment at the time points specified below.

Treatment	Blood sampling times (hours)
Treatment A Run-in with no system followed by an E-TRANS® fentanyl 40 µg system for 24 h with no current activation	Run-in period with no system 0, 2, 4, 6, 8, 12, 16, 20 E-TRANS® fentanyl 40 µg applied without current 0 (preapplication), 2, 4, 6, 8, 12, 16, 20, 24 (system removed), 24.5
Treatment B (2 systems) 6 sequential doses over 1 hour	0 (predose), 0.5, 0.75, 1 (system removed), 1.17, 1.75, 2.5, 3, 4.5, 6, 9, 12, 15, 18, 22
Treatment C 18 sequential doses over 3 hours	0 (predose), 0.5, 1, 2.5, 3 (system removed), 3.17, 3.5, 4, 5, 6, 9, 12, 15, 18, 20, 24
Treatment D 36 sequential doses over 6 hours	0 (predose), 1, 2, 3, 5, 6 (system removed), 6.17, 6.5, 7, 8, 10, 13, 16, 20, 24, 28, 32
Treatment E 80 sequential doses over 13.33 hours	0 (predose), 2, 5, 8, 11, 12.5, 13.33 (system removed), 13.5, 14, 15, 17, 20, 24, 27, 30, 36, 47

Safety: Adverse events (AEs), skin-site assessments, vital signs, EKG, and clinical laboratory results.

Statistical Methods: The primary hypothesis to be tested was that there was no difference in the dose normalized AUC_n between Treatments B, C, D, and E. This hypothesis was tested at a significance level $\alpha = 0.05$, with all tests two-sided.

Descriptive statistics were calculated for the following pharmacokinetic parameters: the maximum observed serum concentrations (C_{max}), time to maximum concentrations (T_{max}), elimination rate constant (k), half-life ($t_{1/2}$), area under the serum concentration time profile from Hour 0 to the last detectable concentration at time t (AUC_t), and AUC extrapolated to infinity. Dose normalized AUC (AUC_n) was determined for Treatments B, C, D, and E as follows:

$AUC_n = AUC_{inf} / 12$: Treatment B
$AUC_n = AUC_{inf} / 18$: Treatment C
$AUC_n = AUC_{inf} / 36$: Treatment D
$AUC_n = AUC_{inf} / 80$: Treatment E

A mixed effects analysis of variance (ANOVA) model, which included treatment, period, sequence, fixed factors, and subject within sequence, was used for the analysis of the log transformed fentanyl AUC_n following Treatments B, C, D, and E (Chow & Liu 1992).

SYNOPSIS

Company: ALZA Corporation
Investigational product: E-TRANS® (fentanyl HCl) System
Active ingredient: fentanyl hydrochloride

Statistical Methods continued: The least square estimate of the mean normalized AUC and the 90% confidence interval around the ratio of any two treatments (Schuirmann 1987) are presented. Compartmental pharmacokinetic modeling using nonlinear regression analysis (NONMEM version 5.1) was also conducted to characterize the serum fentanyl concentration profiles following Treatments B, C, D, and E.

For Treatment A, observed serum concentrations were summarized, and the average absorption rate over the 24-hour application period was estimated by numerical deconvolution.

Pharmacokinetic results: Only data from subjects completing Treatments B, C, D, and E and who had no suspected technical failures are included in the noncompartmental pharmacokinetic comparisons between treatments. Data from all 28 subjects are reported for Treatment A.

To estimate the passive absorption from the E-TRANS® fentanyl system, the system was applied for 24 hours without current activation (Treatment A). Based on the numerical deconvolution of the serum fentanyl profile observed during this treatment, the mean cumulative amount of fentanyl absorbed was 57.4 µg (range: ' — 7 µg), and the mean fentanyl average absorption rate was 2.3 µg/h (range: — h) over the 24-hour application (blood samples were collected through 0.5 hours post system removal).

Mean (SD) Serum Fentanyl Pharmacokinetic Parameter Values Following Treatments

Parameter	Treatments				
	A E-TRANS® 40 µg without current activation 24 h n=28	B E-TRANS® 40 µg 6 sequential doses over 1 h n=20	C E-TRANS® 40 µg 18 sequential doses over 3 h n=20	D E-TRANS® 40 µg 36 sequential doses over 6 h n=20	E E-TRANS® 40 µg 80 sequential doses over 13.33 h n=20
C_{max} (ng/mL)	0.06 (0.05)	0.27 (0.18)	0.72 (0.20)	1.08 (0.48)	2.00 (1.24)
T_{max} (h)	24.15 (1.58)	1.86 (1.79)	3.45 (0.33)	6.12 (0.68)	13.00 (1.93)
$t_{1/2}$ (h) (terminal half-life)	NA	19.2 (6.0)[a]	10.5 (2.5)	10.4 (4.6)	20.5 (7.2)[b]
k (h^{-1}) (elimination rate constant)	NA	0.040 (0.013)[a]	0.070 (0.016)	0.076 (0.025)	0.038 (0.015)[b]
AUC_l[c] (ng·h/mL)	0.53 (0.40)	1.68 (0.83)	4.67 (1.61)	11.26 (4.25)	33.36 (14.04)
AUC_{inf} (ng·h/mL)	NA	2.79 (1.43)	5.75 (2.13)	12.87 (5.32)	39.88 (18.34)
AUC_n = AUC_{inf}/#dose (ng·h/mL)	NA	0.23	0.32	0.36	0.50

NA=Not applicable
[a] n=17
[b] n=19
[c] AUC_l= AUC up to the last detectable time point
Source: Tables 11.1.2-1 to 11.1.2-3

SYNOPSIS

Company: ALZA Corporation **Investigational product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Pharmacokinetic results continued: The mean maximum serum concentrations (C_{max}) for Treatments B, C, D, and E were observed to increase as a function of time and the dose-normalized AUC increased with increasing treatment duration. Results suggest that the dose-normalized AUC increased linearly with both time and number of doses administered.

A compartmental model analysis was conducted to characterize the pharmacokinetics of four E-TRANS® treatments (Treatments B, C, D, and E) and to explain the differences in the AUC/dose ratio between the treatments. Results from the nonlinear regression analysis also suggest that the bioavailability (extent of absorption) increases with the increase in treatment duration.

Safety results: No serious adverse events (SAEs) were reported during the study, and no subjects who received fentanyl withdrew early. Two subjects did not participate in Treatment E (both during Period 3) for personal reasons, but did not terminate from the study. Both subjects were allowed to continue with Periods 4 and 5. Twenty-six subjects completed all treatment periods. With the exception of one report of severe nausea, AEs were mild to moderate. Most AEs were judged related to treatment. Application-site reactions (ASRs) were the most frequently reported AEs, with erythema the most common, occurring in all subjects. Other than ASRs, the most common AE was nausea. AEs were reported at similar rates across all treatment periods. The maximum severity of erythema 24 hours after system removal tended to be greater after longer applications of the E-TRANS® system (Treatment A [24 hours, no current activation] and Treatment E [13.33 hours, 80 doses]). The maximum severity of erythema at the anode site was mild across all treatments. Moderate erythema was observed at the cathode site 24 hours after Treatments A (7 subjects [25.0%]) and E (1 subject [3.8%]). All ASRs resolved without treatment.

Conclusions: To estimate the passive absorption from the E-TRANS® fentanyl system, the system was applied for 24 hours without current activation (Treatment A). Based on the numerical deconvolution of the serum fentanyl profile observed during this treatment, the mean cumulative amount of fentanyl absorbed was 57.4 µg, and the mean fentanyl average absorption rate was 2.3 µg/h over the 24-hour application (blood samples were collected through 0.5 hours post system removal).

Results of the noncompartmental pharmacokinetic analysis suggest that the dose-normalized AUC increases linearly with both time and number of doses administered.

Results from the nonlinear regression analysis also suggest that the bioavailability (extent of absorption) increases with the increase in treatment duration.

No serious adverse events (SAEs) were reported during the study, and no subjects who received fentanyl withdrew early. Application-site reactions (ASRs) were the most frequently reported AEs, with erythema most common. All application site reactions were mild or moderate, considered treatment related, and resolved without treatment. No new safety issues were identified with the E-TRANS® fentanyl systems in this subject population.

Date of the report: 6 May 2003

SYNOPSIS

Company: ALZA Corporation **Investigational product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Title: Effect of Dosing Frequency on Fentanyl Delivery from E-TRANS® (fentanyl HCl) 40 µg System (Protocol C-2001-009-02)

Investigator(s)/Study Center:

Publication (reference): none

Study period: Date first subject treated: 20 October 2001 Date last subject completed: 17 December 2001	**Phase of Development:** I

Objective: To investigate the amount of fentanyl delivered during three different E-TRANS® (fentanyl HCl) [E-TRANS® fentanyl] dosing regimens.

Methodology: This was a single-center, open-label, randomized, three-period, three-treatment, six-sequence crossover design. Each subject received the three treatments of E-TRANS® fentanyl with a 5 to 10 day washout period between each treatment. Each subject received naltrexone as the opioid antagonist starting 14 hours before system application, twice daily during application, and ending 10 to 24 hours post system removal.

Number of subjects (planned and analyzed):
Planned (n=30). Enrolled and received at least one E-TRANS® fentanyl system (n=31). Per Treatment (n=29). Completed three treatments (n=23).

Diagnosis and main criteria for inclusion: Healthy adults between 18 and 45 years of age who provided written consent to participate were allowed to enroll in the study. The following subjects were excluded from participating in the study: subjects with a history or the presence of drug or alcohol dependence/abuse as defined per DSM-IV; a history of smoking or tobacco use within the last 3 months, or subjects who consumed more than 36 oz (1080 mL) of a caffeine-containing beverage per day.

Test product, dose and mode of administration, batch number:

Test Product	E-TRANS® (fentanyl HCl) 40 µg System		
Dose	2 sequential 40 µg doses (each dose delivered over 10 minutes) every hour for a total of 48 doses given over approximately 23 hours and 20 minutes.	6 sequential 40 µg doses (each dose delivered over 10 minutes) every 3 hours for a total of 24 doses given over approximately 10 hours.	80 sequential 40 µg doses (each dose delivered over 10 minutes) for a total of 80 doses given over approximately 13 hours and 20 minutes.
Mode of administration	Transdermal delivery by iontophoresis		
Medication	Treatment A	Treatment B	Treatment C
Code Number	0011807		
Control Number	0109004		
Fentanyl content	10 mg	10 mg	10 mg.
Duration of treatment	23 hours and 20 minutes	10 hours	13 hours and 20 minutes
Duration of trial	4 weeks		

Reference therapy: none

SYNOPSIS

Company: ALZA Corporation **Investigational product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected during each E-TRANS® system treatment at the time points specified below.

	Time Point (hours)		
Study Period	Treatment A 2 sequential 40 µg doses q1h for 23.33 h	Treatment B 6 sequential 40 µg doses q3h for 10 h	Treatment C 80 sequential 40 µg doses over 13.33 h
Start of treatment	0	0	0
Post treatment initiation (hours)	4, 4.17, 4.33, 4.42, 4.5, 4.75, 5, 8, 8.17, 8.33, 8.5, 8.75, 9, 12, 12.17, 12.33, 12.5, 12.75, 13, 16.0, 16.17, 16.33, 16.5, 16.75, 17, 20, 20.17, 20.33, 20.5, 20.75, 21.0, 22.0, 23.0, and 23.17	0.5, 1, 2, 3, 3.33, 3.67, 4, 4.5, 5, 6, 6.5, 7, 7.5, 8, 9, and 9.5	2, 5, 8, 11, and 12.5
System removal (hours)	23.33	10	13.33
Post system removal (hours)	23.42, 23.5, 23.75, 24, 25, 27, 30, 36, and 47	10.25, 10.5, 11, 12, 13, 15, 18, 22, 26, 30, 36, and 47	13.42, 13.75, 14, 15, 17, 20, 24, 27, 30, 36, and 47
Total number of doses	48	24	80

Time point 0 = Initiation of E-TRANS® system treatment

Safety: Adverse events; skin-site assessments; vital signs, EKG, and clinical laboratory results.

Statistical Methods:

The primary hypothesis was that there was no significant difference in the dose-normalized area-under-the-serum-concentration-time profile (AUC_n) between each of the E-TRANS® treatments (Treatments A, B, and C); all tests of the hypothesis were two-sided. Descriptive statistics were used to calculate the following pharmacokinetic parameters: the maximum observed serum concentrations (C_{max}); time to maximum concentrations (T_{max}); elimination rate constant (k); half-life ($t_{1/2}$); and area under the serum concentration time profile for each treatment group (AUC_{21-24} and AUC_{23-24} for Treatment A, AUC_t and AUC extrapolated to infinity [AUC_{inf}] for Treatments B and C). AUC normalized to the number of doses administered in each treatment during the time sample collection period were collected to estimate the AUC was determined as follows:

$AUC_n = AUC_{(23-24)} / 2$: Treatment A

$AUC_n = AUC_{inf} / 24$: Treatment B

$AUC_n = AUC_{inf} / 80$: Treatment C

A mixed effects analysis of variance (ANOVA) model that included treatment, period, sequence as fixed factors, and subject within sequence as a random factor, was used for the analysis of log transformed fentanyl AUC_n (Chow and Liu, 1992). The least square estimate of the ratio of the mean AUC_n and the 90% confidence interval (CI) around the mean ratio of any two treatments (Schuirmann, 1987) was presented.

SYNOPSIS

Company: ALZA Corporation **Investigational product**: E-TRANS® (fentanyl HCl) System **Active ingredient**: fentanyl hydrochloride		

Compartmental pharmacokinetic modeling using nonlinear regression analysis (NONMEM version 5.1) was also conducted to characterize the serum fentanyl concentration profiles following the three E-TRANS® treatments.

Pharmacokinetic results:

Mean (SD) Serum Fentanyl Pharmacokinetic Parameter Values Following Treatments

Parameter	Treatments		
	E-TRANS® (2-sequence) n=23	E-TRANS® (6-sequence) n=23	E-TRANS® (80-sequence) n=23
C_{max} (ng/mL)	1.30 (0.30)	0.91 (0.39)	1.94 (0.43)
T_{max} (h)	22.74 (1.46)	10.07 (0.69)	12.11 (1.24)
$t_{1/2}$ (h) (terminal half-life)	16.1 (5.5)	15.1 (7.4)	22.00 (10.0)
k (h^{-1}) (elimination rate constant)	0.048 (0.015)	0.061 (0.038)	0.037 (0.014)
AUC_{20-21} (ng.h/mL)	1.08 (0.30)	NA	NA
AUC_{23-24} (ng.h/mL)	1.14 (0.26)	NA	NA
[a]AUC_t	NA	8.79 (3.31)	33.15 (8.98)
AUC_{inf} (ng.h/mL)	NA	10.30 (3.80)	40.80 (12.70)
nAUC = AUC/#dose	AUC_{23-24} /2 = 0.57 (0.13)	AUC_{inf} /24 = 0.43 (0.16)	AUC_{inf} /80 = 0.51 (0.16)

NA=Not applicable
[a] AUC_t= AUC up to the last detectable time point.
Source: Tables 11.1.2-1 to 11.1.2-6

Results of the noncompartmental pharmacokinetic analysis showed that dose normalized AUC values for Treatment A (AUC_{23-24}/2) and Treatment C) were bioequivalent (90% confidence interval was 79.99-97.25%). The dose-normalized AUC following Treatment B was 73% and 83% of the dose-normalized AUC following Treatments A and C, respectively.

Compartmental Model Analysis: Both one- and two-compartmental models were fitted to the serum fentanyl concentration data. Based on the objective function, the two-compartment model was selected for further analysis. The observed versus predicted concentration profile using the two-compartment model suggested that the extent of absorption (bioavailability) could vary for different treatments and, further, the bioavailability could increase as a function of time. Separate linear time-dependent bioavailability terms with positive slopes were introduced in the model for each treatment (F=1+ slope x time). The performance of this model suggests that bioavailability increases as a function of time. Furthermore, the time-dependent increase in bioavailability is not likely to be dependent on the frequency of dosing.

Safety results:

- No serious adverse events were reported on study.
- One subject discontinued from the study because of an adverse event, a mild generalized maculopapular rash that was considered possibly related to E-TRANS® fentanyl treatment.
- Application-site erythema was the most frequently reported adverse event after each treatment period and was generally of mild or moderate severity.

SYNOPSIS

Company: ALZA Corporation **Investigational product:** E-TRANS® (fentanyl HCl) System **Active ingredient:** fentanyl hydrochloride		

Safety results (continued):

- The majority of erythema initially reported as moderate had become mild or resolved by 24 hours post-system removal.

Conclusions: Results of the noncompartmental pharmacokinetic analysis showed that dose normalized AUC values for Treatment A ($AUC_{23-24}/2$) and Treatment C were bioequivalent (90% confidence interval was 79.99-97.25%). The dose-normalized AUC following Treatment B was 73% and 83% of the dose-normalized AUC of Treatments A and C, respectively.

A compartmental model analysis was conducted to characterize the pharmacokinetics of all three E-TRANS® treatments and to explain the differences in the AUC/dose ratio between the treatments. Results from the nonlinear regression analysis suggest that the bioavailability (extent of absorption) increases as a function of time over the 24-hour treatment duration. Furthermore, it appears that the time-dependent increase in bioavailability is not likely to be dependent on frequency of dosing for E-TRANS® fentanyl.

No serious AEs were reported during this study. One subject discontinued treatment because of a generalized maculopapular rash that was considered possibly related to study medication. Application-site erythema, of mild or moderate severity, was the most frequently reported AE after each treatment period. The majority of erythema initially reported as moderate had become mild or resolved by 24 hours post-system removal. No new safety issues were identified with E-TRANS® fentanyl in this subject population.

Date of the report: 18 July 2002

SYNOPSIS

Company: ALZA Corporation **Finished product**: E-TRANS® (fentanyl HCl) **Active ingredient**: fentanyl hydrochloride		

Title: Comparison of Pharmacokinetics of Fentanyl After Single and Multiple Applications of E-TRANS® (fentanyl) 40 µg System (Protocol No. C-94-068)	
Investigator(s)/Study Center: —	
Publication (reference): none	
Study period: Date first subject treated: 30 January 1998 Date last subject completed: 5 February 1998	**Phase of Development**: I
Objectives: To compare the pharmacokinetic parameters of fentanyl following single (1 day) and multiple (3 days) applications of the E-TRANS® (fentanyl HCl) System [E-TRANS® (fentanyl)] delivered by 10-minute on-demand doses.	
Methodology: This was a single-center, open-label, two-period, two-treatment, crossover study of single- and multiple-day (3 days) dosing of E-TRANS® (fentanyl). A 1-day washout separated the two treatments.	
Number of subjects (planned and analyzed): Twenty-eight volunteers were to be enrolled to ensure that at least 24 subjects completed the study. Twenty-eight subjects were enrolled in the study and 25 completed both treatments. Only data from subjects completing both treatments were included in the pharmacokinetic comparisons between treatments. All 28 subjects were included in the safety evaluation.	
Diagnosis and main criteria for inclusion: Healthy adults between 18 and 45 years of age who provided written consent to participate were allowed to enroll in the study. Subjects with a history or the presence of drug or alcohol dependence/abuse as defined per DSM-IV, subjects with a history of smoking or tobacco use within the last 3 months, and subjects who consumed more than 36 oz (1080 mL) of a caffeine-containing beverage per day were excluded from the study.	
Test product, dose and mode of administration, batch number:	
Test product	E-TRANS® (fentanyl)
Dose	40 µg delivered over 10 minutes with two 10-minute doses given every 4 hours
Mode of administration	Transdermal delivery by iontophoresis
Applied current/anode surface area	170 µA/2.75 cm^2
Code Number	0007074
Control Number	MV9720363
Duration of treatment	1 day (Treatment A) and 3 days (Treatment B)
Reference therapy: none	

SYNOPSIS

Company: ALZA Corporation **Finished product**: E-TRANS® (fentanyl HCl) **Active ingredient**: fentanyl hydrochloride		

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected throughout the treatment periods and were collected frequently following the on-demand doses delivered at Hour 20 during the 1-day treatment and at Hour 68 during the 3-day treatment. Blood samples were collected before the on-demand dose (at Hour 20 or 68) and at 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, and 105 minutes and 2, 3, and 5 hours after the on-demand dose. Blood samples were also collected on the third day of the 3-day treatment at 48, 49, 50, 51, 52, 54, 56, 60, 64, and 68 hours after the start of the treatment. Some of these samples were collected just before an on-demand dose.

Safety: Adverse events, skin-site assessments, vital signs, clinical laboratory results

Statistical Methods: Serum fentanyl concentrations as a function of time were compared for the single- and multiple-day E-TRANS® (fentanyl) treatment periods. The fentanyl pharmacokinetic parameters C_{max} (maximum observed serum concentrations), T_{max} (time to maximum concentration), and $AUC_{t-(t+5)}$ (the area under the serum concentration time profile from time *t* to time *t+5 hours*) were estimated following the on-demand dose at Hour 20 of the single-day and Hour 68 of the multiple-day treatment (t = Hour 20 or 68) from blood samples collected at 10, 15, 20, 25, 30, 40, and 50 minutes and at 1, 3, and 5 hours after the on-demand dose. The concentrations prior to the on-demand dose (C_{pre}) at 20 hours (1-day treatment) and 68 hours (3-day treatment) were also summarized. The fentanyl pharmacokinetic parameters k (apparent elimination rate constant) and $t_{1/2}$ (apparent half-life) were estimated for both the single- and multiple-day treatments. The apparent elimination rate constant (k) was estimated by linear regression of the log-transformed serum concentrations during the terminal log-linear decline phase. The apparent half-life ($t_{1/2}$) value was calculated as 0.693/k.
Descriptive statistics were calculated for the pharmacokinetic parameters described above. A mixed effects analysis of variance (ANOVA) model that included treatment as a fixed factor and subject as random effect was used for the analysis of the log-transformed fentanyl pharmacokinetic parameters $AUC_{t-(t+5)}$, C_{max}, and C_{pre} and for the analysis of the untransformed half-life values.

An ANOVA model with treatment and subject effect was used to analyze the log-transformed predose concentration at 48, 52, 56, 60, 64, and 68 hours post initiation of the 3-day treatment.

A 90% confidence interval (CI) was constructed for the ratio of the mean $AUC_{t-(t+5)}$ values (log transformed).

The demographics and important clinical variables at entry were summarized for all subjects.

Summary:

Pharmacokinetic Results:

The mean AUC_{20-25} value was significantly lower than the mean AUC_{68-73} value suggesting that the absorption or the disposition of fentanyl changes with multiple-day dosing of the E-TRANS® (fentanyl) system. However, the predose concentrations at Hour 20 and Hour 68 for the 1-day and 3-day treatments, respectively, were significantly different (p=0.0001) from each other suggesting that steady state was not attained by hour 20 of the 1-day treatment. Therefore, to compare the pharmacokinetics of fentanyl following the two treatments, the AUC_{20-25} and AUC_{68-73} values were corrected for the contribution from a previous dose to reflect the AUC_{0-5} values for the dose administered at Hour 20 (1-day treatment) and Hour 68 (3-day treatment). The corrected values for AUC_{20-25} and AUC_{68-73} were not significantly different from each other indicating that the pharmacokinetics of fentanyl is not changing with multiple-day dosing of the

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl HCl) **Active ingredient:** fentanyl hydrochloride		

Pharmacokinetic Results (continued):
E-TRANS® (fentanyl) system. Steady state appears to have been attained by 48 to 60 hours. The 90% CI estimate did not meet the 80 to 125% criterion for bioequivalence; however, the analysis had low power.

Mean (SD) Pharmacokinetic Parameter Values:

	E-TRANS® 40 µg (1 day)	E-TRANS® 40 µg (3 days)	Statistical Outcome[a]
Dose	80 µg q4h	80 µg q4h	
Parameters			
n	25	25	
C_{max} (ng/mL)	0.30 (0.13)	0.48 (0.19)	S p=0.0001
T_{max} (h)	1.68 (1.01)	1.33 (1.01)	NA
$t_{1/2}$ (h)[b] (terminal half-life)	11.4 (7.4)	14.2 (7.1)	S p=0.0001
AUC_{0-5} (ng·h/mL)[c]	1.20 (0.55)	1.88 (0.71)	S p=0.0001
C_{pre} (ng/mL)[d]	0.21 (0.08)	0.34 (0.13)	S p=0.0001
$t_{1/2}'$ and $t_{1/2}''$ (h)[b] (half-life values for decline in concentration)	7.66 (2.22)	9.98 (9.13)	NA
Corrected AUC_{0-5} (ng·h/mL)[c]	0.40 (0.29)	0.54 (0.32)	NS p=0.133

[a] $\alpha = 0.05$, S=Significant, NA=Not applicable, NS=Not significant
[b] n≤23 See Tables 11.1.2-2 and 11.1.2-4.
[c] AUC_{20-25} for the 1-day treatment and AUC_{68-73} for the 3-day treatment.
[d] Concentration at 20 hours for the 1-day treatment and at 68 hours for the 3-day treatment.
Source: Tables 11.1.2-1, 11.1.2-2, 11.1.2-3, 11.1.2-4, and 11.1.2-5; Appendixes 12.1.8-1, 12.1.8-2, 12.1.8-3, 12.1.8-4, 12.1.8-5, 12.2.4-4, and 12.2.4-5

Safety Results: No serious AEs were reported during this study. All AEs were of mild or moderate severity. Most AEs reported during the two treatment periods were application-site reactions (ASRs), all of which were considered mild and probably related to treatment. The AEs other than ASRs reported during the study were not considered related to study drug. No new safety issues were identified with the E-TRANS® (fentanyl) systems studied in this subject population.

SYNOPSIS

Company: ALZA Corporation **Finished product**: E-TRANS® (fentanyl HCl) **Active ingredient**: fentanyl hydrochloride		

Conclusions: Based on AUC values corrected for predose concentration, the pharmacokinetics of fentanyl do not appear to change with multiple-day dosing. Steady state appears to have been attained by 48 to 60 hours. The 90% CI estimate did not meet the 80 to 125% criterion for bioequivalence; however, the analysis had low power.

No new safety issues were identified with the E-TRANS® (fentanyl) systems studied in this subject population.

Date of the report: 6 September 2001

4.2.8 C-93-019 study synopsis

CONFIDENTIAL

Study Synopsis

Protocol Number	C-93-019-00
Protocol Title	The Effect of Site of Application of ETS (fentanyl) on Fentanyl Pharmacokinetics in Healthy Subjects
Study Dates	January 24 to April 8, 1994
Investigators and Facilities	
Sponsor	ALZA Corporation PO Box 10950 950 Page Mill Road Palo Alto, CA 94303-0802
Study Monitor	
Medical Monitor	
Reported By	
Report Date	January 11, 1995
Study Medications and Device	**ETS (fentanyl)** Electrotransport Therapeutic System (ETS) Fentanyl, contained 5 mg of fentanyl and consisted of the following components (assembled at the investigator's facility): Fentanyl anode gel: Code number AA-00705, Control number 500121 ETS (fentanyl) 5 mg Disposable Component ALZA Code number AA-00708, Control number 500121 Model → On-Demand Reusable Controllers set at 150 µA: Code 091106, Control 500127 Lithium batteries, each 3 volts, Code number 84231, Control number 230301 ALZA Corporation Palo Alto, California 94303

Opioid Antagonist
(naltrexone hydrochloride)

Challenge and Rescue Medication
naloxone hydrochloride)

Subjects

A total of 34 healthy subjects, 21 male and 13 female, enrolled in this study; 29 completed all four treatments. The mean age of all enrolled subjects was 26.9 years. Five subjects discontinued prematurely.

Treatments

Subjects received each of the following treatments in a randomized order with ETS (fentanyl) applied as described below for 24 hours and 20 minutes (Treatments A, B, and C) or 5 hours and 20 minutes (Treatment D):

Treatment A: ETS (fentanyl) was applied to the chest immediately prior to initiation of the first dose.

Treatment B: ETS (fentanyl) was applied to the lower inner arm immediately prior to initiation of the first dose.

Treatment C: ETS (fentanyl) was applied to the upper outer arm immediately prior to initiation of the first dose.

Treatment D: ETS (fentanyl) was applied to the upper outer arm for 15 minutes prior to initiation of the first dose.

Objectives

The primary objective of this study was to investigate the pharmacokinetics of fentanyl when ETS (fentanyl) was applied at the following skin sites: upper arm, lower arm, and chest. The secondary objective was to evaluate the effect of a 15-minute application period prior to initiation of the first dose.

Study Plan

During this randomized, open-label, crossover study, each subject received three 24 hour and 20 minute fentanyl treatments and one 5 hour and 20 minute fentanyl treatment. To minimize the opioid effects of fentanyl, each subject received five doses of naltrexone: two before treatment, two during treatment and one 10 hours after the last dose

To determine the pharmacokinetic parameters, blood samples were drawn frequently during each treatment period through 48 hours after treatment initiation (Treatments A, B, and C) or 24 hours after treatment initiation (Treatment D). To ensure safety, each subject was given a complete physical examination (including clinical laboratory tests and electrocardiogram) before and after the study and was asked about any effects during treatment. Heart rate, blood pressure, and respiratory rate were monitored during the study. Topical safety was evaluated by examining the application site for evidence of local effects at 1, 6, and 23.67 hours after ETS (fentanyl) removal.

Results and Conclusions

This single application, multiple administration 24 hours crossover study compared serum fentanyl concentrations after delivery from ETS (fentanyl) administered for 20 minutes every hour at three different sites (chest, lower inner arm, outer upper arm) for 24.33 hours; a fourth treatment, an application on the upper outer arm for 5.33 hours, was included to evaluate the effect of system preapplication on the initial pharmacokinetic profile. The results support the following conclusions:

- For the 24.33 hour ETS (fentanyl) treatments, the serum fentanyl concentration profiles and AUC values at Hour 24 were highest when ETS (fentanyl) was applied to the chest and upper outer arm.

- Based on residual analysis, the amount of fentanyl delivered was greatest when ETS (fentanyl) was applied to the chest or upper outer arm. The mean amount of fentanyl delivered was 1.3 mg, 1.0 mg, and 1.3 mg when applied to the chest, lower inner arm, and outer upper arm, respectively, for 24.33 hours.

- The difference between mean fentanyl AUC values of men and women was not statistically significant.

- The mean serum fentanyl concentration profile of the 15 minute preapplication treatment was similar to the profile obtained when ETS (fentanyl) treatment was initiated immediately after application. This demonstrates that preapplication had no influence on the subsequent delivery of fentanyl.

- The most commonly reported adverse effects were headache, nausea, and dizziness; each was reported by 3 to 4 subjects during one of the treatments.

- Most topical effects were mild to moderate after removal of ETS (fentanyl). The incidence of erythema was lowest when ETS (fentanyl) was applied to the upper outer arm and was less for cathode sites than for anode sites. Nearly all the anode sites on the chest and lower inner arm showed mild to moderate erythema 24 hours after removal; most of the anode sites on the upper outer arm had negligible to mild erythema. The incidence of other observed topical effects was lowest on the upper outer arm or chest compared to those observed on the lower inner arm.

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl) system **Active ingredient:** fentanyl hydrochloride		

Title: Effect of Demographic Factors on Absorption of Fentanyl from E-TRANS® (fentanyl) System (FEN-USA #28) (Protocol No. C-94-060-04)

Investigators/Study Centers:

Publication (reference): none

Study period:	**Phase of Development:** I
Date first subject treated: 11 December 1997 Date last subject completed: 4 March 1999	

Objective: To investigate the effects of demographic factors (age, weight, and race) on the amount of fentanyl absorbed from an E-TRANS® (fentanyl) system.

Methodology: This was a multi-center, open-label, non-randomized, sequential, two-treatment study in eight groups of healthy subjects. Each group was uniquely characterized by three demographic factors. Each subject received an E-TRANS® (fentanyl) treatment (*three sequential 10 minute nominal 40 µg doses delivered every hour for 3 hours*) followed by an IV fentanyl citrate treatment (*thirty minute IV infusion of fentanyl citrate [equivalent to 120 µg fentanyl] every hour for 3 hours*). To antagonize the opioid effects of fentanyl, naltrexone (50 mg) was administered orally to each subject every 12 hours, beginning 14 hours before the start of each fentanyl treatment and ending approximately 7.5 hours after completion of the treatment. There was a minimum 5-day and a maximum 10-day washout period between treatments.

Number of subjects (planned and analyzed): Up to 80 volunteers were to be enrolled to ensure that at least 64 subjects (eight per group) completed the study.

Seventy subjects enrolled in the study and 64 subjects completed both treatments.

The distribution of all serum fentanyl concentration data has been evaluated for each treatment. All observed serum concentration data are listed for all subjects receiving treatment.

A large number of high-concentration samples occurred sporadically among the samples taken during the IV fentanyl treatment. These observations created great uncertainty in the pharmacokinetic parameters for the IV treatment. Therefore, the serum fentanyl concentration data for the IV fentanyl treatment were not further analyzed, and no pharmacokinetic parameters were calculated for the IV fentanyl treatment; IV fentanyl was not used to calculate fentanyl absorption from E-TRANS® (fentanyl).

The mean values for the estimated parameters (C_{max}, AUC_{inf}, and $t_{1/2}$) summarized in the report text include all available subjects. One subject (Subject 3011) had very high concentrations following the E-TRANS® (fentanyl) treatment relative to other subjects in the group. As a result, summary values for the E-TRANS® (fentanyl) pharmacokinetic parameters were also done without this subject.

The statistical analysis was done only with the E-TRANS® (fentanyl) AUC_{inf} data.

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl) system **Active ingredient:** fentanyl hydrochloride		

Diagnosis and main criteria for inclusion:

Healthy adults between 18 and 45 years of age, or greater than 65 years of age, who provided written consent to participate were allowed to enroll in the study.

Individuals were excluded from the study if they had a history or the presence of drug or alcohol dependence/abuse as defined per DSM-IV, a history of smoking or tobacco use within the last 3 months, or consumed more than 24 oz (720 mL) of a caffeine-containing beverage per day.

Test product, dose and mode of administration, batch number:

Test product	E-TRANS® (fentanyl)/transdermal System
Dose	Three sequential 10 minute nominal 40 µg doses delivered every hour for 3 hours (9 doses total)
Mode of administration	Iontophoretic transdermal delivery
Applied current/anode surface area	170 µA/2.75 cm^2
Code number	0007074
Control number	MV9720363
Duration of treatment	1 day

Reference therapy: IV fentanyl citrate—thirty minute IV infusion of fentanyl citrate (equivalent to 120 µg fentanyl) every hour for 3 hours

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected at the same times and throughout the treatment periods for both treatments. Blood samples were collected at the start of drug administration and at the following hours after the start of drug administration: 0.5, 0.58, 0.75, 1.0, 1.25, 1.50, 1.58, 1.75, 2.0, 2.25, 2.5, 2.58, 2.75, 3.0, 6.0, 9.0, 12.0, 18.0, and 24.0.

Safety: Adverse events, skin-site assessments, vital signs, clinical laboratory results

Pharmacokinetic Methods: Serum fentanyl concentrations as a function of time were compared for the E-TRANS® (fentanyl) and IV fentanyl citrate treatments. The following fentanyl pharmacokinetic parameters were estimated only for the E-TRANS® (fentanyl) treatment: C_{max}, T_{max}, **k** (apparent elimination rate constant was estimated by linear regression of the log-transformed serum concentrations during the terminal log-linear decline phase), $t_{1/2}$ (apparent half-life values were calculated as 0.693/k), AUC_t (area under the serum concentration time profile from hour 0 to the last detectable concentration at time t was determined by the linear trapezoidal method), AUC_{inf} (AUC value extrapolated to infinity was calculated as the sum of AUC_t and the area extrapolated to infinity, calculated by the concentration at time t (C_t) divided by k).

Statistical Methods: Descriptive statistics were calculated for the pharmacokinetic parameters described above. The statistical analysis was only done with E-TRANS® AUC_{inf} data.
The primary analysis was an analysis of variance (ANOVA) model testing the effect of demographics on E-TRANS® fentanyl AUC_{inf}. Since there was a 6/4 male/female distribution, this model included four demographic factors (lean versus obese, young versus old, white versus black, and male versus female), as well as the two-factor interactions of these demographic factors.

The least squares mean of the differences between demographic groups and their 95% confidence intervals were calculated.

SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl) system **Active ingredient:** fentanyl hydrochloride		

Pharmacokinetic Summary:

Mean ± SD (n) Fentanyl AUC_{inf} Values Following E-TRANS® (fentanyl) Treatment All Available Subject Data

Age (yrs)	Race/Ethnic Origin	Body Mass	N	AUC_{inf} (ng·h/mL)
18–45	White	Lean	11	3.86 ± 1.79
		Obese	8	2.80 ± 1.01
	Black	Lean	11	5.32 ± 9.90
		[a](Excluding #3011)	10	2.35 ± 1.19
		Obese	9	2.69 ± 0.80
> 65	White	Lean	7	3.43 ± 1.89
		Obese	10	3.13 ± 1.49
	Black	Lean	2	2.72 ± 1.12
		Obese	6	1.93 ± 1.31

[a] This subject had relatively high concentrations following the E-TRANS® (fentanyl) treatment.
Source: Tables 11.1.2-3

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SYNOPSIS

Company: ALZA Corporation **Finished product:** E-TRANS® (fentanyl) system **Active ingredient:** fentanyl hydrochloride		

Results: On the basis of the AUC_{inf}, it was concluded that the demographic factors of age, body weight, race, and gender did not affect the systemic exposure to fentanyl following E-TRANS® (fentanyl) treatment. None of the demographic factors nor their interactions had a statistically significant effect on the AUC_{inf} value following E-TRANS® (fentanyl) treatment. The analysis outcomes were similar regardless of the inclusion or exclusion of Subject 3011; Subject 3011 had concentrations relatively higher than all the other subjects after E-TRANS® (fentanyl) treatment.

Safety Results: No deaths or serious AEs occurred during the study. Most AEs were considered mild or moderate. System application was well tolerated at the skin sites. There were no clear-cut differences in safety among the treatment groups. No new safety issues were identified with the E-TRANS® (fentanyl) systems studied in this subject population.

Conclusions: None of the four demographic factors—weight (lean/obese), age, race, or gender, had a significant effect on the AUC_{inf} value following E-TRANS® (fentanyl) treatment. In addition, the interaction terms between any two demographic factors (eg, age*race) were not significant.

Date of the report: 27 February 2002

38 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

4.3 Consult Review(s)

C-93-023 and C-2001-006-02 study pharmacometrics review by Dr. Meiyu Shen

NDA 21338
Submission Date: September 23, 2003

E-TRANS®
Pharmacometrics Section

Pharmacometrics Review

NDA:	21-338
Product Trade Name:	E-TRANS®
Active Ingredient/s:	fentanyl HCL
Indication:	Management of acute pain
Submission Date:	September 23, 2003
Sponsor:	ALZA Corporation
Type of Submission:	Original
Reviewer date:	March 30, 2004
Pharmacometric Reviewer:	Meiyu Shen, Ph.D., QMR
Pharmacometrician:	He Sun, Ph.D., OCPB
QMR Staff director:	Stella Machado, Ph.D.
Primary NDA Reviewer:	Srikanth Nallani

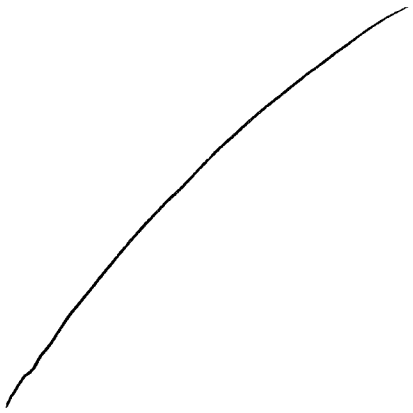
Summary

The sponsor proposed using the patient-activated, on-demand transdermal Electrotransport Therapeutic System (ETS) for fentanyl as an alternative to invasive parenteral delivery of opioids.

Study C-93-023-00 was an open-label study of the safety and efficacy of fentanyl delivered by an ETS. A two-compartment model was selected to describe the fentanyl concentration profiles in the sponsor's report.

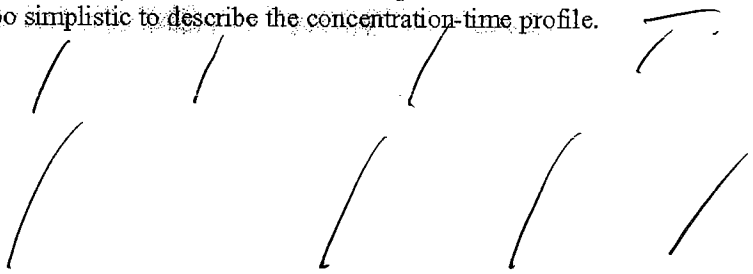
1) This population pharmacokinetic model is not acceptable due to large discrepancies between the individual predicted concentrations and the observed concentrations. Also there is a strong negative trend between weighted residuals and individual predicted concentrations, evidencing the inadequacy of the model.
2) Examination of the estimated population pharmacokinetic parameters reveals that the coefficient of variance (CV) of the between subject variability of the volume of distribution was 266%, which means that the sponsor did not have enough information to estimate the quantity.
3) Incorporating individual demographic variables and their combinations into the structure model did not have a significant effect on reduction of the between-patient variability of clearance (CL) and volume of distribution (Vss).
4) The sponsor did not conduct any simultaneous pharmacokinetic and pharmacodynamic modeling in their report.

The sponsor did not conduct a formal safety and efficacy analysis although they tabulated and described the safety and efficacy data. The sponsor did not conduct any simultaneous pharmacokinetic and pharmacodynamic modeling in their report.



Recommendation

The population pharmacokinetic analysis for adults is not adequate. The structure model treating the patch as infusion was too simplistic to describe the concentration-time profile.



_____Dated_____
Meiyu Shen, Ph.D., Statistician, QMR/OB/OpaSS

_____Dated_____
He Sun, Ph.D., Pharmacometrics, DPE2/OCPB

_____Dated_____
Stella Machado, Ph.D., QMR staff director, QMR/OB/OPaSS

Background

The sponsor proposed using the patient-activated, on-demand transdermal Electrotransport Therapeutic System (ETS) for fentanyl as an alternative to invasive parenteral delivery of opioids.

Objectives

Study C-93-023-00 was an ETS (fentanyl) pilot efficacy and safety study in the treatment of postoperative pain. A total of 899 samples were drawn from 102 patients (50 from Part 1 and 52 from part 2) and analyzed for serum fentanyl concentrations. The primary objective in Part I was to determine if up to six 25 μg fentanyl on-demand doses per hour for 24 hours administered by the patient provided safe and effective management of post-operative pain. The primary objective in Part II was to determine if up to six 40 μg fentanyl on-demand doses per hour for 24 hours administered by the patient provided safe and effective management of post-operative pain. The secondary objective of this study was to evaluate the outcome measures to be used in the pivotal efficacy and safety studies.

Study design

Study C-93-023-00 was an open-label study of the safety and efficacy of fentanyl delivered by an ETS. Patients who were expected to have moderate to severe pain after surgery were enrolled. Patients had the ETS applied for 24 hours and were followed closely for another 12 hours (36 hours total) after ETS application. Topical effects were evaluated 24 hours after ETS removal (48 hours total). Patients could self-administer fentanyl by pressing the on-demand button up to 6 times/hour. In Part I of study, fentanyl doses of 25 μg were delivered over 10 minutes after each demand. In Part II of study, fentanyl doses of 40 μg were delivered over 10 minutes after each demand. The duration of the trial was expected to be five to six months.

Data

In study C-93-023-00, blood samples (5 mL each) were drawn from the selected patients' arm opposite to the one used for the ETS (fentanyl) application, if possible. A total of 14 blood samples (70 mL) were to be drawn from 50 patients in Part 1 of this study during the 24-hour study period. A total of 5 blood samples (25 mL) were drawn from each of 52 patients in Part 2 of this study during the 24-hour study period. The samples were analyzed for serum fentanyl concentrations by Janssen Research Foundation, Beerse, Belgium, using a radioimmunoassay (RIA) method.

Pharmacometric review and findings

Study C-93-023-00

1. Demographics

Demographics Summary
Part 1 - ETS (fentanyl) 25 µg On-demand Dosing

Baseline Variable	ETS (fentanyl) (n=79)
Age (years) - n(%)	79 (100%)
< 41	26 (32.9%)
41 - 65	41 (51.9%)
> 65	12 (15.2%)
Mean ± SD	46 ± 10.1
(Min, Max)	(19, 73)
Sex - n(%)	79 (100%)
Male	13 (16.5%)
Female	66 (83.5%)
Ethnic Origin - n(%)	79 (100%)
Caucasian	61 (77.2%)
Native New Zealand	17 (21.5%)
Asian	1 (1.3%)
Height (cm)	
n	79
Mean ± SD	164 ± 9.9
(Min, Max)	(130, 188)
Weight (kg)	
n	79
Mean ± SD	71 ± 13.7
(Min, Max)	(48, 110)

Table 1

Table 2

Demographics Summary:
Part 2 - ETS (fentanyl) 40 µg On-demand Dosing

Baseline Variable	ETS (fentanyl) (n=174)
Age (Years) - n(%)	174 (100%)
< 41	52 (29.9%)
41 - 55	54 (31.0%)
> 55	68 (39.1%)
Mean ± SD	50 ± 16.3
(Min, Max)	(18, 78)
Sex - n(%)	174 (100%)
Male	37 (21.3%)
Female	137 (78.7%)
Ethnic Origin - n(%)	174 (100%)
Caucasian	150 (86.2%)
Native New Zealand	23 (13.2%)
Hispanic	1 (0.6%)
Height (cm)	
n	174
Mean ± SD	166 ± 7.6
(Min, Max)	(140, 191)
Weight (Kg)	
n	174
Mean ± SD	72 ± 14.5
(Min, Max)	(39, 110)

Table 1 and Table 2 show that many more female patients were enrolled in study than male patients.

2. Population pharmacokientic analysis

A two-compartment model was selected to describe the fentanyl concentration profiles in the report.

a) This population pharmacokinetic model is not adequate since Figure 1 shows evidence of large discrepancies between the individual predicted concentrations and the observed concentrations. In addition, Figure 2 shows that there is a strong negative trend between weighted residuals and individual predicted concentrations.

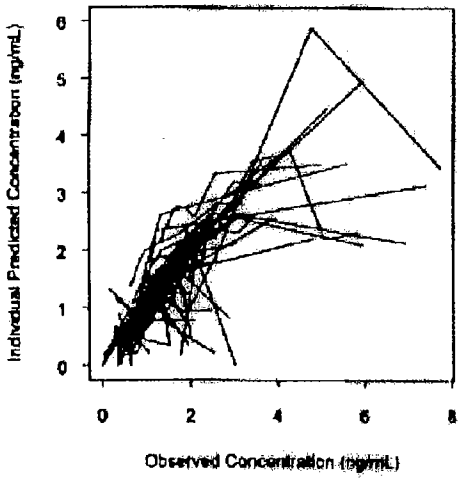


Figure 1 Individual predicted concentration versus observed concentration

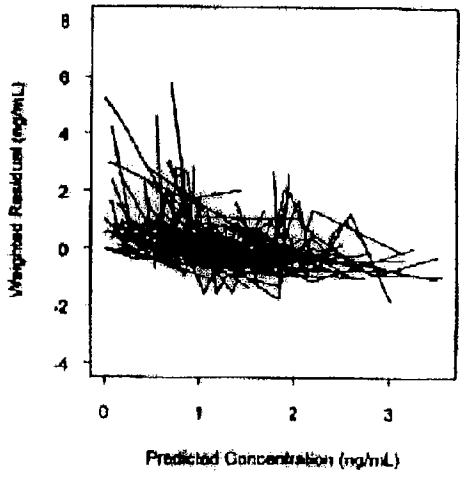


Figure 2 Weighted residual versus predicted observed concentration

b) The estimated population pharmacokinetic parameters are shown in Table 3. Here the coefficient of variance (CV) of the between subject variability of the volume of distribution was 266%, which means that the sponsor did not have enough information to estimate the quantity.

Table 3 Sponsor's analysis

One- and Two-Compartment Modeling of Fentanyl vs Time after IV Infusion and ETS Delivery of Fentanyl (n = 102)

Model	Objective Function	NONMEM Estimates			
(1) One Compartment Model CL = θ_1 V = θ_2	623		θ_1	θ_2	
		Estimate	73.3	86.1	
		CV	5%	26%	
		Betw Subj CV	29%	97%	
		Within Subj CV = 78%			
(2) Two Compartment Model Cl = θ_1 V = θ_2 Q = θ_3 VSS = 515 Ka = 2.7	277		θ_1	θ_2	θ_3
		Estimate	35.1	20.2	103
		CV	10%	12%	8%
		Betw Subj CV	69%	266%	60%
		Within Subj CV = 58%			
(3) Two Compartment Model Cl = θ_1 for 25 µg group = θ_2 for 40 µg group V = θ_3 Q = θ_4 VSS = 515 Ka = 2.7	276		θ_1	θ_2	θ_3	θ_4
		Estimate	36.2	31.3	20.2	103
		CV	10%	15%	12%	8%
		Betw Subj CV	····69%····		265%	61%
		Within Subj CV = 58%				

c) Incorporating individual demographic variables and their combinations into the structure model did not appear to have a significant effect on reduction of the between-patient variability of clearance (CL) and volume of distribution (Vss), see Figure 3, which suggests that inclusion of demographic factors in the structural model might not improve the model fit.

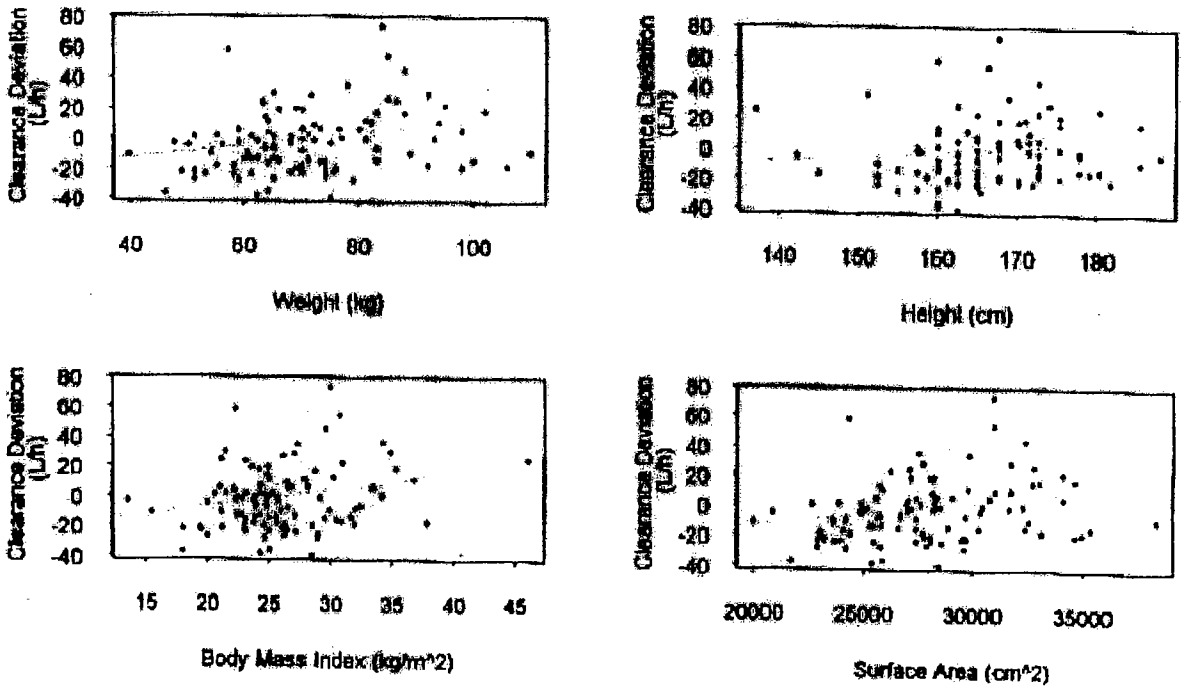
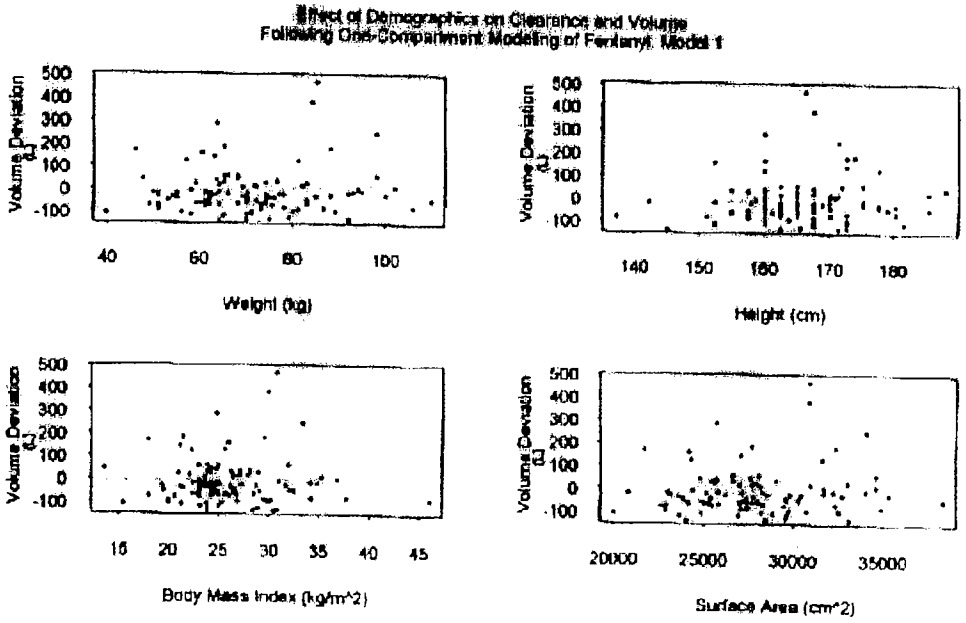


Figure 3 Effect of Demographics on Clearance and Volume of distribution following two-compartment model of fentanyl

3) Safety and efficacy analysis

The sponsor did not conduct a formal safety and efficacy analysis although they tabulated and



described the safety and efficacy data.

4) Pharmacokinetic and pharmacodynamic modeling
The sponsor did not conduct any simultaneous pharmacokinetic and pharmacodynamic modeling for their report.

3 Page(s) Withheld

/ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

Conclusion

The population pharmacokinetic analysis for adults is not ideal. The structure model indeed was over simplistic to describe the concentration-time profile. New analysis of a similar information that can be obtained from other trials is not needed.

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-338	Brand Name	E-TRANS® fentanyl HCl system
OCPB Division (I, II, III)	DPE II	Generic Name	Fentanyl HCl transdermal patch
Medical Division	DACCADP	Drug Class	Opioid Analgesic
OCPB Reviewer	Dr. Srikanth C. Nallani	Indication(s)	Post-operative pain management
OCPB Team Leader	Dr. Suresh Doddapaneni	Dosage Form	Transdermal Electrotransport device
		Dosing Regimen	40 µg per
Date of Submission	9/23/2003	Route of Administration	Skin
Estimated Due Date of OCPB Review	June 30, 2004	Sponsor	Alza Corporation 1900 Charleston Road P.O. Box 7210 Mountain View, CA 94039
PDUFA Due Date	7/23/2004	Priority Classification	Standard
Division Due Date	6/23/2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers				
single dose:	X	4	4	Application of single patch but for multiple doses
multiple dose:	X	1	1	Application of One patch per day for 3 days
Patients-				
single dose:	X	3	2	24 hour administration of drug with single patch

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X	1		Black Vs Caucasian only, Part of demographics study
gender:	X	1		Part of demographics study
pediatrics:				
geriatrics:	X	1	1	Part of demographics study
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	3		
Population Analyses -				
Data rich:				
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability:	X	2	2	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1	1	(Drug Release)
(IVIVC):	X	1	1	
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		15	12	Some studies focus on multiple aspects hence grand total is less than the number marked

Filability and QBR comments		
	"X" if yes	
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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Joan Buenconsejo
6/28/04 11:20:46 AM
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Karl Lin
6/28/04 11:24:28 AM
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Concur with review

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Srikanth Nallani
7/9/04 01:23:53 PM
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Suresh Doddapaneni
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